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

New Feature on NTP Website

In cooperation with the National Library of Medicine, the NTP has incorporated links to chemical-related information contained in the databases in ChemIDPlus. To view these options from the NTP homepage (*http://ntp.niehs.nih.gov/)* select *Testing Status of Agents at NTP* and then enter the chemical name or CAS number to get the testing status. The left sidebar now has options to view *Chemical Properties* and *Toxicity Effects* to access the new links. (The NLM ChemIDPlus Advanced website is found at *http://chem.sis.nlm.nih.gov/chemidplus/).*

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) Meeting

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will meet on December 12, 2005, at the Hilton Alexandria Old Town, 1767 King Street, Alexandria, VA to discuss issues related to toxicological methods that reduce, refine, or replace the use of animals in testing. Specific topics will include nominations to the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and *in vitro* methods for detecting ocular corrosion and irritation. Details about this meeting, as available, will be announced in the Federal Register and posted on the NTP website (http://ntp.niehs.nih.gov select *Advisory Boards and Committees*). This meeting is open to the public and public comment, both written and oral, is welcome.

Contact Information: Dr. Kristina Thayer, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, North Carolina 27709; T: (919) 541-5021; FAX: (919) 541-0295; thayer@niehs.nih.gov

NTP Workshop on High Throughput Screening Assays

The National Toxicology Program (NTP) will sponsor the High Throughput Screening (HTS) Assays Workshop on December 14-15, 2005, at the Hyatt Regency Crystal City, 2799 Jefferson Davis Highway, Arlington, VA. The workshop will provide information about HTS techniques and address the potential utility of this technology for toxicology and the NTP. Plenary presentations will be followed by breakout group sessions to discuss specific issues relating to HTS. Each breakout group will summarize its major points for presentation in plenary on December 15.

The NTP promotes improvements in toxicology test methods that will enhance the program's ability to efficiently evaluate the large number of substances in our environment for which there is little or no information about their potential hazard for human health. As part of the NTP Roadmap, the NTP seeks to identify or develop rapid, mechanism-based assays that can be used to screen large numbers of environmental substance for their potential biological activity. The NTP hopes to use the data from these HTS assays to identify mechanisms of action for further investigation, develop predictive models about how substances might react in biological systems, and prioritize substances for extensive toxicological evaluations. Additional information about the NTP Roadmap is available on the NTP website at http://ntp.niehs.nih.gov. The NTP plans to link the HTS initiative to the NIH molecular libraries program (*http://nihroadmap.nih.gov/molecularlibraries*/).

The HTS Workshop is open to the public with time set-aside for public comments during the plenary session on December 14 and opportunity for the public to attend the breakout group sessions as observers. Details about this workshop, including an on-line registration form, will be posted, as available, on the NTP website (*http://ntp.niehs.nih.gov* see *Meetings and Workshops*). Registration is limited to 100 people.

Contact Information: Dr. Barbara Shane, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, North Carolina 27709; T: (919) 541-4253; FAX: (919) 541-0295; shane@niehs.nih.gov

Technical Reports Review Subcommittee Meeting

The Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors met on September 27-28, 2005, at the NIEHS, Research Triangle Park, NC to peer review the findings and conclusions from draft NTP Technical Reports. The Subcommittee made the recommendations recorded below regarding the findings and conclusions of the reports. These recommendations will be reported to the NTP Board of Scientific Counselors at its next meeting. Additional details about the meeting are available on the NTP website at *http://ntp.niehs.nih.gov* see *Advisory Committees and Board.*

NTP studies of cosmetic formulations

Glycolic acid and Salicylic acid

- The Subcommittee accepted unanimously (6 yes, 0 no) the conclusions as written, no alternation of photocarcinogenesis of simulated solar light by glycolic acid and photoprotection by salicylic acid in male and female SKH-1 mice.

NTP studies of water disinfection by-products

Dibromoacetic acid

- The Subcommittee accepted unanimously (6 yes, 0 no) the conclusions as written, some evidence of carcinogenic activity of dibromoacetic acid in male and female F344/N rats and clear evidence of carcinogenic activity of dibromoacetic acid in male and female B6C3F_1 mice. The Subcommittee noted that the increased incidences in mononuclear cell leukemia in male rats may have been related to chemical exposure.

Dichloroacetic acid

- The Subcommittee accepted (5 yes, 1 no) the conclusions as written, no evidence of carcinogenic activity of dichloroacetic acid in p53 haploinsufficient mice.

Bromodichloromethane

- The Subcommittee accepted unanimously (6 yes, 0 no) the conclusions as written, no evidence of carcinogenic activity of bromodichloromethane in p53 haploinsufficient mice.

Sodium bromate

- The Subcommittee accepted unanimously (6 yes, 0 no) the conclusions as written, no evidence of carcinogenic activity of sodium bromate in p53 haploinsufficient mice.

NTP studies of industrial, manufacturing, or laboratory agents

Divinylbenzene

- The Subcommittee accepted (5 yes, 0 no, 1 abstention) the conclusion as written, equivocal evidence of carcinogenic activity of divinylbenzene in male F344/N rats and female B6C3F_1 mice and no evidence of carcinogenic activity in female F344/N rats and male B6C3F_1 mice.

Methyl isobutyl ketone

- The Subcommittee accepted unanimously (6 yes, 0 no) the conclusions as written, some evidence of carcinogenic activity of methyl isobutyl ketone in male F344/N rats and in male and female B6C3F_1 mice and equivocal evidence of carcinogenic activity in female F344/N rats.

Diisopropylcarbodiimide

- The Subcommittee accepted unanimously (5 yes, 0 no) the conclusions as written, no evidence of carcinogenic activity of diisopropylcarbodiimide in male and female F344/N rats and in male and female B6C3F_1 mice.
- The Subcommittee accepted unanimously (5 yes, 0 no) the conclusions as written, no evidence of carcinogenic activity of diisopropylcarbodiimide in p53 haploinsufficient mice.

4-Methylimidazole

- The Subcommittee accepted unanimously (5 yes, 0 no) the conclusions as written, no evidence of carcinogenic activity of 4-methylimidazole in male F344/N rats, equivocal evidence of carcinogenic activity in female F344/N rats, and clear evidence of carcinogenic activity in male and female B6C3F_1 mice.

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Imaging the Rodent Workshop

A workshop, *Imaging the Rodent*, jointly sponsored by the Center for *In Vivo* Microscopy and the Laboratory of Experimental Pathology at the NIEHS is planned for November 14-15, 2005. The workshop will be held at the Duke Center for Interdisciplinary Engineering, Medicine, and Applied Sciences (CIEMAS) in the auditorium. Information, about the workshop, including on-line registration, will be posted on the website *(www.civm.duhs.duke.edu/)* as available. The registration fee is $25 (fee waived for graduate students with valid student ID.)

The workshop's tentative schedule is as follows:

Nov. 14

1 - 5 PM	Imaging technologies (MR, MR histology, micro-CT, micro x-ray, micro-PET)
5 - 7 PM	Hands-on demonstrations of specialized imaging equipment and software (a light dinner is included)

Nov. 15

8 AM - noon	Applications of imaging technologies

Upcoming Events

November 14-15, 2005	Imaging the Rodent Workshop, Duke Center for Interdisciplinary Engineering, Medicine, and Applied Sciences (CIEMAS) auditorium, Durham, NC
December 12, 2005	Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), Hilton Alexandria Old Town, 1767 King Street, Alexandria, VA
December 14-15, 2005	High Throughput Screening Assays Workshop, Hyatt Regency Crystal City, Arlington, VA

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

Monographs on Amphetamines and Methylphenidate
The NTP-CERHR Monographs on the Potential Human Reproductive and Developmental Effects of Amphetamines and Methylphenidate are now available electronically on the CERHR website (*http://cerhr.niehs.nih.gov*) or on CD-ROM or in printed text from the CERHR (contact information below).

Expert Panel Report on Styrene Available
CERHR held an expert panel meeting on styrene on June 1–3, 2005, to evaluate the available scientific evidence in three primary areas: human exposure, reproductive toxicity, and developmental toxicity. The final expert panel report is available on the website and in hardcopy or on CD-ROM from CERHR. The NTP-CERHR Monograph on styrene is being prepared.

Expert Panel Meeting on DEHP Update
The CERHR convened an expert panel to re-evaluate the reproductive and developmental toxicities of di(2-ethylhexyl)phthalate (DEHP). DEHP is a high production volume chemical used as a plasticizer in the manufacture of a wide variety of consumer products. A previous panel conducted an evaluation in 1999-2000. This meeting was held on October 10–12, 2005, at the Holiday Inn Select Old Town Alexandria in Alexandria, VA. CERHR decided to update the evaluation of DEHP because of (1) its widespread human exposure, (2) public and government interest in its potential adverse health effects, and (3) the large number of relevant papers published since the earlier evaluation. This updated DEHP evaluation examined these more recent studies and reviewed the original panel's conclusions in light of this new information.

The expert panel reaffirmed that exposure to DEHP may pose a hazard to human development. They estimated that general population exposure to DEHP is 1-30 µg/kg body weight/day. Based on this estimate, the expert panel concurred with the 1999-2000 evaluation that there is *minimal concern* that exposure of adults to DEHP adversely affects reproduction.

In assessing the scientific evidence and reaching conclusions for infants and toddlers, the expert panel separately addressed these groups. The expert panel had *some concern* that exposure of male children older than 1 year of age to DEHP levels at the high end of the estimated exposure range for the general population could adversely affect reproductive development. This is a lower level of concern than that expressed by the previous panel. In agreement with the earlier panel, the expert panel had *concern* that exposure of infants younger than 1 year of age to DEHP can adversely affect reproductive development.

The expert panel agreed with the previous evaluation that there is *serious concern* that exposure of infants to DEHP from medical procedures may adversely affect development and function of the male reproductive tract. The panel noted that the benefits of medical procedures could be significant, but that minimizing exposure to DEHP should be a goal.

This evaluation, like the previous one, considered whether exposure to DEHP during pregnancy is a hazard. The expert panel had *some concern* that exposure to general population levels of DEHP during pregnancy may adversely affect male offspring. This is a lower level of concern than that expressed by the previous panel. Further, this expert panel concluded that there was also *concern* for possible effects of exposure to DEHP on male fetuses of women undergoing certain medical treatments where additional exposure to DEHP could occur.

The final expert panel report will be posted on the CERHR website and available for public comment in the near future. The conclusions noted above are those of the DEHP Expert Panel and do not necessarily represent the views of the NTP. Following completion of the public comment period, the NTP will consider the comments along with the expert panel report and any new, relevant information and develop the NTP Brief – a document that gives the NTP's opinion regarding whether exposure to DEHP is a hazard for human reproduction or development. The NTP will then publish the NTP-CERHR monograph on DEHP.

Evaluation Planned for Genistein and Soy Formula
The CERHR announced plans for the evaluation of genistein and soy formula (Federal Register April 13, 2004, Vol. 69, No. 71:19444–19445). Details about the meeting and the draft expert panel report will be published in the Federal Register and available on the CERHR website in January 2006.

Contact Information: Dr. Michael D. Shelby, Director CERHR, NIEHS, 79 TW Alexander Drive, Bldg. 4401, Room 103, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709, T: (919) 541-3455; FAX: (919) 316-4511; shelby@niehs.nih.gov

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

The 5th World Congress on Alternatives and Animal Use in the Life Sciences

NICEATM, NTP/NIEHS, and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), made a strong showing at the 5th World Congress on Alternatives and Animal Use in the Life Sciences, held in Berlin, Germany from August 21-25, 2005. The Congress is the premier international conference on the development, validation, and evaluation of alternative test methods that might be used to reduce, refine, and/or replace the use of animals in regulatory testing strategies. Eleven members of NICEATM and/or NIEHS and 18 members of ICCVAM representing other federal agencies attended the Congress, making 18 platform and 13 poster presentations. The topics covered included:

- Results of a joint NICEATM/European Centre for the Validation of Alternative Methods (ECVAM)-sponsored validation study of 2 *in vitro* cytotoxicity assays for potentially estimating rodent and human acute systemic toxicity.
- ICCVAM's role in validating *in vitro* test methods for endocrine disruptor screening.
- ICCVAM's recommended reference chemicals for the validation of *in vitro* estrogen and androgen receptor binding and transcriptional activation assays.
- An assessment of the performance of 4 different *in vitro* test methods for detecting ocular and severe irritants.
- An evaluation of the under- and over-classification rates of a 1 to 3 rabbit sequential Draize rabbit eye test.
- Current understanding and knowledge gaps of chemically-induced ocular injury and recovery
- Current and potential biomarkers of ocular injury and recovery that might be used to support the development and validation of predictive *in vitro* model systems.

Copies of the NICEATM poster presentations can be found at *http://iccvam.niehs.nih.gov*.

Expert Panel Meeting on *In Vitro* Test Methods to Identify Ocular Corrosives and Severe Irritants

On September 19, 2005, NICEATM, in conjunction with ICCVAM, held a second meeting by public teleconference of the ICCVAM ocular expert panel. The panel was charged to (1) evaluate the accuracy and reliability re-analyses of 4 *in vitro* test methods proposed for detecting ocular corrosives and severe irritants and (2) assess a revised list of proposed reference substances for validation studies on *in vitro* test methods for identifying ocular corrosives and severe irritants. The *in vitro* test methods evaluated were the Bovine Corneal Opacity and Permeability (BCOP) assay, the Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) assay, the Isolated Chicken Eye (ICE) assay, and the Isolated Rabbit Eye (IRE) assay.

At its first meeting on January 11-12, 2005, the expert panel concluded that these 4 test methods, given certain limitations, appear capable of identifying ocular corrosives/severe irritants in a tiered-testing strategy where positives would be classified as severe irritants and negatives would be tested in rabbits (limitations discussed in the expert panel report available at *http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*).
However, for IRE, the expert panel recommended that its accuracy be corroborated using a larger number of substances and that reliability analyses be conducted when additional data became available.

Public comments at that meeting indicated that additional data could be made available for the 4 test methods. The expert panel recommended that NICEATM conduct a reanalysis of the accuracy and reliability of each test method that included those data (*http://iccvam.niehs.nih.gov/methods/ocudocs/reanalysis*.htm). The expert panel report is available at *http://iccvam.niehs.nih.gov/methods/ocudocs/EPreport/ocureport.htm*.

At the September 19 meeting, the expert panel found no basis for changing its conclusions and recommendations established at the January meeting for 3 of the 4 methods (BCOP, ICE and IRE). For HET-CAM, given the increases in both the false positive and the false negative rates, the expert panel concluded that the HET-CAM IS(B) analysis method (time to first appearance of hemorrhage, lysis, and coagulation) may have limited utility for the identification of severe ocular irritants and/or corrosives. The expert panel reaffirmed that the revised list of proposed reference substances is too large if it is intended to be the minimum number of substances required for validation of a new test method. The expert panel did conclude that the list is suitable as a list of candidate substances for use during the validation of *in vitro* ocular toxicity test methods.

The expert panel report from this meeting will be published on the NICEATM/ICCVAM website and made available for public comment in the near future. ICCVAM will consider the 2 expert panel reports, other relevant background materials, all public comments and input from the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM, see information about December meeting, page 1) on this topic in finalizing ICCVAM recommendations for these test methods. The final ICCVAM test recommendations will be forwarded to relevant health and regulatory agencies for their consideration in evaluating potential use.

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NTP Testing Program

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. Any individual or group in the public and private sectors is welcome to make nominations for specific substances or for general issues related to 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 *Testing Information* heading) or by contacting the NTP Office of Chemical Nomination and Selection.

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

Contact information: Dr. Scott Masten, Office of Chemical Nomination and Selection, NIEHS, P.O. Box 12233, MD A3-07, 111 TW Alexander Dr., Research Triangle Park, NC 27709; T: 919-541-5710; masten@niehs.nih.gov

How to Subscribe to the NTP Listserv

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*.

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

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].