UPDATE
National Toxicology Program

JANUARY 2007

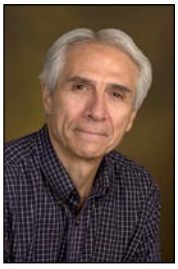
Headquartered at the
National Institute of Environmental
Health Sciences NIH-DHHS

What's Inside:

NTP Scientists Help New Treatment Enter Clinical Trials

(Article By Eddy Ball, NIEHS Environmental Factor, December 2006)

NTP Biologist, Molly Vallant



NTP Chemist, Richard Irwin

In a study published in the November issue of *Human Gene Therapy*, National Toxicology Program Chemist Richard Irwin, Ph.D., and Biologist Molly Vallant collaborated in a detailed toxicity and biodistribution analysis that has moved a novel gene transfer treatment protocol closer to clinical trial. In earlier studies, the protocol demonstrated promise for reducing side effects from radiation therapy for head and neck cancer. As part of the pre-clinical approval process needed to progress to phases 1 and 2 of human clinical studies, the Food and Drug Administration (FDA) required scientists from the National Institute of Dental and Craniofacial Research (NIDCR) to submit animal toxicity studies on the protocol. To get the data and exhaustive analysis needed, researchers from NIDCR and BioReliance Invitrogen Bioservices partnered with experts at NTP to produce a "gold standard" study using Good Laboratory Practices.

Approximately 40,000 patients are diagnosed with head and neck cancers in the United States each year. While survival rates have improved dramatically, the treatment causes severe damage to the fluid-secreting portion, or acinar cells, of the salivary glands that are within the field of radiation. Without enough saliva to lubricate and cleanse the teeth, mouth and throat, patients can experience dry mouth, damage to upper gastrointestinal tract tissues, tooth cavities, inflammation of mucus membranes in the mouth and frequent infections.

People also can have difficultly swallowing, speaking or tasting food, sometimes leading to a significant loss of appetite, considerable discomfort and a marked

(Photos courtesy of Steve McCaw)

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Looking For the Best Ending To a Major Anti-HIV Success Story

(Photo and article first published in November-December issue of The NIH Catalyst, reproduced courtesy of Fran Pollner)

When it comes to reducing the rate of mother-to-child HIV transmission, the elusive perfect is not the enemy of the good; nonetheless, investigators would like to better define and minimize the risk, however small it may currently be, of genetic damage or mitochondrial dysfunction in fetuses and infants exposed to antiretroviral therapy.

To that end, NIEHS and the National Toxicology Program (NTP) have been examining the mitochondrial and potential carcinogenic effects of zidovudine (AZT), the first FDA-approved anti-HIV agent, and other nucleoside reverse transcriptase inhibitors (NTRIs); and NICHD, in collaboration with NIAID, NIDA, NIMH, NIDCD, and NHLBI, has launched the Pediatric HIV/AIDS Cohort Study (PHACS) to assess the long-term safety of fetal and infant exposure to prophylactic antiretroviral therapy.

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Upcoming Events

January 24–26, 2007
CERHR Hydroxyurea Expert Panel Meeting, Radisson Hotel Old Town, Alexandria, VA

February 6, 2007
NICEATM/ICCVAM Pyrogenicity Test Methods Peer Review Meeting, Natcher Conference Center, NIH Campus, Bethesda, MD

March 5-7, 2007
CERHR Bisphenol A Expert Panel Meeting, Radisson Hotel Old Town, Alexandria, VA

May 16-17, 2007
NTP Board of Scientific Counselors Technical Reports Review Subcommittee, NIEHS, Research Triangle Park, NC

June 22, 2007
NTP Board of Scientific Counselors, NIEHS Research Triangle Park, NC

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NTP Scientists Help New Treatment Enter Clinical Trials

decline in quality of life. At the present time, there is no approved corrective treatment for the condition, known as radiation-induced salivary hypofunction.

Although radiation destroys the fluid-producing acinar cells, the ductal cells, which do not produce saliva, are usually not damaged. This observation led NIDCR Chief, Gene Therapy and Therapeutics Branch Bruce Baum, D.M.D., Ph.D., to collaborate in studies of salivary gland repair with then Johns Hopkins University Professor of Medicine Peter Agre, M.D. Agre discovered the water transport protein aquaporin in 1991 and was awarded the Nobel Prize in Chemistry in 2003 for his work.

The scientists hypothesized that an effective treatment could be developed using a recombinant adenoviral vector, similar to a cold virus, to transfer the gene for human aquaporin-1, which forms pores in cell membranes, to ductal cells, turning them into fluid producers. In a series of experiments with radiated animals, including rats, miniature pigs and non-human primates, the investigators found that treatment resulted in a dose-dependent increase in salivary flow to 80 percent of normal, a two to three fold increase over post-radiation levels.

Irwin, Vallant and colleagues conducted detailed and careful studies of vector safety and biodistribution of the vector beyond the oral cavity. Animals were housed individually, treated humanely and anesthetized in accordance with the guidelines during vector administration and follow-up.

Researchers monitored the health of 200 adult male and female rats, divided into four experimental groups per gender, over a 92-day period. Animals in the test groups received injections of the virus containing the gene for aquaporin-1 into the submandibular duct. For toxicity determination purposes, the treatment dose was approximately ten times the corresponding lowest and highest doses proposed for clinical study. Researchers collected saliva, blood and salivary glands from five animals in each staggered start group 48 hours after vector administration.

Researchers observed no clinical or gross pathological signs of adverse toxicological effects in animals after gene transfer. There were no treatment-associated losses of animals. Animals in all groups continued to thrive after treatment, with normal patterns of weight gain and food and water consumption. Except for local, dose-dependent inflammatory changes in the targeted gland, animals showed no severe or permanent damage to the salivary gland and limited vector distribution elsewhere in the body. Despite some gender differences in response to treatment, clinical chemistry indicators of major organ function were normal for all animals. ●

Citation: Zheng C, Goldsmith CM, Mineshiba F, Chiorini JA, Kerr A, Wenk ML, Vallant M, Irwin RD, Baum BJ. 2006. Toxicity and biodistribution of a first-generation recombinant adenoviral vector, encoding aquaporin-1, after retroductal delivery to a single rat submandibular gland. *Hum Gene Ther* 17:1122-1133.

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Looking For the Best Ending To a Major Anti-HIV Success Story

According to John Bucher, deputy director of the Environmental Toxicology Program, NIEHS, and chair of the NIH Research Festival symposium on the benefits and risks of antiretroviral therapy in preventing mother-to-child HIV transmission, antiretroviral HIV regimens are among NTP's top targets of investigation today (cell phone radiation and dietary supplements are two others).

Three NIEHS scientists reported recent findings: **William Copeland**, of the Laboratory of Molecular Genetics, reported on the propensities of NRTIs to induce disruption of mitochondrial DNA replication through inhibition of DNA polymerase-g.

A new NTP study, he said, establishes mitochondrial DNA damage in mouse-pup hearts from perinatal exposure to two NRTIs – AZT and 3TC. A possible cascade of NRTI-induced oncogenic events starts with the inhibition of thymidine kinase 2 and DNA polymerase-g and potentially culminates in activated protooncogenes and cancer.

Robert Sills, of the Laboratory of Experimental Pathology, elaborated on AZT-induced lung tumors in mice after *in utero* exposure. Mutations in the K-ras oncogene and P53 tumor-suppressor gene were among the findings reported in mouse lung tumors.

Kristine Witt, of the Environmental Toxicology Program, noted that NTP studies revealing chromosomal damage in mouse pups were designed to echo human therapeutic levels of AZT. Transplacental exposure alone to low-dose AZT (50 mg/kg) is associated with a 10-fold increase in micronucleated reticulocytes – a standard biomarker of chromosomal damage – in newborn pups.

"These were the findings," she said, "that prompted human studies"—studies in which the frequency of micronucleated reticulocytes in 13 infants exposed prenatally to AZT was 10-fold that found in cord blood of control subjects and in three infants whose HIV-infected mothers had received prenatal antiretroviral therapy that had not included AZT. "Transplacental AZT is genotoxic to erythrocytes," Witt remarked.

(left to right) William Copeland, NIEHS; Lynne Mofenson, NICHD; Kristine Witt, NIEHS; Robert Sills, NIEHS; and panel chair John Bucher, NIEHS

Whether findings of this sort have any long-term clinical consequences, however, remains to be determined.

In addition to transplacental exposure to maternal treatment for HIV during pregnancy and at labor and delivery, infants of HIV-infected mothers also receive prophylactic antiretroviral therapy for the first six weeks of life. About 6,000 to 7,000 HIV-infected women give birth annually in the United States.

The most salient consequence of this treatment is that most offspring of HIV-infected mothers are now shielded from the ravages of HIV infection, a resounding public health success story, observed **Lynne Mofenson**, chief of the Pediatric and Adolescent AIDS Branch, NICHD, and executive secretary of the PHS committee that issues guidelines for HIV/AIDS treatment and prevention of transmission in pregnancy.

Indeed, mother-to-child transmission rates have decreased from 25 percent to 1 percent or less with the use of combination antiretroviral therapy.

Mofenson noted, however, that the long-term clinical effects of *in utero* exposure to these drugs is unknown, as combination regimens have been used for only 8 to 10 years, and the data on mitochondrial dysfunction and genetic toxicity are concerning.

This concern, she added, informs the recommendation for long-term follow-up of uninfected children born to HIV-infected mothers who receive such drugs during pregnancy.

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2006 Science Day Award Winner

Wendy N. Jefferson, Ph.D., Laboratory of Molecular Toxicology, won an award at the Fourth Annual Science Day on November 2 for a poster "Neonatal exposure to the endocrine disruptor genistein adversely affects fertilization rate and oocyte quality" as the *Best Poster Presentation in Environmental Toxicology*.

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Looking For the Best Ending To a Major Anti-HIV Success Story

French studies have suggested that *in utero* antiretroviral exposure may rarely be associated with development of symptoms (primarily neurologic) of mitochondrial dysfunction in young HIV-exposed but uninfected infants; two deaths in the perinatal period in children with such findings have been reported. Other studies in the United States and Europe have not observed these findings, she said, but large numbers of children need to be followed to detect a rare event.

Additionally, there have been reports suggesting that mild, persistent, but clinically insignificant, hematologic abnormalities may be associated with antiretroviral exposure in HIV-exposed uninfected infants. Similar findings have been reported regarding asymptomatic, mild echocardiographic abnormalities.

Mofenson noted that the PHACS study will provide systematic follow-up of several thousand antiretroviral-exposed infants, with a focus on growth, metabolic, cardiac, and neurologic/ neurodevelopmental evaluations. The study, she said, should provide more answers and perhaps clues to which combination regimens may have the fewest risk of long-term adverse effects.

NTP Staff Honored at Awards Ceremony

The NIEHS held its 2006 Director's Annual Honor Awards Ceremony on December 14. Several NTP staff received NIH Merit Awards including:

- **Allen Dearry, Ph.D.** *for exemplary service to the NIEHS and for leadership as Interim Associate Director of the National Toxicology Program.*
- **Deborah McCarley** *for excellent performance in support of the activities of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods.*
- **Michael Shelby, Ph.D.** *for vision, leadership, and dedication to the Center for the Evaluation of Risks to Human Reproduction (CERHR) and its commitment to improve reproductive health and child development.*
- **Kristine Witt, Raymond Tice, Ph.D., and Cynthia Smith, Ph.D.** *for exceptional effort and innovation in launching the NTP high-through-put toxicology screening effort.*
- **Allen Dearry, Ph.D. and Mary Wolfe, Ph.D. in a group award with Steve Akiyama, Ph.D., Richard Freed, Marc Hollander, Joseph (Chip) Hughes, and Nancy Stegman** *for creative and exemplary leadership in assessing information technology infrastructure and its applications across NIEHS.*

The NIH Merit Award is the highest honor award an Institute Director can approve. It recognizes contributions in the areas of leadership, significant scientific research or administrative support, creativity, and notable competence and resourcefulness in improving the scientific or administrative management of the institute.

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NIEHS Researchers Produce Reference Work on Lymphoid Organs

(Article By Eddy Ball, NIEHS Environmental Factor, December 2006)

The September special issue of the journal *Toxicologic Pathology* (Vol. 34, No. 5) holds a unique appeal for NIEHS researchers and provides a valuable reference source for toxicological studies. With its focus on histomorphologic evaluation of lymphoid organs, the issue features over 280 pages of commentary and photomicrographs, as well as a CD with 900 high-quality full-color photomicrographs, most of them from the National Toxicology Program archives at NIEHS.

Under the direction of guest editor and Laboratory of Experimental Pathology (LEP) Senior Scientist Robert Maronpot, D.V.M., the issue presents an illustrated review of the normal structure and pathology of the lymphoid system. This issue was a response to the 2005 Society of Toxicologic Pathology call for a guide to the pathological examination of lymphoid tissues as necessary and pivotal first steps in the assessment of new drugs for immunotoxic potential prior to approval by the Food and Drug Administration. The monograph is also relevant for the histopathological assessment of immunotoxic potential following exposure to environmental agents.

Most of the contributors to the issue are or have been affiliated with the institute. Within the issue, peer-reviewed papers discuss normal structure, function, pathology and enhanced histopathology for lymph nodes, thymus, bone marrow, spleen and mucosa-associated lymphoid tissues. Maronpot wrote the issue overview, "A Monograph on Histomorphologic Evaluation of Lymphoid Organs" and an introduction to "Enhanced Histopathology of Lympoid Tissues." LEP Veterinary Medical Officer Greg Travlos, D.V.M., contributed two papers on bone marrow. The issue also includes a paper on the immunohistochemistry of lymphoid organs and five papers by LEP Pathology Staff Scientist Susan Elmore, D.V.M., dealing with enhanced histopathology.

Although each article features color slides, the majority of the printed slides are reproduced in gray scale. The full-color images, most from hematoxylin and eosin-stained slides, are available on the CD that accompanies the issue and are of suitable resolution for teaching purposes. Individual purchasers may order this important reference work on-line (*http://www.tandf.co.uk/journals/spissue/utxp-si.asp*) for $25.

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NTP Staff Honored at Awards Ceremony

Denise Lasko, Staff Assistant, NTP Liaison and Scientific Review Office, and Bonnie Allen, Administrative Specialist, Toxicology Operations Branch, received special recognition as recipients of the NIEHS Unsung Hero Award. This award recognizes employees for *behind the scenes contributions that keep the NIEHS operating in harmony.*

NIEHS recipients of the DHHS Secretary's Award for Distinguished Service were also recognized during the ceremony as part of the DHHS Group Award for Hurricane Katrina. Among those honored from NTP were **Allen Dearry, Ph.D., William Stokes, D.V.M., Samuel Wilson, M.D.,** and **Mary Wolfe, Ph.D.** This group award was presented to NIH at a DHHS ceremony in Washington in June to recognize relief efforts from the NIEHS, National Cancer Institute, National Center on Minority Health and Health Disparities, and the NIH Office of the Director.

NTP Retreat Considers Program's Directions

(Article By Eddy Ball, NIEHS Environmental Factor, December 2006)

The National Toxicology Program (NTP) held its two-day retreat at the North Carolina Biotechnology Center October 19-20. With some seventy scientists in attendance, the retreat offered the program an opportunity to evaluate its major initiatives, its roadmap and its vision in light of a flat budget and changing conditions. One purpose of the retreat was to gather as many staff together as possible and get them to talk about some of the major issues facing NTP. The retreat gave participants a chance to ask, "Where are we?" and "Where are we going?"

According to the organizing chair for the event, Center for the Evaluation of Risks to Human Reproduction Deputy Director Paul Foster, Ph.D., "This was a time for the members of the NTP to internalize all the information we've gotten from a series of workshops held over the past 18 months" and decide where the program needs to go in the future. Attendees heard reports on the pathology peer review process and the host susceptibility initiative that will evaluate known toxicants in multiple mouse species to tease out potential differences in genetic susceptibility. The group also considered developments in the process of selecting stocks and strains of test animals, how to utilize high throughput screening, how to evaluate tumors that occur as a result of endocrine system changes, and which new biomarkers will be most appropriate for future inclusion in future testing activities. Foster reported that the group made progress in several areas.

Foster pointed to an important consensus that emerged from the meeting. "NTP is planning to move toward more routine use of perinatal dosing. That means we'll expose animals beginning *in utero* in our cancer studies." This new emphasis on *in utero* exposure will establish the beginning point for NTP studies unless investigators can present good reasons for not performing perinatal exposures. The move answers the concerns of many researchers that perinatal exposure for many cancers, for example, may be critical in disease development.

One concern that ran throughout the discussions was process and how to make the program more effective and efficient as it moves into the 21st century. The pathology peer review process, for example, can be unusually time consuming. Other processes, such as nominations of chemicals for testing, have bottlenecks. "Bear in mind that when NTP does its carcinogen bioassays, they are recognized as the gold standard everywhere in the world, and so we don't want to throw the baby out with the bath water," Foster explained. On the other hand, Foster argued that there are places where NTP can compress the nomination-to-report process significantly.

As NTP approaches its thirtieth anniversary in 2008, members also wonder about identity and place. Interim Associate Director Allen Dearry stated that the retreat was not only a good start at addressing NTP's character and redefining its goals, but was also an excellent step forward in implementing many of the ideas and recommendations emerging from the past years' workshops. "It was especially pleasing and gratifying to see so much interest and enthusiasm in moving to make the NTP Roadmap a reality and in initiating a number of new directions," Dearry noted following the retreat.

As NTP considers its place in the larger NIH and DHHS scientific community, its members continue to work to safeguard public health from hazardous chemicals in food and the environment. With more than 80,000 chemicals registered for use in the U.S. and an estimated 2,000 more added each year, the program has its work cut out for it. The NTP retreat and the work to follow in its wake will help this important player in public health fulfill its mission to expand the scientific basis for making public health decisions on the potential toxicity of environmental agents. ●

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee is scheduled to meet on May 16-17, 2007, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC to peer review the findings and conclusions from 7 draft NTP Technical Reports performed in conventional rats and mice. The multigenerational study with ethinyl estradiol was performed using Sprague Dawley rats.

The draft technical reports tentatively scheduled for review are:

TR 550 Cresols	TR 551 Isoeugenol
TR 542 Cumene	TR 552 Propargyl alcohol
TR 547 Ethinyl estradiol (multigenerational study)	TR 546 Sodium dichromate dihydrate (VI)
TR 541 Formamide	

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

Contact information: Dr. Barbara Shane, Executive Secretary, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; T: 919-541-4253; shane@niehs.nih.gov

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

Monograph on DEHP Available

On October 10-12, 2005, an expert panel conducted an updated evaluation of the potential reproductive and developmental toxicities of DEHP. Following a public comment period on this report, CERHR staff prepared a draft NTP Brief that was peer reviewed and made available for public comment.The NTP-CERHR Monograph on the Potential Human

Reproductive and Developmental Effects of Di-(2-ethylhexyl) Phthalate consists of the NTP Brief, expert panel report, and public comments on the expert panel report. This monograph is now available on the CERHR website: http://cerhr.niehs.nih.gov (select *CERHR Reports and Monographs*) and in hardcopy or on CD from CERHR (contact information below).

Draft Genistein and Soy Formula Briefs Available for Comment

CERHR held an expert panel meeting on genistein and soy formula on March 15-17, 2006, in Alexandria, VA. Following the public comment period on the finalized expert panel reports, CERHR staff prepared draft NTP Briefs. The draft NTP Briefs on genistein and soy formula are now available on the CERHR website and in hardcopy or on CD from CERHR (contact information below).

Hydroxyurea Expert Panel Meeting and Draft Report

An expert panel meeting on hydroxyurea is planned for January 24-26, 2007. This public meeting will take place at the Radisson Hotel Old Town, Alexandria, VA. The draft expert panel report and details about this meeting can be found on the CERHR website. The draft report is also available in hardcopy or on CD from CERHR (contact information below).

Bisphenol A Expert Panel Meeting Planned

The expert panel meeting on bisphenol A will take place March 5-7, 2007, at the Radisson Hotel Old Town, Alexandria, VA. The draft expert panel report, information about submitting public comments, and further details about the meeting were announced in the Federal Register (71FR74534) on December 12, 2006.

Contact information: Dr. Michael D. Shelby, Director CERHR, NIH/NIEHS, 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)

Development of ICCVAM/NICEATM 5-Year Plan

Congress has requested of NIEHS that NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in partnership with the relevant federal agencies develop a 5-year plan that addresses (1) research, development, translation, and validation of new and revised non-animal and other alternative assays for integration into federal agency testing programs and (2) the identification of areas of high priority for new and revised non-animal and alternative assays for the replacement, reduction, and refinement (less pain and distress) of animal tests. As part of the activities associated with development of the plan NICEATM/ICCVAM sought public input through a notice published in Federal Register (71FR66172; November 2006) and discussed it at a recent meeting on November 30 of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). Public comments received are posted on the 5-year plan website at: *http://iccvam.niehs.nih.gov/docs/5yearplan.htm*

Scientific Peer Review of *In Vitro* Pyrogenicity Test Methods

NICEATM is convening an independent scientific panel on February 6, 2007, at the NIH Natcher Conference Center, 45 Center Drive, Bethesda, MD, to evaluate the validation status of five *in vitro* pyrogenicity test methods: (1) the human PBMC/IL-6 *in vitro* pyrogen test, (2) the human whole blood/IL-1 *in vitro* pyrogenicity test, (3) human whole blood/IL-1 *in vitro* pyrogenicity test; application of cyropreserved human whole blood, (4) the human whole blood/IL-6 *in vitro* pyrogen test, and (5) an alternative *in vitro* pyrogen test using the human monocytoid cell line MONO MAC-6. These five methods are proposed as replacements for the *in vivo* rabbit pyrogen test. The panel will peer review the draft background review document on each test method and provide comment on draft ICCVAM recommendations for the proposed use of these test methods, draft test method protocols, and draft performance standards. Written public comments on the methods are being solicited through January 26, 2007, and there will be time set aside at the meeting for oral comments. Details about the meeting, including online registration, are available at: *http://iccvam.niehs.nih.gov/methods/pyrogen.htm*

Alternative Methods to Replace the Mouse LD_{50} Assay for Botulinum Toxin Potency Testing Workshop

On November 13 and 14, 2006, NICEATM, ICCVAM, and the European Centre for the Validation of Alternative Methods (ECVAM) co-sponsored a public workshop in Silver Spring, MD on Alternative Methods to Replace the Mouse LD_{50} Assay for Botulinum Toxin Potency Testing. Over 110 participants from nine countries attended including scientists from governmental and academic institutions, national and international regulatory authorities, industry, and the animal welfare community. A poster session with a multinational collection of 10 posters addressed alternative methods for testing botulinum toxin. Workshop presentations and other information can be found at: *http://iccvam.niehs.nih.gov/methods/biolodocs/biolowkshp/wkshpinfo.htm*

Botulinum toxin, the most poisonous substance known, causes paralysis by acting on the nervous system. Botulism has been a public health and ecological hazard for centuries and botulinum toxin is a significant bioterrorism threat. Recently, the toxin has been used to treat many serious and painful medical conditions and as a personal care treatment. The most frequently used method for detecting or assessing the potency of botulinum toxin requires a test called the mouse LD_{50} assay. This assay involves dosing mice with dilutions of the toxin and identifying the dilution at which 50% of the mice die. The workshop goals were to (a) review the state-of-the-science and current knowledge of alternatives that may reduce, replace, and/or refine (less pain and distress) the use of mice for botulinum toxin testing and (b) identify priorities for research, development, and validation efforts to advance the use of alternative methods.

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

The LD_{50} assay has been in use for many years and is currently accepted as the method-of-choice by all U.S. and European regulatory agencies. However, recent advances are affording opportunities for alternative methods that may be faster and more accurate and also may refine, replace, or reduce the use of mice for testing botulinum toxin.

Availability of ICCVAM Biennial Progress Report

The Biennial Progress Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM): 2004-2005 is now available electronically on the NICEATM/ICCVAM website or in hardcopy from NICEATM (contact information below). This report describes ICCVAM's progress during 2004 and 2005. http://iccvam.niehs.nih.gov/about/annrpt/annrpt.htm

Final Background Review Documents for *In Vitro* Ocular Test Methods

NICEATM announces availability of final background review documents (BRDs) for four ocular toxicity test methods: (1) the Bovine Corneal Opacity and Permeability [BCOP] test, (2) the Isolated Chicken Eye [ICE] test, (3) the Isolated Rabbit Eye [IRE] test, and (4) the Hen's Egg Test – Chorioallantoic Membrane [HET-CAM] (NIH Publications 06-4512, 06-4513, 06-4514, and 06-4515, respectively). The BRDs provide the data and analyses used to assess the current validation status of these test methods for identifying ocular corrosives and severe irritants. Electronic copies of the four BRDs are available on the NICEATM/ICCVAM website at http://iccvam.niehs.nih.gov/ or by contacting NICEATM. ●

Contact information: Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709, T: (919) 541-2384; FAX: (919) 541-0947; iccvam@niehs.nih.gov

The 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. 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 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 review and selection process are available on the NTP website: http://ntp.niehs.nih.gov (select Nominations to the Testing Program under the heading *Testing Information*) or by contacting 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, perfluorinated compounds, herbal dietary supplements, photoactive chemicals, brominated flame retardants, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-disrupting substances, and methods for assessing potential cardiac toxicity. A list of study nominations reviewed in previous years along with supporting documents and public comments can be accessed at: http://ntp.niehs.nih.gov/go/nom

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Subscribe to the NTP Listserv

To subscribe to the listserv 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.

The NTP web site 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 web site at http://ntp.niehs.nih.gov (see Resources).

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; FAX: (919) 541-0295; liaison@starbase.niehs.nih.gov

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The NTP Testing Program

All nominations undergo several levels of review before being 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.

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

Recent NTP Publications

NTP Technical Reports:

TOX 72: Toxicity Studies of Sodium Dichromate Dihydrate

TR 525: Toxicology and Carcinogenesis Studies of 2,3,4,7,8-Pentalchlorodibenzofuran (PeCDF)

TR 526: Toxicology and Carcinogenesis Studies of a Mixture of TCDD, PeCDF, and PCB 126

TR 531: Toxicology and Carcinogenesis Studies of a Binary Mixture of PCB 136 and PCB 118

TR 534: Toxicology and Carcinogenesis Studies of Divinylbenzene

TR 535: Toxicology and Carcinogenesis Studies of 4-Methylimidazole

TR 538: Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone

Available at:
http://ntp.niehs.nih.gov/go/reports

CERHR:
NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-(2-ethylhexyl) Phthalate

Available at:
http://cerhr.niehs.nih.gov/reports/index.html

NICEATM:
Biennial Progress Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM): 2004-2005
http://iccvam.niehs.nih.gov/about/annrpt/annrpt.htm

- Current Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants: Bovine Corneal Opacity and Permeability Test Method
- Current Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants: the Isolated Chicken Eye Test Method
- Current Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants: the Isolated Rabbit Eye Test Method
- Current Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants: the Hen's Egg Test – Chorioallantoic Membrane Test Method

Available at:
http://iccvam.niehs.nih.gov/docs/docs.htm#eye