UPDATE National Toxicology Program
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NIEHS to Put More Emphasis on Systematically Assessing the Health Risks of Toxicants; Christopher Portier, Ph.D. Named Associate Director for Risk Assessment

Christopher Portier, Ph.D., will assume a new leadership role as Associate Director for Risk Assessment at the National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health. Dr. Portier will oversee and coordinate risk assessment activities within the NIEHS and apply the results of toxicological studies to national and international efforts dedicated to assessing the human health risks of chemical, drugs, and physical agents. The new position is in line with the Institute's renewed interest in using environmental health sciences to understand human disease and improve human health, according to the NIEHS Director, Dr. David A. Schwartz.

"We are very excited that Dr. Portier will lead this important effort," said Dr. Schwartz. "Dr. Portier has done an extraordinary job in overseeing the activities of the National Toxicology Program, and has developed strong relationships with scientists all over the world. This new NIEHS leadership role will allow him an opportunity to merge the fields of toxicology and environmental health sciences and prepare the world for tomorrow's health challenges."

Dr. Portier has served in many prominent positions within NIEHS since his arrival as a postdoctoral student in 1981. Most recently he has served as the Associate Director of the National Toxicology Program, the Director of the Environmental Toxicology Program, and the Head, Environmental Systems Biology, Laboratory of Molecular Toxicology at the NIEHS.

It was in 2001 when he was appointed to the prestigious position of the Associate Director of the National Toxicology Program (NTP). The NTP is an interagency program whose mission is to coordinate, conduct, and communicate toxicological research across the U.S. government. The NTP is administratively housed at the NIEHS.

The culmination of Dr. Portier's efforts at the NTP is exemplified by his role in developing the landmark document *"A National Toxicology Program for the 21st Century: A Roadmap for the Future,*" which was released in 2005 as part of the NTP 25th Anniversary Celebration in Washington, D.C. The NTP Roadmap outlines a framework by which the NTP will modify, adapt, and improve its programs to better address its mandate in providing scientific information for protection of public health.

"The NIEHS remains fully committed to promoting the goals set forth in the NTP Roadmap," said Dr. Schwartz. "The NTP has an extremely talented and dedicated staff that will keep the important work that the NTP does going strong."

Some of the many other accomplishments achieved by Dr. Portier while at the NTP include developing the first ever evaluation guideline for non-cancer endpoints as part of the NTP's Center for the Evaluation of Risks to Human Reproduction. The NTP has also played a lead role in developing a High Throughput Screening Initiative, which will enable large numbers of environmental substances to be screened for potential health hazards. Dr. Portier has authored more than 150 peer-reviewed publications; 50 book chapters, reports and agency publications in statistics, risk assessment and cancer research.

"Closely linking risk assessment processes to NIEHS research will improve the Nation's ability to make informed public health decisions," said Dr. Portier. "We will be better poised to answer the basic questions inherent to risk assessment, including: Is it possible that this substance poses a hazard to humans? If yes, how much is dangerous? Are humans exposed to this substance and in what ways? Given human exposures and knowing how much is dangerous, what levels would be safe? These are exciting times in health research and being able to focus on bringing cutting edge research into the risk assessment arena will be a challenging new role for me at NIEHS."

Allen Dearry Ph.D., who most recently served as the Director of the Institute's Division of Research, Coordination, Planning and Translation, will act as the Interim Associate Director of the NTP. Dr. Dearry will work closely with other leaders in the NTP during this time of transition. Dr. Dearry served in a variety of high profile science positions while at NIEHS, including the Chief of the Chemical Exposure and Molecular Biology Branch, within the Division of Extramural Research and Training. A national search for a permanent NTP Associate Director will begin in the next three to six months.

Press release January 10, 2006

New NIEHS Website: Genetic Alterations in Cancer (GAC)

The new NIEHS GAC knowledge system is now available on the web (*https://dir-apps.niehs.nih.gov/gac/*). The GAC knowledge system is a comprehensive collection of data compiled from studies on genetic alterations in tumors associated with exposure to specific chemical, physical, or biological agents that can be linked to genes implicated in carcinogenesis. The GAC knowledge system provides access to the results from hundreds of studies of gene mutations, loss of heterozygosity, and/or homozygous deletions in tumors from humans and rodents. The data in the GAC are extracted from studies published in the publicly available, peer-reviewed literature. The knowledge system organizes the data by species, target organ, tumor type and origin, and agent of concern. Data mining features for querying the database summarize results in data tables and graphic profiles. Corresponding reference lists link the publications to their PubMed abstracts.

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The NTP and High Throughput Screening (HTS)

In August 2005, the NIEHS/NTP became a formal participant in the NIH Molecular Libraries Initiative (MLI). The MLI – a part of the NIH Roadmap for Medical Research – is focusing on the use of high-tech screening methods to identify small molecules that can be optimized as chemical probes to study the functions of genes, cells, and biochemical pathways. It is envisioned that these probes will lead to new ways to explore the functions of genes and cell signaling and help scientists learn about key biological processes involved in human health and disease.

This collaborative effort with the NTP and MLI is aimed at assisting the MLI project leaders with development of their screening program by adding a toxicity testing capability to the MLI effort. In addition, this collaboration will allow rapid implementation of the NTP's own HTS initiative, part of the NTP Roadmap for the 21st Century (*http://ntp.niehs.nih.gov/* see "NTP Vision and Roadmap"), by providing the NTP access to established testing laboratories through inter-institute cooperation.

The NTP, through its association with the MLI, has the opportunity to generate information that links data on the biological activity of environment substances generated from HTS assays with toxicity endpoints identified in the NTP's toxicology testing program. The NTP can then use this information to identify mechanisms of action for further investigation, develop predictive models for biological response, and help prioritize substances for further toxicological evaluation.

The NTP hopes to use this technology in the future to screen large numbers of environmental substances as part of its testing program. Through its interaction with the NTP, the MLI components – the National Chemical Genome Center (NCGC) and other Molecular Libraries Screening Center Network (MLSCN) laboratories – will obtain information on biological activity for a wide range of compounds for which their toxicity in laboratory animals and standard *in vitro* assays is known, and will be provided with additional assays to add to their screening battery.

To date, the NTP has provided 1400 chemicals to the NCGC, as well as six HTS cell-based screening assays (three that measure steps integral to apoptosis, two that assess cytotoxicity, and one that measures cell membrane P-glycoprotein activity) and is working to identify other commercially available HTS assays that the NCGC can adapt to its robotics-based systems. Eventually, the chemicals will be distributed to each of the MLSCN laboratories for screening. Data collected on these chemicals from the HTS assays will be maintained in a mutually accessible database for future analysis. To help guide this process, the NTP sponsored the High Throughput Screening Assays Workshop in December to discuss the usefulness of this technology for the NTP and toxicology.

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Upcoming Events

March 15, 2006	Nanotechnology Working Group (NWG) meeting, Holiday Inn Rosslyn at Key Bridge, 1900 N. Fort Myer Dr., Arlington, VA 22209
March 15-17, 2006	CERHR Expert Panel Meeting on Genistein and Soy Formula, Radisson Hotel Old Town, Alexandria, VA 22314
May 22-24, 2006	NTP Workshop: "Hormonally Induced Reproductive Tumors: Relevance of Rodent Bioassays," Marriott Raleigh Crabtree Valley, 4500 Marriott Dr., Raleigh, NC 27612
June 12, 2006	NTP Board of Scientific Counselors Technical Reports Review Subcommittee meeting; NIEHS, 111 TW Alexander Dr., Research Triangle Park, NC 27709

NTP Workshop Scheduled for May 2006

The workshop, "Hormonally Induced Reproductive Tumors: Relevance of Rodent Bioassays," is scheduled for May 22-24, 2006, at the Marriott Raleigh Crabtree Valley, 4500 Marriott Drive, Raleigh, NC 27612. The workshop's goal is to determine the adequacy and relevance to human disease outcome of rodent models for four types of hormonally induced reproductive tumors: ovary, mammary gland, prostate and testis.

The format includes both plenary talks and four breakout groups. Topics for discussion include:

- Dose-response for tumor induction
- Predictiveness of rodent pre-neoplastic events for humans
- Importance of the inclusion of an *in utero* exposure in the etiology of specific tumors
- The concept of "additivity to background" when normal hormones are present with homeostatic control mechanisms

This meeting is open to the public, but registration is limited to 100 people. Time will be set-aside during the plenary session on the first day for public comment. Information about the workshop and on-line registration is available from the NTP website (*http://ntp.niehs.nih.gov/* select "Meetings and Workshops").

Contact Information: Dr. Paul M. Foster, Toxicology Operations Branch, NIH/NIEHS, P.O. Box 12233, MD EC-34, Research Triangle Park, North Carolina 27709; T: (919) 541-2513; FAX: (919) 541-4255; foster2@niehs.nih.gov

NTP Board of Scientific Counselors Nanotechnology Working Group (NWG) to Meet

The NWG will meet on March 15, 2006, at the Holiday Inn Rosslyn at Key Bridge, 1900 N. Fort Myer Drive, Arlington, VA 22209. The NWG was established in 2005 to provide a structured and formal mechanism for bringing stakeholders together to (1) learn about NTP nanotechnology research related to public health, (2) address issues related to that research, and (3) promote dissemination of those discussions to other federal agencies, nanotechnology stakeholders, and the public. The meeting was announced in the Federal Register (70FR74832) and is open to the public. The NTP invites the public to provide comment, both written and oral, on any agenda topic. On-line registration and additional information about the NWG, including charge, roster, and meeting information is available on the NTP website (*http://ntp.niehs.nih.gov/* select "Advisory Board & Committees") or can be obtained by contacting Dr. Kristina Thayer.

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 at Annual Society of Toxicology Meeting

Be sure and stop by the NTP booth (337/339) at the 45th Annual SOT Meeting and ToxExpo at the San Diego Convention Center during the week of March 5-9, 2006. The NTP will post a list of its presentations and posters on its website prior to the meeting. Also plan to visit the booths for the EHP (336/338) and the NIEHS (335) as you tour the ToxExpo.

Technical Reports Review Subcommittee Meetings

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee is tentatively scheduled to meet on June 12, 2006, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC to peer review the findings and conclusions from the following draft NTP Technical Reports:

alpha-Methylstyrene	Genistein (2-year study)
Methylene Blue Trihydrate	Genistein (multigeneration)

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

The Technical Reports Review Subcommittee is also tentatively scheduled to meet on August 28 to review draft NTP Technical Reports for studies conducted in genetically modified mouse models on the following substances: allyl bromide, benzene, phenolphthalein dicyclohexylcarbodiimide, glycidol, and. Details will be announced in a future Federal Register notice.

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

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

Expert Panel Report on DEHP Available

CERHR held an expert panel meeting on di(2-ethylhexyl)phthalate (DEHP) on October 10–12, 2005. The purpose of this meeting was to update information, conclusions, and data needs on human exposure, reproductive toxicity, and developmental toxicity of DEHP. The panel reviewed and evaluated the scientific evidence in over 150 publications on DEHP published since the first panel evaluation. The CERHR phthalates expert panel previously evaluated DEHP and completed its report in October 2000.

The CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of DEHP is available for public comment in electronic (PDF) format on the CERHR website (*http://cerhr.niehs.nih.gov*) and in hardcopy or on CD-ROM from CERHR (contact information below). The public comment period on this report is from November 21, 2005 to February 3, 2006 (extended from January 4, 2006). Public comments will be reviewed by NTP, posted on the CERHR website, and published in the NTP-CERHR monograph on DEHP.

Expert Panel Meeting on Genistein and Soy Formula Scheduled

An expert panel meeting on genistein and soy formula is scheduled for March 15-17, 2006, at the Radisson Hotel Old Town in Alexandria, VA. The draft expert panel reports on genistein and soy formula will be available on January 16, 2006 from the CERHR website or in hardcopy from CERHR and open for public comment. Details about the meeting were announced recently in the Federal Register (70FR74834) and are posted on the CERHR website.

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

Second Expert Panel Report on the Evaluation of the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants

The second report, "The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Expert Panel Evaluation of the Draft Background Review Document Addendum for *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants" is now available on the NICEATM website (*http://iccvam.niehs.nih.gov*) or in hardcopy by contacting NICEATM (contact information below).

This report is a follow-up to a report released in March 2005 that presented findings of an expert panel meeting convened on January 11-12, 2005 to assess the validation status of four test methods: Bovine Corneal Opacity and Permeability (BCOP), Hen's Egg Test - Chorioallantoic Membrane (HET-CAM), Isolated Chicken Eye (ICE), and Isolated Rabbit Eye (IRE). The expert panel report from the January 2005 meeting is available at *http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*. A second expert panel meeting was held on September 19, 2005, because public comments at the January 2005 meeting indicated that additional data could be made available that had not been provided in response to earlier requests for data. Subsequently, NICEATM received additional data and conducted a reanalysis of the accuracy and reliability of each test method that included these new data. The expert panel considered this reanalysis at the September meeting.

ICCVAM will consider the first and second expert panel reports, other relevant background materials, and all comments received from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) in finalizing ICCVAM test method recommendations for these methods. Once finalized, the test method recommendations will be forwarded to appropriate federal agencies for their consideration.

Peer Panel Evaluation of *In Vitro* Testing Methods for Estimating Acute Oral Systemic Toxicity

In collaboration with the European Centre for the Validation of Alternative Methods (ECVAM), NICEATM conducted a multi-laboratory international study to evaluate the usefulness of cytotoxicity data from the BALB/c 3T3 and the Normal Human Keratinocyte (NHK) Neutral Red Uptake (NRU) cytotoxicity assays for estimating the acute oral toxicity potential of test substances. NICEATM is currently finalizing a draft background review document (BRD) describing the background, methods, and results of this validation study. The draft BRD will be made available to the public in early 2006, along with the draft ICCVAM recommendations on the validation status of these test methods and proposed standardized test method protocols. ICCVAM and NICEATM intend to convene a peer review panel to evaluate the validation status of these *in vitro* cytotoxicity assays on May 23, 2006, in Bethesda, MD. The panel will (1) peer review the BRDs for the test methods, and (2) determine whether the data cited in the BRDs support the draft ICCVAM test method

recommendations regarding the proposed usefulness, limitations, and validation status of the test methods. ICCVAM will consider the panel's conclusions and recommendations during its development of recommendations for these test methods. More information about the panel meeting will be provided in a future *Federal Register* notice.

Pyrogenicity Test Methods
In June 2005, ECVAM submitted five *in vitro* human blood cell pyrogenicity tests to the ICCVAM for consideration. These tests are being proposed as replacements for the currently required *in vivo* rabbit test or an *in vitro* test that uses hemolymph collected from the Limulus horseshoe crab [Limulus amoebocyte lysate (LAL) test, also referred to as the bacterial endotoxin test (BET)].

The five *in vitro* pyrogenicity test methods are identified as follows:

- PBMC/IL-6 (the human PBMC/IL-6 *in vitro* pyrogen test)
- WB/IL-1 (the human whole blood/IL-1 *in vitro* pyrogen test)
- cryo WB/IL-1 (the human whole blood/IL-1 *in vitro* pyrogen test: application of cryopreserved human whole blood)
- WB/IL-6 (the human whole blood/IL-6 *in vitro* pyrogen test)
- MM6/IL6 (an alternative *in vitro* pyrogen test using the human monocytoid cell line MONO MAC-6 [MM6])

It is anticipated that a peer review of these methods will take place in 2006.

Alternative Methods for Assessing Potency of Botulinum Toxin
On October 31, 2005, ICCVAM received a nomination from the Humane Society of the United States requesting that alternative test methods to the mouse LD_{50} assay for Botulinum toxin potency testing be assessed and prioritized for prevalidation and validation efforts. A proposed initial key step in this process would be for ICCVAM to organize a workshop coordinated with ECVAM and other appropriate stakeholders to secure the cooperation of individuals and organizations that possess relevant protocols and test data. ICCVAM and NICEATM are currently evaluating whether a workshop is the appropriate first step in addressing this nomination. If convened, a workshop is anticipated to take place in 2006.

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How to 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*.

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].

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.

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, NIH/NIEHS, P.O. Box 12233, MD A3-07, 111 TW Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-5710; FAX: (919) 541-3647; masten@niehs.nih.gov