



APRIL 2006

# UPDATE

National Toxicology Program

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

## Dr. Allen Dearry Assumes Post as Interim Associate Director of the NTP

Allen Dearry, Ph.D., who most recently served as the Director of the NIEHS Division of Research Coordination, Planning, and Translation, is acting as the Interim Associate Director of the NTP. Dr. Dearry assumed this post in January when Dr. Christopher Portier was appointed NIEHS Associate Director for Risk Assessment. Dr. Dearry received a Ph.D. in Anatomy from the University of Pennsylvania, was a postdoctoral fellow at UC Berkeley, and faculty member at Duke University before moving in 1990 to NIH, where he has held a number of research administration positions. Dr. Dearry has been honored to receive a number of NIEHS and NIH awards, as well as two DHHS Secretary's Awards for Distinguished Service for providing outstanding leadership on issues related to possible health effects of exposure to Pfiesteria toxins (1998) and for generating a public health and research response to the World Trade Center disaster (2002). Excited about serving in this key capacity, Dr. Dearry values the NTP's importance for public health and is committed to its mission. Specifically, Dr. Dearry is promoting the goals set forth in the NTP Roadmap and is working closely with NTP Director Dr. David Schwartz and other leaders in the NTP to carry out the roadmap's activities. "This is an exciting time for the NTP as we evaluate our current strategies for testing and explore new opportunities, such as high throughput screening through our collaboration with the NIH Molecular Libraries Initiative," said Dr. Dearry. (See January 2005 NTP Update.) We at the NTP welcome Dr. Dearry to his new post and look forward to a time of creativity and growth.

## NTP Receives Awards at Society of Toxicology (SOT) Annual Meeting in March

Public Health Service Captain William Stokes, Director of the NTP Interagency Center for the Evaluation of Alternative Toxicology Methods (NICEATM) at the NIEHS, was honored with the **Enhancement of Animal Welfare Award** for his contributions to the marked reduction in the use of experimental animals for research. At the NTP, Dr. Stokes is responsible for directing the scientific evaluation of new, revised, or alternative toxicological test methodologies for safety assessment that support improved protection of human health and improved animal welfare. In addition, Dr. Stokes is also Executive Director of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), a group representing 15 federal agencies that review test methods of interagency interest and coordinate related issues on validation, regulatory acceptance, and national and international harmonization. ICCVAM has evaluated and recommended several new test methods now adopted by U.S. and international regulatory authorities that have reduced the number of animals and the pain and distress involved in safety testing.

The Risk Assessment Specialty Section (RASS) selected the paper ***Dose-additive Carcinogenicity of a Defined Mixture of "Dioxin-like Compounds"*** as the winner of the *Best Paper Demonstrating the Application of Risk Assessment* for 2005. NIEHS co-authors are Drs. Nigel J. Walker, Patrick W. Crockett, Abraham Nyska, Amy E. Brix, M. P. Jokinen, D. M. Sells, J. R. Hailey, Michael Easterling, Joseph K. Haseman, Ming Yin, Michael E. Wyde, John R. Bucher, and Christopher J. Portier. Members of the group were honored at the RASS reception March 8 at the SOT meeting in San Diego. The paper published in *Environmental Health Perspectives* [113(1): 43-48] can be viewed at <http://www.ehponline.org/members/2004/7351/7351.html>.

Dr. Julia M. Gohlke, a postdoctoral fellow in the Environmental Toxicology Program at the NIEHS, won a Biological Modeling Special Section (BMSS) student poster award for her presentation ***Elucidation of a Gene Regulatory Network for Forebrain Development Using Bioinformatics Approaches for the Analysis of Compiled Microarray Datasets***. Other contributors to the paper are Dr. Frederick M. Parham, Jr., J. S. Parker, Michael V. Smith, and Dr. Christopher J. Portier. Dr. Gohlke was honored at the SOT BMSS reception on March 8.

## Satellite Symposium at the Annual Society of Toxicologic Pathology Meeting

The NTP will sponsor a pathology satellite symposium on June 17 in conjunction with the Society of Toxicologic Pathology (STP) meeting being held June 18-22, 2006, in Vancouver, British Columbia. This year's NTP satellite symposium will focus on the urinary system. Organized as an annual event for several years, this

interactive symposium serves to promote continuing education on interpreting pathology slides, as well as to generate lively and productive conversation. The symposium is free for meeting attendees, but due to space limitations, registration is required. To register on-line for the STP meeting or the NTP symposium visit the STP meeting website at <http://www.toxpath.org>

## 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 *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 are 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](mailto:foster2@niehs.nih.gov)

## NTP Board of Scientific Counselors Meeting

The NTP Board of Scientific Counselors (BSC) will meet on June 13, 2006, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC. Tentatively, on the agenda for discussion are a summary of the NIEHS' Strategic Plan, an update of NTP Roadmap activities, information about a new NTP program on host susceptibility, and two concept reviews for NTP research proposed through a contract mechanism. The NTP will also seek input from the BSC on testing recommendations for substances nominated to the NTP for study. Items for discussion may be added or modified as the agenda is finalized. Details about this

meeting, as available, will be announced in the *Federal Register* and posted on the NTP website (<http://ntp-server.niehs.nih.gov/>) 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 agenda topic.

**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](mailto:shane@niehs.nih.gov)

## Technical Reports Review Subcommittee Meeting

The NTP Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors is scheduled to convene two meetings during 2006. The first is scheduled for June 12, 2006, at the NIEHS, 111 T.W. Alexander Drive, Research Triangle Park, NC. The subcommittee will peer review the findings and conclusions from four draft NTP Technical Reports.

The draft reports tentatively scheduled for review are:

Genistein	Methylene blue trihydrate
Genistein (multigenerations)	alpha-Methylstyrene

The subcommittee is also scheduled to meet on August 28, 2006, at NIEHS, 111 T.W. Alexander Drive, RTP, NC to peer review the findings and conclusions from five draft NTP Technical Reports in which genetically modified mice strains were used.

The draft reports tentatively scheduled for review are:

Allyl bromide	Glycidol
Benzene	Phenolphthalein
Dicyclohexylcarbodiimide	

Details about these meetings will be announced 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, 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, 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 Meeting on Genistein and Soy Formula

CERHR held an expert panel meeting on genistein and soy formula on March 15-17, 2006, in Alexandria, VA. An independent panel of 14 scientists evaluated information on human exposure, reproductive toxicity, and developmental toxicity of genistein and soy formula.

A summary of the meeting with the expert panel's conclusions is now available on the CERHR website (<http://cerhr.niehs.nih.gov>), and the final expert panel reports on genistein and soy formula will be released for public comment in May 2006. The final reports will be available electronically on the CERHR website and in hardcopy or on CD from CERHR (contact information below). Public comments received on these reports will be posted on the CERHR website.

### Styrene Monograph Available

The NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Styrene is available on the CERHR website; hardcopies and CDs are also available from CERHR.

### Hydroxyurea and Bisphenol A Panels Planned

Separate expert panel meetings on hydroxyurea and bisphenol A are planned for fall 2006 and early 2007, respectively. Draft expert panel reports, information about submitting public comments, and details about the meetings will be announced later this year.

*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*

### Upcoming Events

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
June 13, 2006	NTP Board of Scientific Counselors Meeting; NIEHS, 111 TW Alexander Dr., Research Triangle Park, NC 27709
June 17, 2006	NTP-sponsored Satellite Symposium on the Urinary System in conjunction with the Society of Toxicologic Pathology Meeting, June 18-22, 2006, Vancouver, BC.
August 28, 2006	NTP Board of Scientific Counselors Technical Reports Review Subcommittee Meeting, NIEHS, 111 TW Alexander Dr., Research Triangle Park, NC 27709
September 20-21, 2006	NTP Workshop: "Biomarkers for Toxicology Studies," NIEHS, 111 TW Alexander Dr., Research Triangle Park, Research Triangle Park, NC 27709

## 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 process are available on the NTP website (<http://ntp.niehs.nih.gov> select *Nominations to the Testing Program under 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.

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.

### Study Nominations Currently in Review

A *Federal Register* notice published on April 11, 2006 (71FR18341) formally solicits comment on the 10 new nominations and corresponding study recommendations listed below [available on the NTP website at <http://ntp.niehs.nih.gov/go/21134>]. The NTP Board of Scientific Counselors meeting will review these nominations at its June 13, 2006. The NTP website also provides access to electronic versions of supporting documents for each nomination and further 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 website as they are received and distributed to the NTP Board and NTP staff.

Arbutin: Recommended studies - *In vitro* and *in vivo* metabolism and disposition studies; *in vitro* and *in vivo* genotoxicity studies; emphasis on understanding gastrointestinal metabolism and disposition, identifying experimental animal model representative of humans, and development of appropriate biomarkers

tert-Butylacrylamide: Recommended studies - Metabolism and disposition studies; subchronic toxicity studies; mammalian genotoxicity studies; coordinate with voluntary data development activities of the Extended HPV Program

Ceric Oxide: Recommended studies - Toxicological characterization including chemical disposition and toxicokinetics; comparative inhalation toxicity studies of microscale and nanoscale forms; dermal penetration studies

Diazonaphthoquinone derivatives [Sodium 1,2-naphthoquinone-2-diazide-5-sulfonate; 2,3,4-Trihydroxybenzophenone tris(1,2-naphthoquinonediazide-5-sulfonate); 2,3,4-Trihydroxybenzophenone 1,2-naphthoquinonediazide-5-sulfonate]: Recommended studies

*In vitro* toxicity studies evaluating genotoxicity, immunotoxicity and phototoxicity; dermal penetration studies

3-Dimethylaminopropyl methacrylamide: Recommended studies - Metabolism and disposition studies; genotoxicity studies; subchronic toxicity studies; coordinate with voluntary data development activities through the Extended HPV (EHPV) Program

#### Flame Retardants:

Antimony trioxide: Recommended studies - Chronic toxicity studies (oral route); consider studies of nanoscale form if used in or released during flame retardant applications

Decabromodiphenyl oxide: Recommended studies - Developmental neurotoxicity studies; studies only to be performed if adequate private sector study not identified or planned

Tris(chloropropyl)phosphate, mixture of four isomers: Recommended studies - Subchronic and chronic toxicity studies (oral route); studies to focus on commercial mixture or major isomers present in commercially used mixtures

Phosphonic acid, (3-((hydroxymethyl)amino)-3-oxopropyl)-dimethyl ester: Recommended studies - Subchronic and chronic toxicity studies (oral route); dermal absorption studies

Tris(hydroxymethyl)phosphine oxide: Recommended studies - Subchronic and chronic toxicity studies (oral route); dermal absorption studies

Aromatic Phosphates [tert-Butylphenyl diphenyl phosphate; 2-Ethylhexyl diphenyl phosphate; Isodecyl diphenyl phosphate; Phenol, isopropylated, phosphate (3:1); Tricresyl phosphate; Triphenyl phosphate]: Recommended studies - For one or more representative aromatic phosphates, subchronic and chronic toxicity studies (oral route); neurotoxicity and/or developmental neurotoxicity studies; coordinate with U.S. EPA to pursue additional testing by manufacturers

Gypsum, natural and synthetic forms: Recommended studies - Short-term pulmonary toxicity studies; comparative studies of intratracheal vs. inhalation routes of administration; studies are of relatively low priority given low suspicion of toxicity

N-methyl-3-oxobutanamide: Recommended studies - *In vitro* and *in vivo* genotoxicity studies; include structurally-related diketene compounds and N-phenyl derivative

Phenoxethyl acrylate: Defer study pending voluntary data submission through the Extended HPV Program

Trifluoromethylbenzene: Defer study pending review of (1) production data through the 2006 Toxic Substances Control Act Inventory Update Rule, and (2) Organization for Economic Cooperation and Development Screening Information Data Sets program output

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; [masten@niehs.nih.gov](mailto:masten@niehs.nih.gov)

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

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

NICEATM will convene an independent, scientific panel to evaluate the validation status of the *in vitro* 3T3 and normal human keratinocyte (NHK) neutral red uptake (NRU) basal cytotoxicity test methods for estimating starting doses for *in vivo* acute oral toxicity tests. The meeting will be held on May 23, 2006, at the NIH Natcher Conference Center, 45 Center Drive, Bethesda, MD 20892, and begins at 8:30 a.m. It is open to the public with attendance limited only by the space available. In order to facilitate planning for this meeting, persons wishing to attend the meeting are asked to register by May 12, 2006, on the ICCVAM/NICEATM website (<http://iccvam.niehs.nih.gov>).

The *in vitro* cytotoxicity test methods NHK and NRU are proposed as adjuncts to the *in vivo* acute oral toxicity tests to refine (i.e., to lessen or avoid pain and distress) and/or reduce animal use. At this meeting, the panel will (1) peer review the background review document (BRD) on the 3T3 and NHK cytotoxicity test methods, (2) evaluate the extent that the BRD addresses established validation and acceptance criteria, and (3) provide comment on the draft ICCVAM recommendations on the proposed use of these test methods, draft test method protocols, and draft performance standards. NICEATM invites public comments on the BRD, draft ICCVAM test method recommendations, draft test method protocols, and draft performance standards. Comments should be sent to Dr. William Stokes, NICEATM Director, by May 5, 2006 (contact information below). Additional details about the meeting are available on the ICCVAM/NICEATM website and were published in the *Federal Register* (71FR14229).

### Revised List of Recommended Reference Substances for Validation of *In Vitro* Estrogen and Androgen Receptor Binding and Transcriptional Activation Assays

In a recently released *Federal Register* notice (71FR13597), NICEATM announced the availability of an addendum to the report entitled, "Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Evaluation of *In Vitro* Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays" [NIH Publication 03-4503]. The addendum describes the rationale for proposed revisions to the original list of recommended reference substances for validation of *in vitro* estrogen receptor (ER) and androgen receptor (AR) binding and transcriptional activation (TA) assays. The original list was made publicly available in the *Federal Register* in June 2003 (68FR33171). NICEATM requests public comments on the substances proposed as substitutes for 6 of the 78 substances in the original list. Data are also requested from *in vitro* and *in vivo* studies evaluating the estrogenic and androgenic activity of the 78 substances in the revised list of reference substances. Comments and data should be sent to Dr. Stokes by May 1, 2006; visit the ICCVAM/NICEATM website for more details.

*Contact Information:* Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS 79 TW Alexander Drive, P.O. Box 12233, EC-17, Research Triangle Park, NC 27709; T: (919) 541-2384; FAX: (919) 541-0947; [iccvam@niehs.nih.gov](mailto:iccvam@niehs.nih.gov)

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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](mailto: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](mailto: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](mailto:cdm@niehs.nih.gov) or (919) 541-3419].