UPDATE National Toxicology Program
Headquartered at the National Institute of Environmental Health Sciences NIH-DHHS
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NTP to Celebrate Its History and Present Roadmap for the 21st Century

Plans are underway for a symposium, *The NTP: A Quarter Century of Toxicology for Public Health,* at the National Academy of Sciences, 2100 C Street, NW in Washington, DC on May 10-11, 2005. Talks will reflect on the continually evolving field of toxicology, the contributions and leadership the NTP has provided to the field, and equally important, the challenges and directions the program will face in the future. The NTP will use this forum to unveil its roadmap for the future. Details about the meeting, including agenda and registration form, are posted on the NTP website (http://ntp.niehs.nih.gov) or by contacting Nan Cushing (919-541-0530 or cushing1@niehs.nih.gov) in the NTP Liaison and Scientific Review Office.

In August 2003, the NTP defined its vision for the 21st century and spent more than a year refining it and gaining input from leading researchers from the public and private sectors on a framework for its implementation ("the NTP Roadmap") (see *NTP Updates* January and October 2004).

The NTP Roadmap addresses the directions envisioned for the NTP in the 21st century in three main areas: (1) refining traditional toxicology assays, (2) developing rapid, mechanism-based predictive screens for environmentally induced diseases, and (3) improving the overall utility of NTP products for public health decisions. The NTP Roadmap is available on the NTP website at http://ntp.niehs.nih.gov select *NTP Vision and Roadmap*) or in printed text from the NTP Liaison and Scientific Review Office (liaison@starbase.niehs.nih.gov or 919-541-0530).

NIEHS/NTP Staff Wins Award for Best Paper at Society of Toxicology's Annual Meeting

Staff from the National Institute of Environmental Health Sciences (NIEHS) received *Best Paper* awards at the Annual Meeting of the Society of Toxicology (SOT) in New Orleans in March.

The paper, "Gene Interaction Network Suggests Dioxin Induces a Significant Linkage between Aryl Hydrocarbon Receptor and Retinoic Acid Receptor Beta," was chosen the *Best Paper Advancing the Science of Risk Assessment for 2005* by the Risk Assessment Specialty Section of SOT. The article is published in *Environmental Health Perspectives* [112(2):1217-24, 2004]. The authors on the paper are: Hiroyoshi Toyoshiba, Takeharu Yamanaka, Hideko Sone, Frederick M. Parham, Nigel J. Walker, Jeanelle Martinez, and Christopher J. Portier.

Paul Foster, who joined the NIEHS from CIIT Centers for Health Research, was also honored for his paper selected as *Best Paper* from the Reproductive and Developmental Toxicology Specialty Section of SOT. The paper, "Dose-Dependent Alterations in Gene Expression and Testosterone Synthesis in the Fetal Testes of Male Rats Exposed to Di (n-butyl) phthalate," appears in *Toxicological Sciences* (81:60-68, 2004). The authors on the paper are: Kim Lehmann, Suzanne Phillips, Madhabananda Sar, Foster and Kevin Gaido.

Cancer and the Environment Wins Plain Language Award

Drs. Ronald Melnick and George Lucier (retired) of the NIEHS were part of a team that authored the booklet, *Cancer and the Environment: What You Need to Know, What You Can Do*. Prepared as a joint effort by the National Cancer Institute (NCI) and the NIEHS and released in 2003, the authors dedicated the booklet's publication to Susan Sieber Fabro (1942-2002), a NCI scientist who provided the leadership to make the booklet a reality. The booklet is available in electronic format on the NTP website (http://ntp.niehs.nih.gov select *Publications, Technical Reports and Abstracts*). The recipients will be honored at a ceremony at 2 p.m. on Wednesday, April 27, 2005, at the Lipsett Auditorium in the Clinical Center at the National Institutes of Health.

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

The NTP has developed and refined a vision for toxicology in the 21st century ("NTP Vision") and a roadmap for implementing that vision ("NTP Roadmap", see page 1 this issue) to strategically position the program at the forefront for providing scientific data and the interpretation of those data for public health decision-making. As part of the NTP Roadmap, the program will convene a series of public workshops beginning with *Animal Models for the NTP Rodent Cancer Bioassay: Strains & Stocks - Should We Switch?* to review aspects of the existing testing program.

The workshop will be held June 16-17, 2005, at the NIEHS in Research Triangle Park, NC. Its goal is to seek scientific input as to whether the NTP should continue to use both the F344 rat and B6C3F1 mouse models in the cancer bioassay, use other strains, and/or use multiple strains. The NTP invites public comments on the appropriateness of the F344N and B6C3F1 models currently used and the submission of historical control data for rodent models that the NTP might consider at the workshop.

A copy of the agenda and any additional information on the workshop, including participants and background materials, will be posted on the NTP website when available (http://ntp.niehs.nih.gov select *Meetings and Workshops*).

The workshop will begin at 8:30 a.m. each day and end at 5 p.m. on June 16 and approximately 12 p.m. on June 17. It is open to the public with attendance limited only by space available. **Please note that a photo ID is required to access the NIEHS campus**. Individuals who plan to attend are asked to register with Dr. Angela King-Herbert (contact information below).

Future workshops will address other study design issues such as diet, length of study, and age at exposure. The overall purpose of the workshop series is to improve the ability of NTP bioassays to identify substances that may pose a carcinogenic or other health hazard for humans.

Contact Information: Dr. Angela King-Herbert, NIH/NIEHS, P.O. Box 12233, MD B3-06, Research Triangle Park, North Carolina 27709; T: (919) 541-3464; FAX: (919) 541-7666; kingher1@niehs.nih.gov

NTP Board of Scientific Counselors Meeting

The NTP Board of Scientific Counselors will meet on June 23-24, 2005, in the Rodbell Auditorium in the Rall Building at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC.

Tentatively, on the agenda for discussion are reports on NTP initiatives to enhance toxicology and on a workshop relating to this initiative. Recent activities of the NTP Technical Reports Review Subcommittee and the Center for the Evaluation of Risks to Human Reproduction will be presented. The Board will hear about the Interagency Committee for Chemical Evaluation and Coordination's recommendations for nominations to the NTP for testing. Additional items will be added as the agenda is finalized.

Details 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. 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, Executive Secretary, 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

How to Subscribe to the NTP List-serv

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

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

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].

Upcoming Events

May 10-11, 2005	The National Toxicology Program: A Quarter Century of Toxicology for Public Health, National Academy of Sciences, 2100 C Street, Washington, DC 20001
May 11-12, 2005	*Mechanisms of Chemically Induced Ocular Injury and Recovery,* Natcher Conference Center, 45 Center Drive, NIH, Bethesda, MD.
May 13, 2005	*Minimizing Pain and Distress in Ocular Toxicity Testing*, Natcher Conference Center, 45 Center Drive, NIH, Bethesda, MD
June 1–3, 2005	CERHR Expert Panel Meeting on Styrene, Holiday Inn Select Old Town Alexandria, Alexandria, VA
June 16-17,2005	NTP Workshop *Animal Models for the NTP Rodent Cancer Bioassay: Strains & Stocks–Should We Switch?*" NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC
June 23-24, 2005	NTP Board of Scientific Counselors Meeting, NIEHS, Research Triangle Park, NC
Sept. 27-28, 2005	NTP Technical Reports Review Subcommittee Meeting, NIEHS, Research Triangle Park, NC, Research Triangle Park, NC

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

The SACATM meeting tentatively scheduled for May 24 in Bethesda, Maryland is cancelled and will be rescheduled for late fall 2005. As information about the meeting is available, it will be posted on the NTP website (http//:ntp.niehs.nih.gov select *Advisory Board and Committees*) and announced in the Federal Register and *NTP Update*. Questions can be directed to Dr. Kristina Thayer, Executive Secretary.

Contact Information: Dr. Kristina Thayer, Executive Secretary, 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 Technical Reports Review Subcommittee Meeting

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

These draft reports are tentatively scheduled for review:

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

Details 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. This meeting is 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, North Carolina 27709; T: (919) 541-4253; FAX: (919) 541-0295; shane@niehs.nih.gov

Invites Nomination to Testing Program

The NTP has a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern. The NTP accepts nominations for new toxicological studies, for specific studies, or for general issues related to potential health hazards of occupational and environmental exposures at any time from any one such as labor unions, academic scientists, federal and state agencies, industry, and the general public.

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 the heading *Research*) or by

contacting Dr. Scott Masten in 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, herbal dietary supplements, radio-frequency radiation emissions from cellular telephones, photoactive chemicals, brominated flame retardants, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-disrupting substances, and methods for assessing potential cardiac toxicity.

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

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

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

Acrylamide Monograph

The NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide is now available electronically on the CERHR website http://cerhr.niehs.nih.gov; hardcopies and CDs are also available from CERHR (see contact information below).

Expert Panel Reports on Amphetamines and Methylphenidate

CERHR held an expert panel meeting on amphetamines and methylphenidate on January 10–12, 2005, at the Holiday Inn Select Old Town Alexandria in Alexandria, VA. The final expert panel report for each chemical is available for public comment on March 21, 2005, and the period for public comment closes May 5, 2005. These two reports are available electronically on the CERHR website or in hardcopy or on CD from CERHR. Public comments received on these reports will be posted on the CERHR website.

Styrene

An expert panel evaluation of styrene is planned for June 1–3, 2005, at the Holiday Inn Select Old Town Alexandria in Alexandria, VA. Details were published in the Federal Register on March 9 (70FR11680). The draft expert panel report on styrene is available electronically on the CERHR website or in hardcopy or on CD from CERHR. The period for public comment on this draft report closes May 2, 2005. Time is set-aside at the expert panel meeting on June 1, 2005, for oral public comments. Individuals wishing to make oral public comments are asked to contact Dr. Michael D. Shelby (see contact information below).

DEHP

In a Federal Register (70FR6024) published February 4, 2005, CERHR announced plans to convene an expert panel to update its evaluation of di(2-ethylhexyl)phthalate (DEHP). The notice solicited public comments, data, and nominations of scientists to serve on the expert panel. The expert panel meeting is anticipated to take place in the fall of 2005.

Contact Information: *Dr. Michael D. Shelby, Director CERHR, NIH/NIEHS, 79 TW Alexander Drive, Bldg. 4401, Room 103, PO 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)

Ocular Toxicity Scientific Symposia

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in collaboration with the European Center for the Validation of Alternative Methods (ECVAM) will sponsor two ocular toxicity symposia: *Mechanisms of Chemically Induced Ocular Injury and Recovery* (May 11-12, 2005) and *Minimizing Pain and Distress in Ocular Toxicity Testing* (May 13, 2005), at the Natcher Conference Center, National Institutes of Health, Bethesda, MD.

The symposia's main goal is to review the state-of-the-science and the pathophysiology and mechanisms of chemically induced ocular injury and recovery (reversibility versus irreversibility) in order to advance the development of test systems to meet regulatory testing requirements. These requirements provide for protection of human health while reducing, refining (less pain and distress), and/or replacing the use of animals. Other goals are to: (1) review the current understanding of the sources and mechanisms of pain and distress in ocular toxicity testing; (2) identify current best practices for preventing, recognizing and alleviating ocular pain and distress; and (3) identify additional research, development, and validation studies necessary to support scientifically valid ocular testing procedures that avoid pain and distress. Additional information about

these symposia can be found on the NICEATM/ICCVAM website (http://iccvam.niehs.nih.gov).

2nd Request for Data on Chemicals Evaluated by *In Vitro* or *In Vivo* Ocular Irritancy Test Methods

ICCVAM and NICEATM are collaborating with the ECVAM to evaluate the validation status of *in vitro* methods for assessing ocular irritation/corrosion. Data were previously requested (69FR15859, available at http://iccvam.niehs.nih.gov/) and used to prepare draft Background Review Documents (BRD) for four methods [(1) The Bovine Corneal Opacity and Permeability (BCOP) test; (2) the Isolated Rabbit Eye (IRE) test or the Rabbit Enucleated Eye Test (REET); (3) the Isolated Chicken Eye (ICE) test or the Chicken Enucleated Eye Test (CEET); and (4) the Hen's Egg Test--Chorion Allantoic Membrane (HET-CAM)], and to compile a database of *in vivo* data. ICCVAM and NICEATM are now finalizing these BRDs and want to ensure the inclusion of all available data. NICEATM is issuing this second request for data generated using standardized *in vitro* and *in vivo* test methods for identifying severe, moderate, mild, or non-irritating substances. In addition, NICEATM requests high quality data from standardized ocular irritancy test methods using rabbits and *in vivo* data generated from procedures/protocols that might alleviate or reduce pain and suffering (e.g., topical and systemic analgesic). These data will be used to evaluate the validation status of existing *in vitro* test methods for ocular irritancy/corrosion and to develop a list of substances with high quality *in vivo* data that can be considered as reference chemicals for future validation studies. Data from other *in vitro* methods used to assess reversible ocular irritation effects or non-irritation are also requested.

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

NICEATM in collaboration with ICCVAM is planning to convene an independent peer review panel to evaluate the validation status of *in vitro* cytotoxicity assays for estimating *in vivo* acute oral toxicity. The panel will evaluate the usefulness, limitations, accuracy, and reliability of these test methods for their intended purpose. NICEATM requests nominations of scientists for consideration as potential panel members. Conclusions and recommendations from the panel will be considered by ICCVAM in the development of test method recommendations and performance standards for these test methods. Data from standard *in vivo* acute oral toxicity testing and *in vitro* cytotoxicity testing are also requested.

Non-Animal Methods and Approaches for Determining the Skin and Eye Irritation Potential of Antimicrobial Cleaning Product Formulations

ICCVAM and NICEATM request the submission of data that would assist in the evaluation of the validation status of non-animal methods and approaches for determining the potential for skin and eye irritation from exposure to antimicrobial cleaning product formulations. Additionally, NICEATM also requests nominations of expert scientists for consideration as potential members of an independent scientific expert panel to evaluate proposed methods and approaches. ICCVAM will consider the conclusions and recommendations from the expert panel in developing recommendations on the validation status of these methods for their intended use.

Contact Information: Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS, 79 TW Alexander Drive, Bldg. 4401, PO Box 12233, Research Triangle Park, NC; T: (919) 541-2384; FAX: (919) 541-0947; iccvam@niehs.nih.gov

Report on Carcinogens

The Department of Health and Human Services released the Report on Carcinogens Eleventh Edition (11th RoC) on January 31, 2005, adding 17 substances to the growing list of cancer-causing agents and bringing the total to 246. For the first time ever, viruses are listed in the report: hepatitis B virus, hepatitis C virus, and some human papillomaviruses that cause common sexually transmitted diseases. Other new listings include lead and lead compounds, X-rays, compounds found in grilled meats, and a host of substances used in textile dyes, paints and inks. The full report is available the NTP website (http://ntp.niehs.nih.gov select *Report on Carcinogens*).

Prepared by the NTP, the RoC is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data on (1) the carcinogenicity, genotoxicity, and biologic mechanisms of the listings in humans and/or animals; (2) the potential for exposure to them, and (3) the regulations promulgated by federal agencies to limit exposures.

The 11th RoC lists cancer-causing agents in two categories -- "known to be human carcinogens" and "reasonably anticipated to be human carcinogens." The report now contains 58 "known" and 188 "reasonably anticipated" listings. Federal law requires the Secretary of the Department of Health and Human Services to publish the report every two years.

New Listings to the 11th RoC

Substances added to the "known" category:
Hepatitis B virus and hepatitis C virus
Human papillomaviruses
X-radiation and gamma-radiation
Neutrons

Substances added to the "reasonably anticipated" category:
1-Amino-2,4-dibromoanthraquinone
Cobalt sulfate
Diazoaminobenzene
MeIQ, MeIQx, and PhIP
- MeIQ is 2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline
- MeIQx is 2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline
- PhIP is 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

Lead and lead compounds
Naphthalene
Nitrobenzene
Nitromethane
4,4'-Thiodianiline

NTP Requests Nominations to the RoC

The NTP solicits and encourages the broadest participation from interested individuals or parties in nominating agents, substances, mixtures, or exposure circumstances for listing in or delisting from the RoC. Nominations should contain a rationale for the listing or delisting and appropriate supporting background information and relevant data when available (e.g., journal articles, NTP Technical Reports, IARC listings, exposure surveys, release inventories). Nominations should be directed to Dr. C. W. Jameson.

Contact Information: Dr. C.W. Jameson, Head, Report on Carcinogens, NIEHS/NIH, 79 Alexander Drive, Rm. 3118, PO Box 12233, MD EC-14, Research Triangle Park, NC 27709; T: (919) 541-4096; FAX: (919) 541-0144; jameson@niehs.nih.gov