November 2000

NTP UPDATE

National Toxicology Program

NTP LIAISON & SCIENTIFIC REVIEW OFFICE

Sandra V. Lange
Director

(919) 541-0530
Fax: (919) 541-0295
liaison@starbase.niehs.nih.gov

National Institute of Environmental Health Sciences / National Institutes of Health
P.O. Box 12233
MD: A3-01
Research Triangle Park, NC 27709-2233

DEPARTMENT OF HEALTH & HUMAN SERVICES

What's Inside

We are pleased to provide the information included in this bulletin to update our readers on NTP programs and initiatives, as well as to highlight upcoming meetings. We invite public input and participation in all aspects of our programs.

Christopher J. Portier Named Acting Associate Director National Toxicology Program

Effective July 1, Dr. Kenneth Olden named Dr. Christopher J. Portier Acting Associate Director of the NTP and Acting Director of the Environmental Toxicology Program at the National Institute of Environmental Health Sciences. As Chief of the NIEHS Laboratory of Computational Biology and Risk Analysis, he has been a leader in the development of biologically based dose response models by applying the power of computational biology to experimental data. These models are becoming increasingly used by regulatory agencies in their risk assessments. He is also actively involved in the development and application of scientifically-driven methods of analysis to address problems in environmental health. Dr. Portier's extensive interagency and international activities and his leadership in several national and international risk assessment efforts, including the recent NIEHS health assessment of electric and magnetic fields, will contribute significantly to the goals of the NTP.

American Public Health Association Creates Award in Tribute to David Rall

Dr. David P. Rall, first director of the NTP and past director of the NIEHS, died in November 1999. The American Public Health Association (APHA) has created a permanent award in tribute to Dr. Rall who brought scientific research to bear on policy making in environmental health and whose science-based advocacy advanced public health and prevention across many fields and in many fora. The David P. Rall Award for Advocacy in Public Health will be awarded annually to an individual who has made outstanding contributions to public health through science-based advocacy. The 2000 recipient of the Rall Award is Dr. Eula Bingham, University of Cincinnati. Dr. Bingham has had a distinguished career as a researcher in occupational and environmental health, served as Assistant Secretary in the U.S. Department of Labor, and has contributed significantly to public health through numerous science-based advocacy efforts and programs. She will receive the Rall Award on November 13 at the annual APHA meeting in Boston, Massachusetts. Additional information is available on the Internet - http://www.apha.org/sections/Awards/rall/RallInvitation.htm.

The NTP Update is issued approximately four times each year. To subscribe to the "list-server" and receive the NTP Update as well as other NTP news and announcements electronically, register on-line at http://ntp-server.niehs.nih.gov, *send email to* ntpmail-request@list.niehs.nih.gov *with the word "subscribe" as the body of the message, or contact the NTP Office of Liaison and Scientific Review (see first page).*

Additional information about the NTP along with announcements of meetings, publications, study results and its centers is available on the Internet at http://ntp-server.niehs.nih.gov.

Environmental Health Service (EHIS) maintains the library of NTP Technical Reports and adds new reports as available. To gain access to these reports, contact EHIS on-line at http://ehis.niehs.nih.gov *or call 1-800-315-3010 or 919-541-3841.*

Upcoming Workshops

PCR-Based Approaches to Identify and Quantitate Botanicals in Dietary Supplements

The NIEHS and NIH Office of Dietary Supplements is co-sponsoring a workshop at the NIEHS in Research Triangle Park, North Carolina on November 2-3, 2000. Organizers of this workshop include Dr. Michael McClure and Dr. Tom Burka of the NIEHS and Dr. Dennis Lubahn, Director of the NIEHS funded Center for Phytochemical and Phytonutrient Studies in Human Disease at the University of Missouri at Columbia.

Characterization of botanical products used as dietary supplements poses a significant analytical challenge. Polymerase Chain Reaction (PCR)-based techniques are just beginning to be used to characterize botanical products and this technology offers many advantages over currently used methods. Goals of the workshop will be to gain additional information that can be used in assessing this method's usefulness and in planning future programs.

Many botanical products are plant extracts and while they are often very complex mixtures, modern analytical chemistry (e.g., LC- or GC-MS) offers powerful methods for characterization. Botanicals composed of plant parts pose a different sort of challenge. While it is possible to characterize them by microscopic examination, the method is tedious and only qualitative. If successful, PCR-based technology might allow the extraction, storage, and distribution of DNA from botanicals as reference standards based upon identified variations in nucleotide sequences. In addition, quantitative comparison of these specific sequences to general sequences found in plants would facilitate estimations of their purity.

For additional information about this workshop contact Dr. Michael E. McClure, NIEHS; t: 919-541-5327 or mm461n@nih.gov.

Alternative Toxicological Methods for the New Millennium: Science and Application

Under the National Defense Authorization Act and the National Institutes of Health Revitalization Act, the Department of Defense and the NIH are directed to establish programs to reduce, refine, and replace the use of research animals in research and testing. A conference is being held November 28 – December 1, 2000 at the Lister Hill Center, National Library of Medicine, NIH in Bethesda, Maryland to present the latest issues, research, and trends toward addressing those needs. Advance registration is $85 ($25 for students) and $99 at the door. General information and the registration form are available on the ICCVAM website, http://iccvam.niehs.nih.gov. Completed registrations forms should be sent to Ms. Deborah Bilotto, Booz Allen & Hamilton, Inc., 1309-R Continential Drive, Abingdon, Maryland 21009; t: 410-612-8247; f: 410-612-9968; bilotto_deborah@bah.com. Individuals interested in presenting a talk or poster should contact Dr. Max Kline (t: 508-655-7596 or klein_max@bah.com.) at the address above.

Evaluation of Alternative Methods for Carcinogenicity Testing Workshop

The NTP is participating in an industry/government consortium of Federal agencies and 25 pharmaceutical companies to study the utility of a number of alternative assays designed to augment or replace the two-year rodent bioassay. The NTP is testing six chemicals in the transgenic Tg.AC model by two routes of administration. A workshop co-sponsored by the International Life Sciences Institute (ILSI), NIEHS, and U.S. EPA is planned for November 1-3, 2000 in Leesburg, Virginia at the Lansdowne Resort. This workshop will provide a forum for discussing the scientific data from the consortium effort and the evolving state of the science regarding development and application of new methodologies for carcinogenicity testing. Additional details about registration, preliminary program, and lodging are available from ILSI (http://www.ilsi.org or f: 202-659-3859).

NTP Boards

NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meets in December

The second set of nominations for listing or delisting in the 10th Edition of the RoC will be peer reviewed by the RoC Subcommittee at its meeting December 13-15, 2000 at the Wyndham City Center, 1143 New Hampshire Avenue, NW, Washington, DC. This meeting is open to the public and begins at 9:30 AM on Wednesday, December 13 and 8:30 AM on Thursday and Friday, December 14 and 15. The table below lists the nominations and their tentative order for review.

The NTP invites interested parties to attend the peer review and if desired to provide oral comments at the meeting or to submit written comments to the Executive Secretary by December 1, 2000 for the Subcommittee's consideration. A draft agenda is available by contacting Dr. Mary S. Wolfe, Board Executive Secretary (t: 919-541-3971; f: 919-541-0295; wolfe@niehs.nih.gov).

Background documents on these nominations are available electronically on the NTP home page (http://ntp-server.niehs.nih.gov) or in hard copy by contacting Central Data Management, NIEHS/NTP, P.O. Box 12233 MD E1-02, Research Triangle Park, NC 27709; t: 919-541-341; f: 919-541-3687; e-mail: CDM@niehs.nih.gov. Comments or questions about the nominations or Report on Carcinogens should be directed to Dr. C. W. Jameson (t: 919-541-4096 or jameson@niehs.nih.gov).

Nomination	Use	Reviewed for	Review order
Broad Spectrum UV Radiation and UVA, UVB and UVC	Solar and artificial sources of ultraviolet radiation	Listing	1
Chloramphenicol	Used widely as an antibiotic since the 1950s.	Listing	6
Estrogens, Steroidal	Widely used in oral contraceptives and in post-menopausal therapy for women.	Listing	5
Metallic Nickel & Nickel Alloys	Widely used in commercial applications for over 100 years.	Listing	4
Methyleugenol	Flavoring agent used in jellies, baked goods, nonalcoholic beverages, candy, and ice cream. Also used as a fragrance for many perfumes, and soaps.	Listing	3
Talc (Asbestiform and Non-Asbestiform)	Asbestiform talc (i.e. talc containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing. Non-asbestiform talc (i.e. talc not containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing and exposure to general population occurs through the use of products such as cosmetics.	Listing	7
Trichloroethylene	Widely used as a solvent with 80-90% used worldwide for degreasing metals.	Upgrading to a known human carcinogen	2
Wood Dust	Estimated that at least two million people are routinely exposed occupationally to wood dust worldwide. Non-occupational exposure also occurs. The highest exposures have generally been reported in wood furniture and cabinet manufacture, especially during machine sanding and similar operations.	Listing	8

NTP Advisory Committee for Alternative Toxicological Methods (ACATM) to Meet

A meeting of the NTP ACATM will be held from 9:00 AM to 5:00 PM on November 28, 2000 in the Director's Board Room, National Library of Medicine, National Institutes of Health Campus, Building 38, 8600 Rockville Pike, Bethesda, Maryland. This NTP Board provides advice on the activities and priorities of the NTP Center for the Evaluation of Alternative Toxicological Methods and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and on ways to foster partnership activities and productive interactions among all stakeholders. This meeting is open to the public and time will be set aside for public comments.

Tentatively on the agenda is an update about the implementation of the ICCVAM recommended method, Local Lymph Node Assay, and reports from several meetings including the peer review on the Up-and-Down Procedure for assessing acute oral toxicity, the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity, and the expert panel meeting on the Frog Embryo Teratogenesis Assay - *Xenopus* (FETAX). Additional details about the meeting, a draft agenda, and committee roster can be obtained by contacting Dr. Mary S. Wolfe, Committee Executive Secretary, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709; t: 919-541-3971; f: 919-541-0295; wolfe@niehs.nih.gov.

NTP Centers

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

NTP Solicits Comments on Expert Panel's Phthalate Esters Reports

Following a one-year review, a 16-member scientific Expert Panel has completed its evaluation of the potential reproductive and developmental toxicity of seven phthalate esters:

- butyl benzyl phthalate
- di(2-ethylhexyl) phthalate
- di-isodecyl phthalate
- di-isononyl phthalate
- di-n-butyl phthalate
- di-n-hexyl phthalate
- di-n-octyl phthalate

The seven phthalate esters reports, which incorporate the Expert Panel's conclusions, are available electronically on the CERHR website (http://cerhr.niehs.nih.gov) or in hard copy by contacting Ms. Harriet McCollum, CERHR, 1800 diagonal Road, Suite 500, Alexandria, VA; t: 703-838-9440; f: 703-684-2223.

The CERHR invites public comment on the reports and any received will be reviewed and included in the NTP Center Report. Comments should be directed to Dr. Michael Shelby, Director, CERHR, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709; f: 919-541-4634. The NTP Center Report will contain the Expert Panel Report, public comments received on the Expert Panel Report, and any new and relevant information received since completion of the expert panel review. This document will be transmitted to Federal and State agencies, the public, and scientific community.

Phthalates are used as plasticizers in a wide range of polyvinyl chloride-based consumer products. These phthalate esters were initially chosen for evaluation by the CERHR based upon their production volume, extent of human exposures, use in children's products, published evidence of reproductive on developmental toxicity, and public concern.

Center Initiates Review of Methanol

The CERHR is planning an evaluation of the reproductive and developmental effects of methanol in late 2000/early 2001 in the Washington, DC area. This meeting will be open to the public with time allotted for oral public comment.

Methanol is a commercially important, high production volume chemical (10.54 billion pounds, US production, 1993) that has a high potential for occupational, consumer, and environmental exposure. The Center is currently soliciting public input concerning methanol (*e.g.*, toxicology information from completed, ongoing, and planned studies; production data; human exposure

information; use patterns; and environmental occurrence) and nominations of individuals qualified to serve on the expert panel. Questions regarding the review should be directed to Dr. Shelby at the address shown above.

Center Solicits New Nominations

The CERHR conducts reviews on man-made or naturally occurring chemicals or chemical mixtures and welcomes the nomination of chemicals for future evaluations. This process is open to all interested individuals and groups. Nominations should include the chemical's name, Chemical Abstract Service registry number (if known), justification for the nomination, and as possible, references or articles on the chemical and its potential reproductive or developmental toxicity. Nominations can be directed to Dr. John Moore, CERHR, 1800 diagonal Road, Suite 500, Alexandria, VA; t: 703-838-9440; f: 703-684-2223.

NTP Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Center Organizes In Vitro Methods for Assessing Acute Systemic Toxicity Workshop

The Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) and the NTP Center for the Evaluation of alternative Toxicological Methods held an international workshop October 17-20, 2000 in Arlington, Virginia. The goal of this meeting was to assess the current status of *in vitro* test methods for evaluating the acute systemic toxicity potential of chemicals and to make recommendations for validation efforts necessary to characterize the usefulness and limitations of existing methods. Background materials provided for the workshop are available at http://iccvam.niehs.nih.gov/IV_doc.htm. A workshop report that includes recommendations for future research and development efforts will be developed and posted on the ICCVAM website in the near future.

Workshop Proceedings

NTP Endocrine Disruptors Low-Dose Peer Review

At the request of the U.S EPA, the NTP convened a 36-member scientific panel to evaluate reported low-dose effects and dose-response relationships of endocrine disrupting chemicals for reproductive and developmental endpoints. This peer review was held October 10-12, 2000 in Research Triangle Park, North Carolina and was well attended with 175 registrants. The U.S. EPA is interested in knowing whether or not its guidelines for reproductive and developmental toxicity testing are adequate for endocrine active chemicals. For this meeting "low-dose effects" referred to biological changes that occur in the range of human exposures or at doses that are lower than those typically used in the U.S. EPA's standard testing paradigm.

The panel was divided into five subpanels (Bisphenol A, Estradiol and Other Estrogens, Androgens and Antiandrogens, Biological Factors and Study Design, and Statistics and Dose-Response Modeling). The panel was charged with examining data from major, selected studies (excluding studies on dioxin and dioxin-like compounds) supporting the presence or absence of low-dose effects in laboratory animals that could be relevant for human health assessments and evaluating the shape of the dose-response curve for endocrine active substances in the low-dose region.

This peer review created a unique and novel model to resolve a controversial, but very important environmental health issue. Principal investigators of the primary research groups active in this field provided their research data on selected parameters for independent statistical analysis. Data from 38 studies were evaluated by the Statistics and Dose-Response Modeling Subpanel prior to the meeting and the analysis were provided to the other subpanels. In addition, the principal investigators were present at the meeting to give formal presentations of their findings and have informal discussions with the various subpanels. This unique, scientific peer review provided an open,

transparent, and objective review and evaluation of the scientific evidence showing the presence or absence of low-dose effects of endocrine disrupting agents and an opportunity for participation by all stakeholders. Information from this peer review defines the knowledge base and uncertainties within this field and, as such, helps to strengthen the link between science and the regulatory decision-making process.

On the final day of the meeting, individual subpanels presented preliminary findings from their deliberations and these are summarized briefly. The Panel concluded that low-dose effects have been demonstrated for estradiol and some estrogenic compounds. For other estrogenic compounds, results from different laboratories indicate the presence or absence of low-dose effects and for those studies, which represent attempts to replicate early results, the Panel identified study design differences that may account for the discrepancies in experimental outcomes. Androgens and antiandrogens have not been adequately studied for low-dose effects as defined by this peer review. The shape of the dose-response curve for endocrine disrupting agents would depend upon numerous factors and may be monotonic, linear, or threshold-appearing. The Panel identified areas for which additional research is needed and recommended specific issues with respect to study design and biological and environmental factors that should be carefully considered in designing future experiments and characterizing effects. An NTP summary is available on the NTP website (http://ntp-server.niehs.nih.gov).

Individual subpanels will each prepare a report of their conclusions noting areas of consensus and disagreement. The subpanels are also asked to identify areas for which research is needed to resolve ambiguities. The NTP will receive these reports and synthesize this information into a single peer review report on which the NTP will solicit public comment. The NTP will incorporate comments, as appropriate, into its final transmission to the U.S. EPA in spring 2001. When complete, this NTP report will be posted on the NTP website (http://ntp-server.niehs.nih.gov) or can be obtained from the NTP Liaison and Scientific Review Office (see first page).

This final document should provide a strong scientific foundation upon which the U.S. EPA and other national and international agencies can base decisions regarding the selection of dose, endpoints, animal models, and testing regimes when designing reproductive and developmental studies of endocrine active agents.

NIEHS Holds Public Meeting to Discuss Recommendations for Agent Orange Research

The NIEHS convened a public meeting, August 18, 2000, in Monterey, Calfornia to receive expert opinion from a 15-member scientific panel and stakeholders on issues related to Agent Orange/ dioxin research. The panel was asked to recommend research that would improve the understanding of the potential for detrimental health and environmental effects arising from exposure to Agent Orange, dioxin, and related compounds and to identify scientific issues and concerns that would be associated with the conduct of such studies in Vietnam. Four panel members provided brief summary presentations describing the defoliants heavily used in Vietnam during military operations, the contaminants (especially dioxin) in these agents, the recorded locations of defoliant use, epidemiology literature on health effects of Agent Orange contaminants, and current U.S./Vietnamese research efforts directed toward health issues. In addition, about a dozen attendees from the audience made statements some of which were addressed and discussed further by the panel.

Several general issues were noted that would impact the development of a research program in Vietnam such as coordination with other U.S. research program, the methods for use in assessing exposure, and the geographic distribution of herbicide application in Vietnam. Data gaps were identified for which research is needed; these primarily focus on the health of children, the elderly, and women. Within these populations specific areas for research include effects on reproduction and development, the immune system, frequency of diabetes, and

endocrine status. The panel also noted that research on the incidence of reproductive/ hormonal cancers in men and women would be instructive if large populations of sufficiently exposed individuals can be identified. The NIEHS will use this information and these recommendations as a guide in discussions with Vietnamese scientists about developing a joint research program. A meeting with the Vietnamese scientists is being planned for late November or early December 2000.

Of Mice, Humans and Models: Future Research Directions for Improving Risk Assessment Methods

On August 16-18, 2000, NIOSH, NIEHS, U.S. EPA, American Chemical Council (ACC), and the United Auto Workers co-sponsored a workshop. The focus of this meeting was to review new developments and directions in epidemiology, toxicology, and mathematical modeling as they pertain to risk assessment and to develop research proposals targeted toward improving risk assessment methodology. Breakout group discussions focused on three areas: human studies, toxicology, and modeling, and on the third day following presentations from individual breakout groups, representatives from various funding agencies including NIOSH, NIEHS, U.S. EPA, and ACC led a panel discussion about current research funding and its future directions. Proceedings from this workshop will be published in *Human and Ecological Risk Assessment* in 2001. For additional information contact Dr. Mark Toraason, NIOSH C23, 4674 Columbia Parkway, Cincinnati, OH 45226; t: 513-533-8207; f: 513-533-8138; mht1@cdc.gov.

NTP Events Calendar

Date	Event	Sponsor/Organizer
November 1-3, 2000	**Evaluation of Alternative Methods for Carcinogenicity Testing** Lansdowne Resort, Leesburg, VA 20176 Contact: http://www.ilsi.org or f: 202-659-3859	International Life Sciences Institute, NIEHS & U.S. EPA
November 2-3, 2000	**PCR-Based Approaches to Identify and Quantitate Botanicals in Dietary Supplements** National Institute of Environmental Health Sciences, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709; Contact: Dr. Michael E. McClure, NIEHS; t: 919-541-5327; f: 919-541-5064; mm461n@nih.gov	NIEHS & NIH Office of Dietary Supplements
November 28, 2000	**NTP Advisory Committee on Alternative Toxicological Methods** 9:00 AM to 5:00 PM Director's Board Room, National Library of Medicine, National Institutes of Health, Building 38, 8600 Rockville Pike, Bethesda, MD; Open to public and public comments are welcome Contact: Dr. Mary S. Wolfe, Executive Secretary, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709; t: 919-541-3971; f: 919-541-0295; wolfe@niehs.nih.gov	NTP
November 28 - December 1, 2000	**Alternative Toxicological Methods for the New Millennium: Science and Application** Lister Hill Center, National Library of Medicine, NIH, Bethesda, MD Registration fee: $85 in advance ($25 students); $99 at door Registration form: http://iccvam.niehs.nih.gov/DoDConf.pdf Contact: Ms. Deborah Bilotto, Booz Allen & Hamilton, Inc., 1309-R Continental Drive, Abingdon, MD 21009; t: 410-612-8247; f: 410-612-9968; bilotto_deborah@bah.com.	Department of Defense & NIEHS
December 13 - 15, 2000	**NTP Board of Scientific Counselors Report on Carcinogens Subcommittee** Begins at 9:30 AM on December 13 and 8:30 AM on December 14-15 Wyndham City Center Hotel, 1143 New Hampshire Avenue, NW, Washington, DC; Open to public and public comments are welcome Contact: Dr. Mary S. Wolfe, Executive Secretary, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709; t: 919-541-3971; f: 919-541-0295; wolfe@niehs.nih.gov	NTP