NTP UPDATE

NATIONAL TOXICOLOGY PROGRAM October 2001

Headquartered at the
National Institute of
Environmental Health Sciences
National Institutes of Health
Research Triangle Park, NC

Department of Health &
Human Services

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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

NIEHS / NTP at APHA

Genomics and Environmental Health

A special session sponsored by the National Institute of Environmental Health Sciences (NIEHS) and the NTP entitled, "Genomics and Environmental Health: Enhancing the Public Health Impact of the Research Programs of the NIEHS and NTP," will be presented at 4:30 p.m. on October 24 at the annual American Public Health Association (APHA) meeting in Atlanta, GA. The session will take place in the Summit Room of the Atlanta Marriott Marquis.

The NIEHS has a long history of basic and practical research on a wide range of topics of importance to environmental and public health, both through its intramural research and extramural grants programs. Included in these programs are the rodent toxicology and carcinogenesis testing programs of the NTP. These studies have provided a uniform, high quality database on which many regulatory decisions are based. Scientific advances in biomarker research, genomics and proteomics could substantially reduce the time and expense involved in generating information and hold great promise for improving the quality and relevance of the research products of these programs. Advances in genetics are being applied to the field of environmental medicine with the intention of giving doctors a way to intervene early in a disease process caused by environmental exposures. Programs are being developed or are underway that place an emphasis on integrating research findings with information on actual human exposures to various toxicants to provide direct estimates of environmental effects linked to human reproduction and human cancer. This discussion session will highlight some of the existing and planned research programs of the NIEHS and the NTP with the hope of receiving feedback from the public health community, about their relevance and potential impact.

For additional information about this session visit the APHA web site at:
http://apha.confex.com/apha/129am/techprogram/session_7254.htm

Visit Us at APHA - Booth #1034

The NTP will exhibit at the APHA Public Health Exposition, which takes place at the Georgia World Congress Center, October 21-24, 2001. The Expo is the largest and most diverse public health exhibit featuring more than 550 booths of information, state-of-the-art products, and services geared towards public health professionals.

The NIEHS and the *Environmental Health Perspectives* (EHP), the NIEHS scientific journal, will also have exhibits at the Expo. Check out booths # 1036 (NIEHS) and #929 (EHP) if you are in the area. NIEHS / NTP have much to share!

NTP Congratulates Dr. David Michaels - Recipient of the David P. Rall Award for Advocacy in Public Health

The David P. Rall Award for Advocacy in Public Health is awarded to an individual who has made outstanding contributions to public health through science-based advocacy. This award is in tribute to David P. Rall, MD, PhD, Director of the NIEHS from 1971-1990 and founding Director of the NTP. Dr. Rall brought scientific research to bear on policy making in environmental health and his science-based advocacy advanced public health and prevention across many fields and in many fora. This prize is endowed by the Alliance to End Childhood Lead Poisoning and made possible by the contributions of scores of individuals and organizations inspired by Dr. Rall's life work.

Last year the NTP congratulated the first-ever Rall Award winner, Dr. Eula Bingham PhD, MS. Dr. Bingham is currently a professor of environmental health at the University of Cincinnati College of Medicine and was recognized for "her outstanding record of accomplishments in fighting to protect workers, consumers, and citizens from the danger of environmental and industrial disease."

This year we extend congratulations to the 2001 award recipient, David Michaels, PhD, MPH. Dr. Michaels is an epidemiologist who has made extraordinary contributions to public health through science-based advocacy for regulatory and public policy in his work in both academia and government agencies.

Dr. Michaels is currently active in many areas. He is as a research professor of Epidemiology in the Department of Environmental and Occupational Health at George Washington University; a visiting associate professor at the Albert Einstein College of Medicine, Department of Epidemiology and Social Medicine; and an adjunct associate professor at the Mount Sinai School of Medicine, Department of Community and Preventive Medicine. In his position as Assistant Secretary for Environment, Safety and Health at the US Department of Energy (1998 - 2001), he had primary responsibility for protecting the health and safety of workers, the neighboring communities, and the environment surrounding the nation's nuclear weapons complex.

Congratulations Dr. Michaels!

Leadership in the NTP / ETP

Director of the NTP Office of Liaison and Scientific Review Retires

Sandy Lange, Director of the NTP Office of Liaison and Scientific Review, for the past nine years, retired on September 1. Countless friends, family, and colleagues gathered at the NIEHS on September 4 to celebrate Ms. Lange's 33-year career at NIEHS.

Beginning her career at NIEHS in 1967, Ms. Lange joined the Institute a year into its establishment. Upon retirement, she was the longest serving NIEHS employee, having seen, been a part of, and coordinated many of the Institute's firsts.

Ms. Lange's career at NIEHS is one respected, recognized, and admired by many. She served in many important NIEHS areas including, administrative assistant, administrative officer, staff assistant to the Director, Director of the Office of Communications and in 1992, she became the Director of the NTP Office of Liaison and Scientific Review and assistant to the Environmental Toxicology Program (ETP) Director. As the Director of the NTP Office of Liaison and Scientific Review, Lange said it has been her job to "communicate the best science to the broadest group of people in a way they can be empowered with it and understand it." And that she has done and continues to do.

Dr. George Lucier, former Director of the ETP expressed it best saying, "Sandy has become a pillar of the NIEHS, but more importantly a pillar of public health. Her enduring commitment to linking good science to public health policy has been inspiring to many others and me. I feel very fortunate to have worked with Sandy for many years, especially within the context of the National Toxicology Program. Her broad and accurate understanding and integration of science, politics, and human nature, provided a template from which I learned and benefited, allowing me to move forward with greater confidence."

We are very honored to have Ms. Lange continue to work with us as she contributes her leadership and expertise to the U.S. - Vietnam cooperative research program (see page 13).

We want to extend our deepest gratitude and appreciation for all Ms. Lange has done and continues to do for the NIEHS, the NTP and the public, during her career serving the American people. We congratulate her on a job well done and thank her for giving so much of her time, energy and life to us.

New Leadership Announced for the ETP

A year after serving as Acting Director of the ETP of the NIEHS and Acting Associate Director of the NTP, Dr. Christopher J. Portier has been selected to head these programs on a permanent basis. Dr. Portier retains his position as chief of the ETP's Laboratory of Computational Biology and Risk Analysis.

Dr. Portier has been a leader in the development of biologically based dose-response models by applying the power of computational biology to experimental data. He currently has a leadership role in the U.S. - Vietnam cooperative research program (see page 13) and continues to be involved in interagency and international risk assessment efforts including the NIEHS health assessment of electric and magnetic fields.

John Pritchard, PhD, is the new Associate Director for Research and will coordinate research efforts between the intramural and extramural branches and

the NTP. Currently Dr. Pritchard also serves as Chief of the Laboratory of Pharmacology and Chemistry in ETP.

Director of the NIEHS and the NTP, Kenneth Olden, PhD, said Portier has many responsibilities, and Prichard will assume responsibility for overseeing and coordinating research efforts. Olden said merging the research efforts of intramural, extramural and the NTP has been one of his objectives for some time. He feels the result will be better science all the way around.

Strategic Planning by the ETP

The role of the ETP includes both basic research in environmental science and directing the activities of the NTP. Rapid development of new technologies, particularly in genomics, bioinformatics and imaging, holds the promise of generating more information per animal and using it in increasingly penetrating ways to address the impact of the environment on human health and disease. The NTP is in the forefront of this NIEHS-wide effort. Our challenge is to merge the new technologies into our research to insure that the best scientific data are readily accessible to a broad spectrum of users, and to provide intelligent interpretation of these data. To do so, the program's structure must be flexible enough to incorporate new methodologies into the NTP's array of testing tools and contain sufficient scientific expertise to use the results of this testing in both protecting public health and formulating research strategies to address major uncertainties.

To facilitate strategic planning that capitalizes on this opportunity, an ETP retreat was held August 22-23 in Wilmington, NC to address the question "How should the ETP position itself to meet the public health challenges of today and tomorrow?". Led by Dr. John Pritchard, PhD, ETP Associate Director for Research, NIEHS scientists and outside experts gathered to discuss recommendations for strengthening and expanding the program.

In the opening plenary session, Dr. Kenneth Olden, Director of the NIEHS and NTP, challenged attendees "to go where the puck is going" in developing research strategies and investigating new technologies to obtain the best science that protects public health. Dr. Christopher Portier, ETP Director, addressed the status of the current program and outlined future challenges. Guest speakers, Dr. Shelley Hearne, Executive Director of the Trust for America's Health, and Bernard Goldstein, Dean of Graduate School of Public Health at the University of Pittsburgh, presented talks on public health issues and challenges facing our nation. This was followed by talks on new technologies by Drs. Christopher Bradfield of the University of Wisconsin (genomics), Bruce Weir of the North Carolina State University (bioinformatics), and Allen Johnson of Duke University (imaging/*in vivo* microscopy).

Five breakout groups met to focus on the integration of new technologies into the ETP research and testing programs. These breakout groups were: Cancer, Reproduction and Development, Other Toxicological Endpoints, Pathology, and Bioinformatics and Data Analysis. The groups individually discussed targeted questions concerning the current and future directions of the ETP and the NTP for their topic areas. ETP staff is currently reviewing input and recommendations from the retreat and will use this information to develop the program's strategy for the future.

New NIEHS Scientific Director

Biochemist Lutz Birnbaumer, PhD, is NIEHS's new Scientific Director as of October 1, 2001.

Dr. Birnbaumer comes to NIEHS from the University of California-Los Angeles (UCLA). At UCLA he served as professor and chair of the Department of Molecular, Cell and Developmental Biology, professor of Anesthesiology and Biological Chemistry, and a full member of UCLA's Institute of Molecular Biology, Brain Research Institute and Jonsson Comprehensive Cancer Center.

An author of 250 research articles, Dr. Birnbaumer has been a member of the NIEHS Board of Scientific Councilors, which peer reviews the Institute's intramural science. He has also had associations with the Salk Institute, the American Heart Association and the Pew Charitable Trusts. He has taught international graduate courses in cell

biology in Belgium, Argentina and Sweden and was a visiting professor at nearly 60 teaching institutions, including the Cleveland Clinic, Mount Sinai School of Medicine, Harvard University, Duke University and the University of North Carolina-Chapel Hill.

J. Carl Barrett, PhD, was scientific director of NIEHS until last year. He was with NIEHS for 23 years. Paul Nettesheim, MD, DMS, served as acting scientific director in the interim.

NTP Boards

October 18 NTP Technical Report Review

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee met October 18, 2001 at the NIEHS in Research Triangle Park, North Carolina. This subcommittee provides independent scientific peer review of draft technical reports of NTP long-term toxicology and carcinogenesis studies. The candidate technical reports for this review included: vanadium pentoxide, riddelliine, 2,4-hexadienal and diazoaminobenzene. The peer review was open to the public and time was available for public comment on the reports.

- **Vanadium pentoxide** is commercially the most important compound of vanadium and presents a potential occupational hazard during the cleaning of oil-fired boilers and furnaces, the handling of catalysts, and during the refining, processing, or burning of vanadium-rich mineral ores or fossil fuels.
- **Riddelliine** belongs to a class of toxic pyrrolizidine alkaloids and is isolated from plants of the *genera Crotalaria*, *Amsinckia*, and *Senecio* that grow in the western United States. Cattle, horses, and sheep that ingest these plants succumb to their toxic effects. Riddelliine residues have been found in meat, milk, and honey, and the plants may contaminate human food sources.
- **2,4-Hexadienal**, a colorless to yellow liquid with a pungent "green" or citrus odor, is used as a food additive for flavor enhancement, as a fragrance agent, as a starting material or intermediate in synthetic reactions in the chemical and pharmaceutical industries, as a fumigant, and as a corrosion inhibitor for steel.
- **Diazoaminobenzene** is used as an intermediate, complexing agent, and polymer additive. It is also an impurity in certain color additives used in cosmetics, food products, and pharmaceuticals. Diazoaminobenzene was selected for metabolism and toxicity studies based on the potential for worker exposure from its use in laboratories, positive Salmonella typhimurium data, its presence as an impurity in foods and cosmetics, and the lack of adequate toxicity data.

Subcommittee action son these reports are available on the NTP web site. Printed copies of these draft reports are available from: Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709; T: 919-541-3419; F: 919-541-3687; cdm@niehs.nih.gov.

For additional information, contact Dr. Mary S. Wolfe, NTP Executive Secretary at: 919-541-3971 or wolfe@niehs.nih.gov.

Report on Carcinogens

9th Edition - TCDD/Dioxin Addendum

Prepared by the NTP, the *Report on Carcinogens* (*RoC*) identifies substances -- such as metals, pesticides, drugs, and natural and synthetic chemicals -- mixtures or exposure circumstances that are "known" or are "reasonably anticipated" to be human carcinogens, and to which a significant number of Americans are exposed.

The 9th Edition of the *RoC* is the most recent and was published in May 2000. An addendum to the 9th *RoC* was published in January 2001 and issued to change the listing of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin CAS No. 1746-01-6, also known as "TCDD" or "Dioxin," to a "known to be human carcinogen," from its previous listing as "reasonably anticipated to be a human carcinogen." Publication of the addendum followed the ruling by the US Court of Appeals for the District of Columbia Circuit denying the request for an injunction to prevent the listing of TCDD as a "known human carcinogen" in the 9th Report, pending appeal of the district court's decision upholding the listing. The proposal to list TCDD as a "known human carcinogen" was reviewed in the same way and at the same time as the other new listings for the 9th

RoC. The review procedure is outlined in Section V of the 9th *RoC* and on the NTP web site.

The revised 9th RoC that contains all addendum materials is available on the Internet from the NTP web page at http://ntp-server.niehs.nih.gov/NewHomeRoC/AboutRoC.html *or by contacting Dr. C.W. Jameson, Head, Report on Carcinogens (contact information below).*

10th Edition of the *Report on Carcinogens*

Scientific review of the nominations being considered for inclusion in the 10th edition of the *RoC* is completed. This group of nominations includes the following:

- **Beryllium and Beryllium Compounds**
  Used in fiber optics and cellular network communications systems, aerospace, defense and other industry applications. Reviewed for possible change to a known human carcinogen.
- **2,3-Dibromo-1-propanol**
  Used as a flame retardant, as an intermediate in the preparation of the flame-retardant tris(2,3-dibromopropyl) phosphate, and as an intermediate in the manufacture of pesticides and pharmaceutical preparations.
- **2,2-Bis-(Bromomethyl) –1,3-propanediol**
  Used as a fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam.
- **Dyes Metabolized to 3,3 -Dimethoxybenzidine (Dimethoxybenzidine Dyes as a Class)**
  Dyes formerly widely used for leather, paper, plastics, rubber, and textile industries.
- **Dyes Metabolized to 3,3-Dimethylbenzidine (Dimethylbenzidine Dyes as a Class)**
  Dyes formerly widely used for leather, paper, plastics, rubber, and textile industries.
- **IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)**
  Found in cooked meat and fish.
- **Styrene-7,8-oxide**
  Used mainly in the preparation of fragrances and in some epoxy resin formulations.
- **Vinyl Bromide**
  Used commercially since 1968, primarily in the manufacture of flame retardant synthetic fibers.
- **Vinyl Fluoride**
  Used commercially since the 1960s, in the production of polyvinylfluoride that is used for plastics.
- **Broad Spectrum UV Radiation and UVA and UVB and UVC**
  Solar and artificial sources of ultraviolet radiation.
- **Chloramphenicol**
  Used widely as an antibiotic since the 1950s. Veterinary use of chloramphenicol has resulted in the occurrence of residues in animal-derived food.
- **Estrogens, Steroidal**
  Estrogens are widely used in oral contraceptives and in post-menopausal therapy for women.
- **Methyleugenol**
  Flavoring agent used in jellies, baked goods, nonalcoholic beverages, candy, and ice cream. Also used as a fragrance for many perfumes and soaps.
- **Nickel (metallic) & Certain Nickel Alloys**
  Widely used in commercial applications for over 100 years.
- **Trichloroethylene**
  Trichloroethylene is widely used as a solvent with 80-90% used worldwide for degreasing metals.
- **Wood Dust**
  It is 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.

The NTP will review the recommendations from all review committees, including the Federal interagency NTP Executive Committee, and will consider all public comments received throughout the process in making decisions regarding the NTP recommendations to the Secretary, Department of Health and Human Services, for listing of the nominated substances in the 10th *RoC*. The 10th RoC is scheduled for submission to Congress in 2002.

Final public comments for all nominations have been received. A table of the recommendations for these nominations from the three scientific peer review committees for listing in the 10th RoC can be accessed through the NTP home page on the web at: http://ntp-server.niehs.nih.gov/ *or by contacting Dr. C. W. Jameson at the address provided below.*

All public comments as well as background documents, provided to the review committees and the public, are available in PDF version on the web site referenced above. Hard copies of these documents are available upon request.

11th Edition of the *Report on Carcinogens*

The NTP initiated scientific review of the nominations under consideration for inclusion in the 11th edition of the *RoC*, which is scheduled for publication in 2004. This group of nominations includes the following:

- **1-Amino-2,4-dibromoanthraquinone**, a vat dye used in the textile industry.
- **2-Amino-3,4-dimethylimidazo[4,5-f]quinoline** (or MeIQ), a substance formed in food during heating or cooking and found in cooked meat and fish.
- **Cobalt Sulfate**, which is used in electroplating and electrochemical industries; as a coloring agent for ceramics; as a drying agent in inks, paints, varnishes and linoleum; and as a mineral supplement in animal feed.
- **Diazoaminobenzene (DAAB)**, which is used to promote adhesion of natural rubber to steel, as a polymer additive and an intermediate in the production of a number of pesticides, dyes and other industrial chemicals.
- **Diethanolamine (DEA)**, which is used in machine oils and metal cutting fluids and in the preparation of liquid laundry and dishwashing detergents, cosmetics, shampoos and hair conditioners, as well as in textile processing and other industrial uses.
- **Hepatitis B Virus (HBV)**, a small DNA-enveloped virus that is transmitted through contact with blood and blood products or other body fluids.
- **Hepatitis C Virus (HCV),** an RNA-enveloped virus mainly transmitted in blood as is HBV above.
- **High Risk Human Papillomaviruses (HPVs)**, small non-enveloped viruses that infect genital mucous membranes. HPV infections are common throughout the world.
- **X-radiation and gamma radiation**, used in medical diagnosis and treatment, and produced in the use of atomic weapons.
- **Neutrons**, which may affect patients getting neutron radiotherapy and the passengers and crew of aircraft, which are naturally bombarded by the particles.
- **Naphthalene**, which is used in making many industrial chemicals and as an ingredient in some mothballs and toilet bowl deodorants.
- **Nitrobenzene**, which is used in the production of aniline, a major chemical intermediate in the production of dyes.
- **Nitromethane**, a stabilizer added to many halogenated solvents and aerosol propellants.
- **Occupational Exposure to Lead or Lead Compounds**, major occupational exposures are in the lead smelting and refining industries, battery-manufacturing plants, steel welding or cutting operations, construction, and firing ranges.
- **Phenylimidazopyridine**, which, like MeIQ (second item above), is formed in food during heating and cooking and is found in cooked meat and fish.
- **4,4'-Thiodianiline**, which is an intermediate in the manufacture of several dyes.

The NTP is currently soliciting initial public comment on this set of nominations. Comments should be directed to Dr. C. W. Jameson at the address listed below.

The criteria and a description of the RoC review process can be obtained through the NTP homepage: http://ntp-server.niehs.nih.gov (*see Report on Carcinogens) or by contacting Dr. Jameson (see below).*

NTP Requests Nominations for Future Evaluation for Listing/Delisting in 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*. When possible, nominations should contain a rationale for the listing or delisting and appropriate supporting background information and relevant data (e.g., journal articles, NTP Technical Reports, IARC listings, exposure surveys, release inventories). Nominations should be directed to Dr. Jameson at the following address.

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

NTP TESTING PROGRAM

NTP Chemical Testing Nominations

The NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) makes testing recommendations on nominated substances and serves as the first level of review in the NTP's formal chemical nomination and selection process. Recently, the ICCEC met and evaluated a group of substances nominated to the NTP for toxicology and carcinogenicity testing. Notice of this meeting including a request for public comment on these nominations and the ICCEC's testing recommendations was published in the Federal Register July 25, 2001 (66FR38717).

The nominated substances under consideration include environmental contaminants, industrial chemicals, and consumer products. The substances for which the ICCEC recommends one or more types of toxicity testing are:

- Bladderwrack
- Cylindrospermopsin
- Epigallocatechin-3-gallate
- 2-Ethylhexyl-*p*-dimethylaminobenzoic acid
- Grape seed and pine bark extracts
- Metalworking fluids
- Methyl tetrahydrofuran
- Polybrominated diphenyl ethers

The nominated substances for which a testing recommendation is deferred pending the receipt and consideration of additional information are:

- *n*-Butyl bromide
- Methyl soyate

The nominated substances for which no testing is recommended at this time are:

- Apigenin
- Dibenzofuran
- Diphenolic acid

Additional opportunity for public comment will be provided at a future NTP Board of Scientific Counselors meeting. Following this review by the NTP Board and further review and approval of the testing recommendations by the NTP Executive Committee, the appropriate NTP studies will be designed and implemented as resources and time permits. Further information is available on the web at: http://ntp-server.niehs.nih.gov/htdocs/Liason/ICCEC010508FR.html

NTP Solicits Input and Nominations of Agents for Study

The nomination and selection process is integral to the effective operation and success of the NTP's testing program with respect to its testing of chemicals of greatest public health concern. The NTP solicits nominations of new chemicals and agents for study from multiple sources including academia, industry, labor unions, Federal and State agencies and the general public.

NTP studies include research and testing of selected chemicals and agents in order to characterize their toxicity and determine possible adverse effects that might be associated with human and environmental exposure. Health-related effects addressed include subchronic toxicity, genetic toxicity, chronic toxicity and carcinogenicity, as well as effects on reproduction and development and the immune, respiratory and central nervous systems. Studies are also designed to address specific data gaps for priority substances such as biological fate, mechanisms of toxicity and other adverse effects that may be of human health concern. Data generated from NTP studies are critical to strengthening the science base used by regulatory agencies for assessments of human health hazards associated with exposure to those chemicals and agents studied. The NTP also supports an active program to develop and validate new and improved assays for chemical toxicity and test methods and systems that eliminate or minimize the use of laboratory animals.

Each nomination is considered carefully in order to maximize the use of available resources. Chemicals or other agents for which a significant portion of the population are known to be exposed and for which there is a lack of available adequate toxicological information are the best candidates for study.

The NTP invites the submission of nominations. All nominations should be accompanied by a rationale for study, i.e. populations exposed, source of exposure, any known adverse health effects, etc. When possible, nominations should also be accompanied by available information describing production and use, possible adverse effects associated with exposure, as well as a chemical name, structure and CAS number. The NTP considers each nomination as it is received and conducts a literature search to supplement any supporting documentation on the nomination prior to its review and prioritization for future evaluation. The nominator is informed of the status of the nomination as it moves through the review, selection and testing process.

In addition to formal nominations for study, comments on testing directions and priorities are welcome. Some current testing initiatives include the study of botanical dietary supplements, drinking water contaminants, occupational exposures and mixtures, and DNA-based therapeutic agents. It is

important, however, to emphasize that the NTP seeks the broadest participation in the nomination process and nominations need not be limited to any of these areas.

Nominations and inquires regarding nominations or testing initiatives should be addressed to: Dr. Scott Masten, Office of Chemical Nomination and Selection, NIEHS, P.O. Box 12233, MD B3-10, Research Triangle Park, NC 27709; T: (919) 541-5710; F: (919) 558-7067; masten@niehs.nih.gov.

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

The NTP and the NIEHS established CERHR in June 1998. The purpose of the Center is to provide timely and unbiased, scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction, including development, which may be caused by agents to which humans are exposed.

Review of Phthalate Esters Nears Completion

The Phthalate Expert Panel completed its evaluation of the following seven phthalate esters for potential reproductive and developmental toxicity in July 2000.

- 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

Public comments on these reports were received through December 11, 2000. The CERHR is in the process of preparing its Center Reports on these seven phthalates.

The Expert Panel Reports for the individual phthalates are available electronically on the CERHR's web site, http://cerhr.niehs.nih.gov *or in hardcopy by contacting the Center (contact information provided below).*

CERHR Evaluation of Methanol

The CERHR Methanol Expert Panel met in Alexandria, VA on October 15-17, 2001 to conduct its evaluation of methanol. 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. This meeting was open to the public and time was made available for oral public comments.

Further information on this meeting is posted on the CERHR web site. Questions and requests for additional information should be directed to Dr. Michael Shelby, Director CERHR (see contact information below).

CERHR Evaluation of Bromopropanes

The CERHR Bromopropanes Expert Panel will meet in Herndon, VA on December 5-7, 2001 to conduct its evaluations of 1-bromopropane and 2-bromopropane. The bromopropanes were selected for evaluation based upon several factors including the reported human reproductive toxicity of 2-bromopropane, the use of 1-bromopropane as a solvent and component of some spray adhesives, the proposed new uses as replacements for ozone depleting hydrochlorofluorocarbons and chlorinated solvents, and a substantial data base on reproductive and developmental toxicity. The Bromopropanes Expert Panel draft reports (sections 1-4) will be available for public comment in mid-October, 2001.This meeting will be open to the public and time will be available for oral public comments.

Further information on this meeting will be provided through the Federal Register and posted on the CERHR web site. Questions and requests for additional information should be directed to Dr. Michael Shelby, Director CERHR (see contact information below).

Future Reviews

An evaluation of ethylene glycol will be conducted in 2002. The panel membership and meeting schedule are yet to be determined.

CERHR Prepares Guidelines for Expert Panels

Public comments on the CERHR draft guidelines for expert panels were received from April 25 to June 11, 2001. The draft guidelines are available on the CERHR web site and are currently under revision. These guidelines will aid in preparation of the Expert Panel Reports, promote understanding among panel members regarding the evaluation process, and help facilitate consistency among reports.

CERHR Solicits Nominations

The CERHR conducts reviews on man-made or naturally occurring chemicals or chemical mixtures and welcomes the nomination of chemicals for future evaluations. Nominations are welcome from all interested individuals and groups. Nominations should include the chemical's name, Chemical Abstract Service registry number (if known), and a justification for the nomination. As possible, reference or submit articles on the chemical and its potential reproductive or developmental toxicity.

Nominations can be submitted through the CERHR web site, choose Nominate a Chemical, or directly to: Dr. Michael Shelby, Director, CERHR, NIEHS, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709; T: 919-541-3455; F: 919-541-4636; shelby@niehs.nih.gov.

CERHR Web Site

http://cerhr.niehs.nih.gov

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

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) collaborate to develop, validate, and achieve regulatory acceptance of new and improved test methods, including methods that will reduce, refine, and replace animal use. The ICCVAM was established in 1997 to coordinate cross-agency issues on the development, validation, acceptance, and national/international harmonization of toxicological test methods. ICCVAM was established as a permanent committee by the ICCVAM Authorization Act of 2000 (Public Law 106-545).

Update on Recent ICCVAM/NICEATM Meetings

International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity

ICCVAM and NICEATM organized an international workshop October 17-20, 2000 in Arlington, VA. The goals of the workshop were to: 1) assess the current status of *in vitro* test methods for evaluating the acute systemic toxicity potential of chemicals, 2) recommend validation efforts necessary to further characterize existing methods, and 3) to identify research and development needed to further improve the usefulness of *in vitro* methods for acute toxicity. The four major topics discussed were:

- *in vitro* screening methods for assessing acute toxicity
- *in vitro* methods for toxicokinetic determinations
- *in vitro* methods for predicting organ-specific toxicity
- chemical data sets for validation of *in vitro* acute toxicity test methods.

The final Workshop Report and a guidance document that describes how in vitro methods can be used to estimate the starting dose for animal studies are now available on the ICCVAM/NICEATM web site at: http://iccvam.niehs.nih.gov/methods/invitro.htm

Both report's availability and a request for public comment were announced in a recently published Federal Register notice (Vol. 66, No. 189, pp. 49686-49687, Sept. 28, 2001) which can be viewed at: http://iccvam.niehs.nih.gov/docs/FR/6649686.htm

Public comments are requested by November 13, 2001 and should be submitted to Dr. Stokes, Director, NICEATM (see contact information that follows).

Peer Review Teleconference Meeting on the Up-and-Down Procedure for Acute Oral Toxicity

A public teleconference meeting of the Up-and-Down Procedure (UDP) independent scientific peer review panel (Panel) was held on Tuesday, August 21, 2001 in Research Triangle Park, NC. The agenda for this meeting focused on a discussion of the following: 1) the revised draft UDP, modified in response to recommendations from the July 2000 Panel meeting; 2) a proposed procedure for calculating the confidence interval for the estimated LD50; and 3) a software program to aid in dose selection, test-stopping decisions, calculation of an estimated LD50, and calculation of a confidence interval around the LD50.

The revised draft UDP was proposed by the U.S. Environmental Protection Agency (EPA) to ICCVAM as an alternate for the existing conventional LD50 test (EPA 870.1100) used to evaluate the acute oral toxicity of chemicals. A previous version of the draft UDP was reviewed by the UDP Peer Review Panel at a meeting on July 25, 2000 organized by NICEATM and ICCVAM. The proposed procedure for calculating the confidence interval for the estimated LD50 is a statistical calculation and does not require the use of test animals beyond what is needed to estimate the LD50. This procedure helps to place the estimated LD50 in a statistical context for hazard and risk assessment purposes.

Because the generation of parameters for this revised draft UDP is computationally intensive, the EPA developed a simple-to-use software program to aid in dose selection, test-stopping decisions, calculation of an estimate of the LD50, and calculation of a confidence interval around the LD50.

The Peer Review Panel's final report is currently being finalized and will be made available for public comment in an upcoming Federal Register notice and on the ICCVAM/NICEATM web site in the near future.

Current Test Method Activities

***In Vitro* Corrosivity Methods**

Three alternative *in vitro* test methods – EpiDerm™, EPISKIN™, and the Rat Skin Transcutaneous Electrical Resistance (TER) assay – were developed and have subsequently been accepted as replacement assays for traditional *in vivo* corrosivity testing in the European Union. The evaluation of these assays was part of an expedited ICCVAM review of the validation status and possible current uses of *in vitro* test methods to assess the dermal corrosivity potential of chemicals and chemical mixtures. This ICCVAM expedited test method review process will accelerate interagency consideration of these test methods, thereby avoiding duplication of effort and unnecessary delays in recommending useful test methods to Federal agencies in accordance with Public Law 106-545.

EpiDerm™ and EPISKIN™ utilize a three-dimensional human skin model comprised of a reconstructed epidermis and a functional stratum corneum to which the test chemical is applied and subsequent cell viability is measured. Rat Skin TER assesses the skin corrosivity of a chemical by applying the test material to the epidermal surface of a rat skin disc for two and 24 hours; subsequently, the transcutaneous electrical resistance (TER) of the skin disc is measured.

The Background Review Document and proposed ICCVAM recommendations were made available to the public for comment in a Federal Register notice (Vol. 66, No. 189, pp. 49686-49687, September 28, 2001) and are available on the Internet at: http://iccvam.niehs.nih.gov/methods/epiddocs/epis_brd.pdf. *Public comments are requested by November 13, 2001 and should be submitted to Dr. Stokes, NICEATM Director (see contact information that follows).*

Endocrine Disruptor Screening Methods

ICCVAM and NICEATM are planning an Independent Peer Review Panel meeting to assess the validation status of several *in vitro* assays proposed for use in the EPA's Endocrine Disruptor Screening Program (EDSP). The proposed estrogen and androgen receptor binding and transcriptional activation assays are relevant for screening purposes

in the EDSP because a number of chemical substances may alter natural endocrine processes in the body by binding with estrogen and/or androgen receptors and either initiating or inhibiting sex hormone dependent gene activation. NICEATM is currently preparing background review documents (BRDs) on *in vitro* estrogen receptor and androgen receptor binding and transcriptional activation assays. The documents will provide comprehensive reviews of available data and related information necessary to evaluate the validation status of these assays.

A request for data and nominations of expert scientists to serve on the peer review panel for evaluation of these in vitro endocrine disruptor screening methods was announced in a recent Federal Register notice with submission requested by May 23, 2001 (Vol. 66, No. 57, pp. 16278-16279, March 23, 2001). This Federal Register notice may be found on the Internet at http://iccvam.niehs.nih.gov/methods/endocrine.htm

The Peer Review Panel meeting is scheduled to take place on May 21-22, 2002 in Durham, NC. Details of this meeting will be announced in an upcoming Federal Register notice and posted on the ICCVAM/NICEATM web site at: http://iccvam.niehs.nih.gov/methods/endocrine.htm

Future Meeting

Acute Toxicity Testing Workshop

ICCVAM in partnership with the EPA, the NIEHS, and the International Life Sciences Institute will sponsor a training workshop on new alternative *in vitro* and *in vivo* methods for assessing acute oral toxicity. The workshop will be held February 19-21, 2002 at the National Institutes of Health Natcher Conference Center, Bethesda, MD.

Additional information pertaining to registration and participation will be available in the near future on the ICCVAM/NICEATM web site.

For further information on ICCVAM and NICEATM, please visit the web site at http://iccvam.niehs.nih.gov/ *or contact: Dr. William S. Stokes, Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Environmental Toxicology Program, NIEHS/NTP, MD EC-17, P. O. Box 12233, Research Triangle Park, NC 27709; T: 919-541-7997; F: 919-541-0947;* niceatm@niehs.nih.gov

UPCOMING WORKSHOPS

Assessment of the Potential Allergenicity of Genetically Modified Foods - Meeting Rescheduled

The general public and the scientific community are increasingly concerned regarding the potential toxicity of genetically modified (GM) foods. Of specific interest is the ability of GM proteins to elicit potentially harmful immunologic responses including hypersensitivity and/or autoimmunity.

The lack of information on the potential toxicity of these products has created a considerable backlash against the producers and users of these crops. To address these issues, the NTP along with the EPA and the U.S. Food and Drug Administration is sponsoring a workshop on the safety assessment of GM foods.

Originally scheduled to be held September 24-26, the meeting will now be held December 10-12, 2001 in Research Triangle Park, NC. The goals of this meeting are to examine the current state of knowledge in this area, to identify the critical issues regarding GM materials, and to develop testing strategies for examining the toxicity of these compounds. Participants will include experts in food allergy, GM crops, and the regulatory aspects of these products.

For registration information, contact Ms. Angie Sanders, NTP Office of Liaison and Scientific Review, 111 T.W. Alexander Drive, NIEHS, MD A3-02, Research Triangle Park, NC 27709: T: 919-541-0530); F: 919-541-0295; sanders5@niehs.nih.gov

For additional information or to view the registration package, please access the meeting web page located on the NTP web site: http://ntp-server.niehs.nih.gov/htdocs/Liason/GMFoodPg.html

Gene Expression and Proteomics in Environmental Health Research

This symposium, conducted by the National Center for Toxicogenomics (NCT), will be held December 3-4, 2001, in the Natcher Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD. The goal of the symposium is to bring together outstanding experts in the fields of functional genomics, proteomics, toxicology, informatics, and database development. The new science of toxicogenomics aims to discover mechanisms by combining clinical, genomic, and proteomic knowledge into a common framework for understanding the biochemical and genetic pathways to disease. The meeting format will consist of presentations by invited speakers as well as discussion leaders to facilitate a free exchange of information. The symposium is designed to bring together a diverse group of scientists working in the areas of gene environment interactions, toxicology, genomics, informatics, and database development.

The NIEHS recently established the NCT to coordinate an international research effort for developing the field of toxicogenomics. Toxicogenomics is a new scientific field that elucidates how the entire genome is involved in biological responses of organisms exposed to environmental toxicants/stressors. It combines information from studies of genomic-scale mRNA profiling (by microarray analysis), cell-wide or tissue-wide protein profiling (proteomics), genetic susceptibility, and computational models to understand the roles of gene-environment interactions in disease.

For further information about this symposium, visit the NCT web site at:
http://www.niehs.nih.gov/nct/workshop.htm

For additional information about the NCT visit its web site at: http://www.niehs.nih.gov/nct/home.htm *or contact Dr. Raymond W. Tennant, Director, NCT, NIEHS, P.O. Box 12233, MD F1-05, Research Triangle Park, NC 27709; T: 919-541-4141; F: 919-541-1460;* tennant@niehs.nih.gov

Vietnam-United States Scientific Conference on Human Health and Environmental Effects of Agent Orange/Dioxins

This conference will be held March 3-6, 2002 at the Daewoo Hotel, Hanoi, Vietnam, and is being organized under the auspices of a joint U.S.-Vietnam cooperative research program on the health and environmental effects of Agent Orange/dioxin. In July 2001 the governments of Vietnam and the United States agreed to organize a conference that would bring together experts throughout the world to provide a broad assessment of the data available on the health and environmental effects of Agent Orange/dioxin and the needs for future research. This conference will be used to identify future research directions and provide a foundation for future cooperative research projects and funding.

Conference Goals

- Exchange of current scientific information on the health and environmental effects of Agent Orange/dioxins.
- Exchange of current scientific information on remediation measures to reduce exposures to Agent Orange/dioxins in humans and the environment.
- Examine the current state of knowledge and identify future research needs.

Topics to be Covered

Invited speakers will address specific issues on:

- health effects of Agent Orange/dioxin
- birth outcome
- other health effects in women and children
- cancer risks
- non-cancer health outcomes
- global levels of dioxins and related compounds in human tissues
- methods for reducing human body burdens
- environmental effects of Agent Orange/dioxin
- environmental levels in Vietnam, the United States and elsewhere
- environmental fate and transport
- environmental remediation
- ecological effects on animals and plants

Simultaneous Breakout Sessions

Human Health Effects
Reproduction and Development

Human Exposure and Body Burden Reduction
Cancer
Immunology
Endocrinology

Environmental Effects
Environmental Sampling: Methods and Results
Clean up and Restoration: Methods and Techniques
Fate and Transport
Ecosystems Impacts

Poster Sessions

Posters will facilitate further discussion and examination of topics related to the current scientific understanding of the health and environmental effects of Agent Orange/dioxin. If you are interested in presenting a poster, please check "request for instructions for abstract submission and poster instructions" when responding for registration and/or additional information.

Special Sessions

Educational training sessions and/or field trips are being explored and would be scheduled to precede the Conference Opening on Sunday, March 3.

Conference Organizing Committee

United States

- Dr. Christopher Portier, National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH)
- Dr. Walter Rogan, NIEHS, NIH
- Dr. William Farland, US EPA
- Dr. Drue Barrett, Centers for Disease Control and Prevention
- Dr. Linda Schwartz, School of Nursing, Yale University
- Dr. Brenda Eskenazi, University of California - Berkeley
- Ms. Sandra Lange, NIEHS, NIH (US Coordinator)

Vietnam

- Prof. Dr. Le Ngoc Trong, Vice Minister, Ministry of Health
- Dr. Nguyen Ngoc Sinh, Director General, National Environment Agency
- Dr. Nguyen Van Tuong, Hanoi Medicine College, Ministry of Health
- Dr. Tran Van Phuong, Ministry of Health (Vietnamese Coordinator)
- Mr. Tran Van Tu, Ministry of Foreign Affairs
- Dr. Dang Vinh Thien, Vietnam Association on Conservation of Nature and Environment Protection
- Dr. Tran Manh Hung, General Association of Medicine and Pharmacy of Vietnam

Additional conference and registration information can be obtained by contacting the NTP Office of Liaison and Scientific Review, NIEHS, P.O. Box 12233, MD: A3-01 Research Triangle Park, NC 27709 USA, T: 919-541-0530; F: 919-541-0295; liaison@starbase.niehs.nih.gov

Background information on the U.S.-Vietnam Cooperative Research Program can be found at: http://www.niehs.nih.gov/external/usvcrp/home.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 online 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 Information Service (EHIS) maintains the library of NTP Technical Reports and adds new reports as available. To gain access to these reports, contact EHIS online at: http://ehis.niehs.nih.gov or call 1-800-315-3010 or 919-541-3841.