The National Toxicology Program

UPDATE

October 2002

Headquartered at the National Institute of Environmental Health Sciences NIH

NTP Collaborations

The NTP has developed or is developing formal collaborations with a number of non-U.S. agencies to establish efficient means to avoid duplication of efforts in toxicology testing. The Ramazzini Foundation (Bologna, Italy) has been conducting chronic exposure carcinogenicity studies in Sprague-Dawley rats for over 25 years. The NTP has begun collaboration with the Ramazzini Foundation to create sufficiently similar protocols, similar quality assurance and similar reporting between the two agencies. The first phase of this collaboration has begun with the Ramazzini Foundation using the NTP's data acquisition and analysis databases to store and analyze some of its data. In addition, a researcher from the Ramazzini Foundation is visiting NIEHS for two years to gain expertise in the use of molecular biology tools in cancer testing.

The World Health Organization (WHO) International Electric and Magnetic Fields (EMF) Project has been coordinating research on the health effects of EMF including those generated by cellular telephone technologies. The NTP is developing exposure systems and study designs to test for potential toxicity from radio-frequency emissions in the cellular range. The NTP has set-up a collaboration with the WHO to coordinate its activities with other groups world-wide and to facilitate workshops that keep all interested parties updated on current research.

The Korean Government has begun the development of a National Toxicology Program. The lead scientists for this program visited the NIEHS September 4-11 to meet with NTP scientific staff and attended the September 5-6 NTP Board of Scientific Counselors Technical Reports Review Subcommittee meeting. Our NTP scientists will be visiting Korea in November to formalize discussions on these collaboration and coordination efforts.

Visit NTP at APHA – Booth #948

The NTP will exhibit at the 130th Annual Meeting & Exposition for the American Public Health Association being held November 9-13, 2002, at the Pennsylvania Convention Center in Philadelphia. The Expo, with over 600 booths, is a central gathering place for information, state-of-the-art products, and services geared to public health professionals.

The NIEHS and *Environmental Health Perspectives* (EHP), the NIEHS scientific journal, will also exhibit at the Expo. Be sure to check out booths #948 (NTP), #946 (NIEHS) and #949 (EHP).

What's inside …

NTP Board of Scientific Counselors

Technical Reports Review Subcommittee Met September 5-6

The Technical Reports Review Subcommittee met September 5-6, 2002, at the National Institute of Environmental Health Sciences (NIEHS) to review technical reports for five long-term toxicology and carcinogenesis studies. These studies used Fisher 344/N rats and/or B6C3F1 mice. This is a standing subcommittee of the NTP Board; a roster is available on the NTP web site (http://ntp-server.niehs.nih.gov, select Mission).

Five categories of evidence of carcinogenic activity are used in the NTP Technical Report (TR) series to summarize the strength of the evidence observed in each experiment: two categories for positive results (clear evidence and some evidence); one category for uncertain findings (equivocal evidence); one category for no observable effects (no evidence); and one category for experiments that cannot be evaluated because of major flaws (inadequate study). The Subcommittee's recommendation for each report is listed below.

- ***trans*-Cinnamaldehyde (TR 514)** – flavoring and fragrance ingredient; the primary component of cinnamon oil.

No evidence of carcinogenic activity in male and female rats and in male and female mice.

- **Decalin (TR 513)** – industrial solvent for fats, resins, oils, waxes, and naphthalene; a substitute for turpentine; a constituent of motor fuels and lubricants.

Clear evidence of carcinogenic activity in male rats, no evidence of carcinogenic activity in female rats and in male mice, and equivocal evidence of carcinogenic activity in female mice.

- **Dipropylene glycol (TR 511)** – component of air and room fresheners, household cleansers, cosmetic formulations, auto paints, and antifreeze.

No evidence of carcinogenic activity in male and female rats and in male and female mice.

- **Elmiron® (TR 512)** – used in the treatment of thrombosis and hyperlipidemia and for relief of urinary bladder pain associated with interstitial cystitis.

No evidence of carcinogenic activity in male and female rats and some evidence of carcinogenic activity in male and female mice.

- **Urethane + ethanol (TR 510)** – Urethane is a by-product of fermentation and occurs in breads and alcoholic beverages. The effect of urethane was studied in combination with alcohol (ethanol).

Urethane: clear evidence of carcinogenic activity in male and female mice.
Ethanol: the study design was inadequate to determine the carcinogenic activity in male and female mice.
Urethane + ethanol: weak evidence of an interaction of ethanol on the carcinogenicity of urethane in mice.

The Subcommittee also reviewed and discussed two additional reports that evaluated the effect of topical exposure to pentaerythritol triacrylate and trimethylolpropane triacrylate in the transgenic mouse model Tg.AC. The NTP withdrew consideration by the Subcommittee of the conclusions for carcinogenic activity and asked them instead to discuss broad issues regarding the interpretation and reporting of these studies. The NTP plans to report on these studies in its Toxicity Report series.

- **Pentaerythritol triacrylate** – representative multifunctional acrylate used in photocurable inks and coatings and as an ingredient of acrylic glues, adhesives, and sealants.

- **Trimethylolpropane triacrylate** – representative multifunctional acrylate used in photocurable inks and coatings, acrylic glues, paper and wood impregnates, wire and cable extrusion, and polymerconcrete composites.

Abstracts and data from NTP Technical Reports are available from the NTP web site (http://ntp-server.niehs.nih.gov, select NTP Study Information). Once completed, these reports can be procured from Environmental Health Perspectives (http://ehp.niehs.nih.gov or 800-315-3010) in print and electronic formats.

Summary minutes from the Subcommittee will be available in the future from the NTP web site (select Meetings) or Central Data Management (919-541-3419 or cdm@niehs.nih.gov).

Meeting of the Report on Carcinogens Subcommittee Set

The Report on Carcinogens (RoC) Subcommittee, a standing subcommittee of the NTP Board, provides independent scientific peer review of substances (including agents, mixtures, and exposure circumstances) nominated for listing in or delisting (removal) from the RoC.

The RoC Subcommittee is scheduled to meet on November 19-20, 2002, in Bethesda, Maryland at the Hyatt Regency Bethesda, One Bethesda Metro Center, 7400 Wisconsin Avenue to review nominations to the 11th Edition of the RoC. This meeting is open to the public and time will be set aside for public comments on each of the nominations. Oral and written public comments are welcome on any nomination being reviewed at this meeting (see below for information about providing public comments).

Tentatively planned for review are:

- **1-Amino-2,4-dibromoanthraquinone**
- **Cobalt sulfate heptahydrate**
- **Diethanolamine**
- **Naphthalene**
- **Nitrobenzene**
- **Nitromethane**
- **Selected Heterocyclic Amines (3 nominations)**
  - **2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ)**
  - **2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx)**
  - **2-Amino-1-methyl-6- phenylimidazo[4,5-*b*]pyridine (PhIP)**
- **4,4'-Thiodianiline**

Meeting plans were published in the Federal Register (September 20, 2002: Vol. 67, No. 183 pages 59301 – 59303) and this notice is posted on the NTP web site (http://ntp-server.niehs.nih.gov),

The background documents for the nominations are posted on the NTP web site (select Report on Carcinogens) or available, as supplies last, in hardcopy from Dr. C.W. Jameson (see below).

Contact information: Dr. C.W. Jameson, Head, Report on Carcinogens, NIEHS, 79 TW Alexander Drive, Room 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

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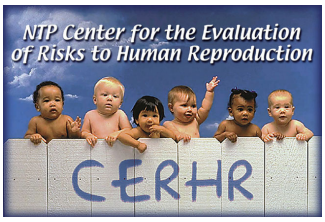
Public Comments at NTP RoC Subcommittee Meeting

The NTP invites written and oral comments at the November 19-20 meeting of the NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee. Persons are asked to register by November 4, 2002, for making oral comments. Seven minutes will be allotted for each oral public presentation and, if time permits, may be extended up to 10 minutes. Each organization is allowed one time slot for an oral presentation per nomination to the RoC. Speakers are requested to provide, if possible, a written copy of their statement by November 4th electronically or by mail or fax to the NTP Executive Secretary (contact information below) for distribution to the RoC Subcommittee prior to the meeting. Persons can register on-site to give oral comments; however, time allowed for presentations by on-site registrants may be less then that for pre-registered speakers and will be determined by the number of persons registered. If registering on-site to speak, the presenter is requested to provide 25 copies of the statement.

Written comments can supplement or be submitted in lieu of an oral presentation and should be received by November 4th to allow time for review by the RoC Subcommittee members and NTP staff. Registration to present oral comments, submission of written comments, and questions about NTP Board meetings should be directed to the NTP Executive Secretary. Information about public comments at this meeting was published in the Federal Register (September 20, 2002: Vol. 67, No. 183 pages 59301 – 59303); this notice is posted on the NTP web site (http://ntp-server.niehs.nih.gov).

Contact information: NTP Executive Secretary, NTP Liaison and Scientific Review Office, NIEHS, P.O. Box 12233, MD A3-01, 111 TW Alexander Dr., Research Triangle Park, NC 27709; T: 919-541-0530; F: 919-541-0295; liaison@starbase.niehs.nih.gov

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



The CERHR serves as an environmental health information resource. It provides 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.

The CERHR conducts reviews on man-made or naturally occurring chemicals or chemical mixtures and welcomes the nomination of chemicals for future evaluations from all interested individuals and groups at any time. Nominations should include the chemical's name, Chemical Abstract Service (CAS) registry number (if known), and a justification for the nomination. As possible, information on the chemical and its potential reproductive or developmental toxicity is also requested. Nominations can be submitted through the CERHR web site (http://cerhr.niehs.nih.gov, select Nominate a Chemical) or directly to the CERHR (contact information below). The CERHR also invites submission, at any time, of recent, relevant toxicology or human exposure studies for chemicals under evaluation.

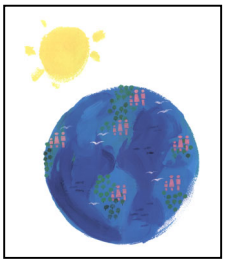
Future Review of Ethylene Glycol and Propylene Gycol

CERHR will hold an expert panel meeting, tentatively scheduled for February 11-13, 2003, in Alexandria, Virginia, to evaluate the potential reproductive and developmental toxicities of ethylene glycol and propylene glycol. Additional details will be published in the Federal Register in the near future.

Ethylene glycol is a high-production-volume chemical used chiefly in antifreeze for heating and cooling systems. Propylene glycol, similar in structure to ethylene glycol, is used as an antifreeze, de-icing solution, and in various paints and coatings. Propylene glycol is also approved for use in various food additives, drugs, and cosmetics.

Contact information: Dr. Michael Shelby, Director, CERHR, NIEHS, P.O. Box 12233, MD EC-32, 79 TW Alexander Drive, Research Triangle Park, NC 27709; T: 919-541-3455; shelby@niehs.nih.gov

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



The NICEATM and the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) collaborate to facilitate development, validation, scientific review, and regulatory acceptance of new and improved test methods, including methods that will reduce, refine, or replace animal use.

SACATM to Meet

The first meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is scheduled for December 5, 2002. As details for this meeting are worked out, they will be posted on the NTP (http://ntp-server.niehs.nih) and NICEATM/ICCVAM (http://iccvam.niehs.nih.gov) web sites and announced in the Federal Register.

In response to the ICCVAM Authorization Act of 2000, the NIEHS established the new federally chartered advisory committee SACATM. This committee will provide advice on the statutorily mandated activities of the ICCVAM and on activities of the NICEATM, including ways to foster partnerships and communication with interested parties. A copy of the charter is posted on the NICEATM/ICCVAM web site (http://iccvam.niehs.nih.gov) or available from

the NTP Liaison and Scientific Review Office (contact information at bottom of page 5).

Joint In Vitro Validation Study

In collaboration with the EPA and the European Centre for the Validation of Alternative Methods (ECVAM), NICEATM has begun a multi-laboratory validation study on *in vitro* methods for estimating acute oral toxicity of chemicals. This effort will standardize and evaluate 2 Neutral Red Uptake assays using BALB/c 3T3 and Normal Human Keratinocyte cells. The study will determine the usefulness of *in vitro* data for estimating starting doses for animal studies that may further reduce animal use and mortality. The study will also generate a high quality database of basal cytotoxicity data that can be used to determine additional specialized assays necessary for improving the accuracy of *in vitro* assessments.

Seventy-two chemicals representing the six acute toxicity hazard classifications in the Globally Harmonized Classification Scheme will be tested. Two U.S. laboratories and one European laboratory are participating. Testing will proceed in three phases designed to facilitate standardization and optimization of the test method protocols before the majority of chemicals are tested. Phase I began in August 2002. The program anticipates that all testing will be completed by December 2003.

Endocrine Disruptor Screening Assays – Availability of Panel Report

The NICEATM in conjunction with the ICCVAM held an expert panel meeting, May 21-22, 2002, to assess the validation status of several *in vitro* assays, including estrogen receptor (ER) and androgen receptor (AR) binding assays and ER and AR transcriptional activation assays, proposed for use in the U.S. Environmental Protection Agency's Endocrine Disruptor

Screening Program (see NTP Update, March 2002).

The NICEATM announces the availability of the report from that meeting, "The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Expert Panel Report on the Current Status of *In Vitro* Test Methods for Detecting Endocrine Disruptors," and a list of substances proposed by the ICCVAM Endocrine Disruptor Working Group (EDWG) for the validation of *in vitro* endocrine disruptor screening methods. The report and list of substances are available electronically on the ICCVAM/NICEATM web site or in hardcopy from NICEATM (see contact information below). The public is invited to submit written comments on the report and the proposed list of substances. A formal announcement will be made in the Federal Register and this notice will be posted on the ICCVAM/NICEATM web site.

The expert panel report, the final list of proposed substances for validation, and the ICCVAM recommendations will be compiled into a report and forwarded to the Director of the NIEHS and the heads of appropriate Federal agencies and posted on the ICCVAM/ NICEATM web site. The NIEHS and the Federal agencies will consider these recommendations and comments to determine if and how (chemicals and laboratories) additional validation studies will be conducted. If a decision is made to conduct validation studies on *in vitro* ER and AR assays, an independent peer review panel will be convened to review the results of these studies and to propose minimum performance criteria.

Contact information: Dr. William Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, MD EC-17, 79 TW Alexander Dr., Research Triangle Park, NC 27709; T: 919-541-2384; niceatm@niehs.nih.gov

How to Subscribe to the NTP List-server

The NTP Update is issued approximately 4 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 or send email 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-server.niehs.nih.gov.

The Environmental Health Perspectives (EHP) maintains issues of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports and adds new reports as available. To gain access to these reports, contact EHP online at: http://ehp.niehs.nih.gov or call 1-800-315-3010 or 919-541-3841.

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; F: 919-541-0295; liaison@starbase.niehs.nih.gov

Revised Booklet Available: Questions and Answers about EMF

Under the Electric and Magnetic Fields (EMF) Research and Public Information Dissemination (RAPID) Program, the NIEHS conducted a 6-year (1993-1999), multi-faceted and multi-disciplinary program of research, communication and evaluation on the potential health hazard(s) associated with exposure to EMF from the generation, transmission or use of electric power. At the conclusion of this program, the NIEHS prepared a report for the Congress (http://www.niehs.nih.gov/emfrapid).

As part of the EMF RAPID Program, the NIEHS and the U.S. Department of Energy published a booklet, "Questions and Answers about EMF," in 1995 that explained basic principles of EMF, provided an overview of the results of major research studies, and summarized conclusions of expert panel reviews. The NIEHS has now updated that booklet to include information available since 1999. The booklet identifies some sources of EMF exposures and some simple steps for limiting exposure. Hopefully it will be useful in helping the public reach its own conclusions about EMF-related health effects.

The booklet is available free-of-charge on the Internet (http://www.niehs.nih.gov/emfrapid) or in hardcopy, as supplies last (CDM, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709; cdm@niehs.nih.gov).

NTP Testing Program

The NTP has a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern. The program continually solicits and welcomes the nomination of agents for study from all interested groups, such as labor unions, academia, federal and state agencies, industry, and the general public.

The NTP Office of Chemical Nomination and Selections handles the receipt of nominations and comments on testing initiatives or nominations (contact information below). As possible, the NTP asks that nominators provide background information describing the agent's use and production, possible adverse health effects or concerns associated with exposure, and the chemical name and Chemical Abstract Service (CAS) registry number. Details about the nomination process are available on the NTP web site (http://ntp-server.niehs.nih.gov, select How to Nominate Substances) or by contacting the NTP Office of Chemical Nomination and Selection.

All nominations undergo several levels of review before the NTP selects agents for study and designs and implements toxicological studies. 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 agents evaluated.

Current areas of focus in the NTP's testing program include potential safety issues associated with herbal medicines, radio-frequency radiation emissions from cellular telephones, hexavalent chromium in drinking water, photoactive chemicals, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-disrupting agents.

Contact information: Dr. Scott Masten, Office of Chemical Nomination and Selection, NIEHS, P.O. Box 12233, MD A3-07, 111 TW Alexander Dr., Research Triangle Park, NC 27709; T: 919-541-5710; masten@niehs.nih.gov