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Toxicology  
Program

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*We are pleased to provide the following information to update our readers on programs and initiatives of the NTP, as well as to highlight meetings open to the public scheduled for the remainder of 1999. We invite public input and participation in all aspects of our programs.*

*We also sadly announce the recent death of the NTP's first director, Dr. David R. Rall ([see attachment](#))*

- [Public Meeting on RoC Process Rescheduled \(October 21-22\)](#)
- [NTP Board to Review new RoC Nominations \(January 21-21, 2000 \(rescheduled from December 16-17\)\)](#)
- [Review of Phthalates Continues \(December 15-17\)](#)
- [Evaluation of FETAX Assay: Public Input Requested](#)
- [NTP Requests Input and Nominations for New Chemicals for Study](#)

*Many of you have subscribed to our "list-server" and are receiving these "Updates" and news announcements electronically. If you wish to discontinue the paper mailings, please let us know at [cdm@niehs.nih.gov](mailto:cdm@niehs.nih.gov) To subscribe to the list-server write to <http://ntp-server.niehs.nih.gov> or send email to [ntpmail-request@list.niehs.nih.gov](mailto:ntpmail-request@list.niehs.nih.gov) with the word "subscribe" as the body of the message.*

Visit the NTP Exhibit at the American Public Health Association (APHA) Annual Meeting November 7-10, 1999 in Chicago, Illinois (Booth #398B)

## **NTP Public Meeting on the Report on Carcinogens (RoC) Has Been Rescheduled**

A public meeting originally scheduled for September 15 and postponed due to weather conditions posed by Hurricane Floyd has been rescheduled for October 21 and 22 at the DoubleTree Hotel Rockville (1750 Rockville Pike, Rockville, MD). Fifty-four speakers registered for the September 15 meeting. The meeting has been rescheduled for two days to better accommodate the registered and additional speakers and to ensure the opportunity for open discussion of issues that are raised.

The meeting provides all interested parties an opportunity to express their views about the review process and/or the evaluation criteria that have been used in the reviews of both the 8th and the 9th RoCs. The process used for reviewing nominations for listing or delisting in the Reports involves multiple levels of scientific review and opportunities for public comment and participation. Comments have been received from individuals concerning the reviews for the 8th and 9th Reports and have identified several areas where possible changes should be considered. The public meeting will provide an opportunity for dialogue regarding the process and an opportunity for all persons with an interest to provide their insights as well as their comments on the views expressed by others. Attendance at the meeting is limited only by the space available.

### **Meeting Agenda**

The meeting will begin at 9 am each day, with on-site registration at 8:30 am on October 21. The meeting will conclude at 5 pm on October 21 and at 5 p.m. October 22 or the conclusion of the public comment and discussion, if sooner.

NTP staff will briefly summarize the process and the listing criteria from approximately 9:00 am to 10 am on October 21. The remainder of the time will be devoted to public comments by all interested parties and discussion of issues raised. Dr. Bernard Goldstein, Director of the Environmental and Occupational

Health Sciences Institute of Rutgers and the University of Medicine and Dentistry of New Jersey, will serve as chair and moderator for the day. Dr. Goldstein, with the assistance of NTP Board of

Scientific Counselors members, will identify issues raised by speakers and lead discussion sessions on the issues throughout the meeting.

### **Public Input Encouraged**

Meeting attendees are invited to make formal presentations, participate in the discussions, and/or submit written comments.

**Oral comments:** Each speaker will be asked to identify their sponsoring organization (if any). The time allotted for each presentation will be largely dependent upon the number of individuals who register to speak at this two-day meeting. Speakers will be registered and assigned time on a first-come, first-serve basis. Registration to speak at this meeting will be accepted until the 9 a.m. start of the meeting. It is anticipated that at least 10 minutes will be available for each presenter to address the panel. When oral comments are read from printed copy, it is requested that 10 copies of the text be provided when registering at the meeting to be distributed to the panel members and to supplement the record of the meeting.

**Written comments** are welcome and can be sent to Ms. Angie Wilson, NIEHS, Bldg. 101, P.O. Box 12233, A3-07, Research Triangle Park, NC 27709 or at [wilson9@niehs.nih.gov](mailto:wilson9@niehs.nih.gov). Written comments must include name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any). All comments previously submitted for the

September 15 meeting will be considered.

### **Registration for the Meeting**

Pre-registration is encouraged to facilitate planning. Please notify Ms. Angie Wilson by mail at NIEHS, Building 101, Room A328, P.O. Box 12233, Research Triangle Park NC 27709, by phone at (919) 541-3971, by FAX at (919) 541-0295, or by e-mail at [wilson9@niehs.nih.gov](mailto:wilson9@niehs.nih.gov). Please indicate if you wish to make an oral presentation. On site registration will be available the morning of October 21, 1999 from 8:30 am to 9:00 am. If possible, those wishing to speak should provide a written copy of their statement or talking points before the October 21 meeting, to assist the Chair and Board Members in identifying issues for discussion and to supplement the record of the meeting. Those registering on site are requested to bring 10 copies of their statement or talking points. Written statements should supplement and may expand on the oral presentation, or may be submitted in lieu of an oral presentation. When registering to comment, please provide your name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any).

*Additional background including "Questions & Answers on the RoC" can also be accessed on-line at:*  
<http://ntp-staff.niehs.nih.gov/NewHomeRoc/AboutRoC.html>



### **January 20-21: [NTP Board to Review Nominations for the 10th RoC](#)**

The NTP Board of Scientific Counselors will review the first group of substances being considered for listing/delisting in the 10th edition of the RoC on January 20-21, 2000 (originally planned for December 16-17, 1999). The meeting will take place at the Crystal City Marriott in Arlington, Virginia.

### **Meeting Agenda**

The following 11 substances or exposure circumstances will be reviewed:

- Beryllium and Beryllium Compounds (CAS No. 7440-41-7)
- 2,2-bis-(bromomethyl)-1,3-propanediol /3296-90-0
- 2,3-Dibromo-1-Propanol /96-13-9
- Dyes Metabolized to Dimethoxybenzidine (Dimethoxybenzidine Dyes as a Class)
- Dyes Metabolized to Dimethylbenzidine (Dimethylbenzidine Dyes as a Class)
- IQ (2-Amino-3-methylimidazo[4,5-f]quinoline) /76180-96-6
- Styrene-7,8-oxide /96-09-3
- Vinyl Bromide /593-60-2
- Vinyl Fluoride /75-02-5

The meeting agenda will include opportunity for public comments on all substances.

### **Background Summary Documents**

Background documents on each nomination to be reviewed will be available to the public by November 1, 1999. These background documents include all available data relevant to the criteria for inclusion or removal of candidate substances or exposure circumstances in the RoC.

*Draft background documents can be accessed on the web at:*  
<http://ntp-staff.niehs.nih.gov/NewHomeRoc/AboutRoc.html>

*Paper copies can be obtained from:*

*Dr. C. W. Jameson*

National Toxicology Program  
79 Alexander Drive, Bldg. 4401  
Room 3127, MD EC-14  
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### **Registration for the Meeting**

Individuals wishing to comment on any of the nominations to be discussed at this meeting should contact Ms. Angie Wilson at the address shown below. The deadline for receipt of written comments to be considered for this meeting will be December 1, 1999. An agenda for the meeting, roster of committee members, and additional information regarding the meeting will be available from Ms. Wilson by November 1. Ms. Wilson can be reached at NIEHS/PO Box 12233, Research Triangle Park, NC 27709, phone (919) 541-3971 or fax: (919) 541-0295 and by email: [wilson9@niehs.nih.gov](mailto:wilson9@niehs.nih.gov)

Additional information on the nominations and the RoC can be found at <http://ntp-server.niehs.nih.gov> or in the July issue of the Update.



## **Review of Phthalates**

### **Background**

The NTP Center for the Evaluation of Risks to Human Reproduction was established to provide timely and unbiased, scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction, including development, caused by agents to which humans may be exposed. The first evaluation of the Center is a Review of Phthalates.

### **The Phthalates Under Review are:**

Butyl benzyl phthalate, di(2-ethylhexyl) phthalate, di-isodecyl phthalate, di-isononyl phthalate, di-n-butyl phthalate, di-n-hexyl phthalate, and di-n-octyl phthalate. The phthalates were selected based on their high production volume, extent of human exposures, use in children's products, and/or published evidence of reproductive or developmental toxicity.

The Center conducted its first Expert Panel meeting August 17-19, 1999 in Alexandria, Virginia. Fifteen scientific experts met to evaluate literature on the reproductive and developmental toxicity of the seven phthalate esters listed above. In addition to their own deliberations, the Panel heard presentations from 3 groups (Health Care Without Harm, Chemical Manufacturers Association, American Council on Science and Health) that had conducted reviews of the potential health effects of phthalates, as well as comments from the public. The product of the expert panel will be a scientific monograph on each of the selected phthalates addressing the possible reproductive and developmental toxicity of these chemicals and the potential for human hazard. The monographs will include data evaluations, an integrated evaluation of the data, and a consensus statement on each chemical evaluated. These monographs will be published in Environmental Health Perspectives and will be available on the web at <http://cerhr.niehs.nih.gov/>

Prior to this meeting, panelists reviewed existing literature in their areas of expertise and provided other Panel members with their summary evaluations. This effort involved the review of nearly 1,000 reports or publications covering animal and human studies in general, developmental, and reproductive toxicity and information on human exposure. During the meeting, the Panel began the process of writing integrated evaluation documents that address the nature and consistency of the literature reviewed, relevancy of experimental models to humans, and

human exposure. The work of the Panel was not completed. Integrated evaluation documents were drafted and reviewed by the full Panel for the following 3 phthalates: butyl benzyl phthalate, di(2-ethylhexyl)phthalate, and di-n-octyl phthalate. The integrated evaluations on the four remaining chemicals (di-isodecyl phthalate, di-isononyl phthalate, di-n-butyl phthalate, and di-n-hexyl phthalate) are being revised or written and will be discussed when the Expert Panel is reconvened.

**The Phthalate Panel Members are:** Robert Kavlock, PhD (Chair) EPA/ORD; Kim Boekelheide, MD, PhD, Brown University; Robert Chapin, PhD, NIEHS; Michael Cunningham, PhD, NIEHS; Elaine Faustman, PhD, University of Washington; Paul Foster, PhD, Chemical Industry Institute of Toxicology; Mari Golub, PhD, Cal/EPA; Rogene Henderson, PhD, Inhalation Toxicology Research Institute; Irwin Hinberg, PhD, Health Canada; Ruth Little, ScD, NIEHS; Jennifer Seed, PhD, EPA/OPPT; Katherine Shea, MD, University of North Carolina; Rochelle Tyl, PhD, Research Triangle Institute; Paige Williams, PhD, Harvard University; and Timothy Zacharewski, PhD, Michigan State University.

### **Phthalate Expert Panel Continues Review, December 15-17**

The integrated evaluations on the four remaining chemicals (di-isodecyl phthalate, di-isononyl phthalate, di-n-butyl phthalate, and di-n-hexyl phthalate) will be discussed at the Expert Panel meeting being held December 15-17. Following agreement on the integrated evaluations, consensus summary statements will be developed by the Panel members for each of the seven phthalates. These narrative statements will reflect a consensus opinion of the Panel as to the developmental and reproductive toxicity of these chemicals in experimental models and will address the potential significance of these results to human reproduction and development.

The review will take place from December 15-17 at Hawthorn Suites Hotel (300 Meredith Drive, Durham, NC 27713). The entire meeting is open to the public. Attendance will be limited only by the availability of space.

### **Preliminary Agenda**

#### **December 15 (Beginning at 8:30 a.m.)**

Opening remarks by Dr. Michael Shelby, NIEHS and Director of the Center, Dr. John A. Moore, CERHR, and Dr. Robert Kavlock, EPA and Chair of the Expert Panel on Phthalates.

The three previously written integrated evaluations and the four new ones (di-isodecyl phthalate, di-isononyl phthalate, di-n-butyl phthalate, and di-n-hexyl phthalate) will be discussed in plenary session. Following agreement on the integrated evaluations, panel discussion will follow to identify areas where there is broad panel agreement as well as issues requiring further discussion by workgroups of the panel.

#### **December 16 (8:30 a.m.)**

The meeting will focus on drafting summary statements on the seven phthalate esters. This will be accomplished through an iterative series of workgroup discussions and plenary sessions.

#### **December 17**

Summary statements reflecting significant conclusions and judgements reached by the panel workgroups for each of the phthalates will be presented, discussed, and agreed to by the entire expert panel in plenary session.

Closing comments.

### **Registration for the Meeting**

Contact:

Ms. Peggy Sheren, CERHR, 1800 Diagonal Road, Suite 500, Alexandria, VA 22314-2808, Phone: (703) 838-9440.

For additional information on the NTP Center and the Phthalates Review see the July 1999 Update or the web at: <http://cerhr.niehs.nih.gov/>



## **Evaluation of the Frog Embryo Teratogenesis Assay--Xenopus (FETAX)**

### **Background**

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), with participation by 14 Federal regulatory and research agencies and programs, was established in 1997 to facilitate cross-agency communication and coordination on issues relating to validation, acceptance, and national/international harmonization of toxicological test methods. The Committee seeks to promote the scientific validation and regulatory acceptance of toxicological test methods that will enhance agencies' ability to assess risks and make decisions, and that will refine, reduce, and replace animal use whenever possible. The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), provides administrative and technical support for ICCVAM, and serves as a communication and information resource. NICEATM and ICCVAM collaborate to carry out related activities needed to develop, validate, and achieve regulatory acceptance of new and improved test methods applicable to Federal agencies.

### **Evaluation of FETAX**

ICCVAM and NICEATM are currently planning an Expert Panel Meeting to assess the current validation status of the Frog Embryo Teratogenesis Assay-Xenopus (FETAX), a method proposed for evaluating the developmental toxicity potential of chemicals (Bantle JA, 1995, FETAX--A Developmental Toxicity Assay Using Frog Embryos, Fundamentals of Aquatic Toxicology, 2nd ed., G.M. Rand, ed, Taylor and Francis, USA, pp. 207-230). Possible applications of FETAX to human health and environmental assessments may include screening and prioritizing compounds for further testing, evaluating complex mixtures and environmental samples, and as supplemental information in a weight-of-evidence evaluation of toxicity hazards. NICEATM is preparing a background document summarizing the initial studies and the performance characteristics of FETAX. The Expert Panel will evaluate the conclusions presented in the background document and address the potential uses of FETAX. The Expert Panel will address additional test method development and validation efforts that should be considered that might further enhance and characterize the usefulness of FETAX for various applications and other relevant aspects of the Xenopus model.

### **Request for Data**

The NTP Center solicits data and information from completed, ongoing, or planned studies using or evaluating FETAX. Information should address the criteria for validation and regulatory acceptance provided in NIH publication 97-3981, "Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods" (<http://ntp-staff.niehs.nih.gov/htdocs/ICCVAM/iccvam.html>). Where possible, data and information should adhere to the guidance provided in the document, "Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to ICCVAM" (<http://iccvam.niehs.nih.gov/doc1.htm>), which is available on request from the NTP Center at the address provided below. Information submitted in response to this request will be incorporated into the background material provided to the Expert Panel. Meeting information, including date, location, and availability of the background document, will be announced.

**Correspondence should be directed to:**

Dr. William S. Stokes

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods,  
Environmental Toxicology Program  
NIEHS/NTP, MD EC-17, PO Box 12233, Research Triangle Park, NC 27709;  
919-541-3398 (phone); 919-541-0947 (fax); iccvam@niehs.nih.gov (e-mail).



## **NTP Requests Input and Nominations for New Chemicals for Study**

The NTP requests nominations of chemicals and agents for study from all 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 toxicity and determine possible adverse effects that may be associated with human and environmental exposure. Health-related effects addressed include chronic toxicity and carcinogenicity, as well as reproductive, developmental, genetic, immunological and neurological toxicity. Studies are also designed to address data gaps for specific chemicals such as fate and mechanisms of chemical toxicity and other effects that may be of human health concern. Data developed by NTP is critical to assessments of human health hazards associated with exposure to those chemicals and agents studied. NTP also supports an active program to develop and validate new and improved assays for chemical toxicity and assays that eliminate or minimize the use of laboratory animals.

Significant time and resources are consumed by the selection and testing of a single substance, so that each nomination must be considered carefully before final selection for NTP testing. Chemicals or agents for which a significant portion of the population is known to be exposed and for which there is a lack of adequate toxicological information available are the best candidates for study. All submitted 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 will consider each nomination as it is received. Information received supporting each nomination will be supplemented with an additional literature search, and all material will be carefully reviewed by the NIEHS Nomination Faculty to establish priority for study. The nominator will be informed of the status of his/her nomination as it moves through the selection and testing process. In addition to formal nominations for study, comments on testing directions and priorities are welcome.

**Please send all nominations and relevant information to:**

Dr. Scott Masten  
Office of Chemical Nomination and Selection (B3-10)  
NIEHS  
P.O. Box 12233  
Research Triangle Park, NC 27709

*Or visit the NTP web page to find more detailed information about the NTP chemical nomination and selection process as well as how to submit nominations online:*

<http://ntp-staff.niehs.nih.gov/NomPage/noms.html>



*Visit the NTP Home Page at <http://ntp-server.niehs.nih.gov>  
NTP Reports Available Online at <http://ehis.niehs.nih.gov>*