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NTP Update

National Toxicology Program

NATIONAL TOXICOLOGY PROGRAM LIAISON AND SCIENTIFIC REVIEW OFFICE

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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

NATIONAL INSTITUTES OF HEALTH

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 in 2000. We invite public input and participation in all aspects of our programs.

- Public Input Solicited on Chemicals and Substances for NTP Study
- Report on Carcinogens (RoC)
- NTP Centers:
  - NTP Center for the Evaluation of Risks to Human Reproduction
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
  - ***New*** NTP Center of Phototoxicology
- Upcoming Meetings:
  - NTP Board of Scientific Counselors
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  - Low Dose Issues for Endocrine Disruptors
  - Risk Assessment Workshop
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- Workshop Summary: The Role of Human Exposure Assessment in the Prevention of Environmental Disease
- Environmental Health Information Service

The NTP Update is issued approximately four times each year. To subscribe to the "list-server" and receive these "Updates" and news 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.

Public Input Solicited on Chemicals and Substances for NTP Study

Nominations for NTP studies undergo several levels of review before toxicological studies are designed and implemented. The Interagency Committee for Chemical Evaluation and Coordination (ICCEC) serves as the first interagency level of review for NTP nominations. Following ICCEC review, input from the public is solicited before further review by the NTP Board of Scientific Counselors and the NTP Executive Committee.

Interested parties are encouraged to provide comments or supplementary information on the nominated substances and on the ICCEC's recommendations for testing or no testing. The Program would welcome receiving toxicology and carcinogenesis information from completed, ongoing, or planned studies, as well as information on current production levels, human exposure, use patterns, or environmental occurrence for any of the following substances:

Chemicals, Substances and Agents Recommended for Testing

1-Bromopropane [106-94-5] and 2-Bromopropane [75-26-3] are halogenated industrial solvents with reported increasing production and use. **Chitosan [9012-76-4]** is a carbohydrate polymer derived from the natural compound chitin and used as a dietary supplement and in other commercial applications. **DNA-based products** are DNA-based therapeutic agents that are manufactured in a variety of forms and have many potential applications in human medicine. **Juglone [481-39-0**] is a napthoquinone compound found naturally in walnuts and used as a component of dietary supplements and in dyes. **Potassium ferricyanide [13746-66-2]** is used in photographic processing and other industrial applications. For **Radio frequency radiation emissions of wireless communication devices**, there is widespread human exposure through the use of cellular phones and concern that current regulations may not be adequately protective of human health.

Chemicals and Substances for Which No Testing is Recommended

Cafestol [469-83-0] and Kahweol [6894-43-5] are natural compounds found in coffee that raise cholesterol levels and modulate metabolic pathways. **Plumbagin [481-42-5]** is a naturally occurring napthoquinone compound similar to Juglone with potential chemopreventive properties.

Chemicals and Substances Deferred for Additional Information

Ethylenebis(tetrabromo-phthalimide) [32588-76-4] is a high production volume industrial flame retardant used in plastics and other polymers. **Terpinolene [586-62-9]** is a high production volume industrial chemical used in foods and fragrances that also occurs naturally. **Tetrabromophthalic anhydride [632-79-1]** is a high production volume industrial flame retardant used in resins and the manufacture of other flame retardants. **Texanol benzyl phthalate [16883-83-3] or [32333-99-6]** is a high production volume industrial chemical used as a plasticizer in vinyl resins and polyurethane foams.

To provide comments or information, please contact Dr. William Eastin at the address given below. Comments are requested by May 1, 2000.

Contact may be made by mail to: Dr. William Eastin, NIEHS/NTP, P. O. Box 12233, Research Triangle Park, North Carolina 27709; by telephone at (919) 541-7941; by FAX at (919) 541-3687; or by email at eastin@niehs.nih.gov

For additional information on the NTP Chemical Nomination and Selection process or to submit new nominations for NTP studies online, visit the NTP Chemical Nomination and Selection web page at: http://ntp-staff.niehs.nih.gov/NomPage/noms.html

Or send 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

Report on Carcinogens (RoC)

Final Comments Requested on Nine Substances Recently Reviewed for Listing/Delisting (10th Report)

In 1999 and early 2000, nine substances were reviewed for listing in the Tenth Report. These substances and the recommendations from three scientific peer reviews of the nominations are shown in the attached table (Table 1).

The NTP solicits final public comment to supplement any previously submitted comments or to provide comments for the first time on any substance identified in the attached table. A 60-day comment period will open upon release of a *Federal Register* notice expected to be published in early April. The NTP will review the recommendations of each of the review committees and consider the public comments received throughout the process in making decisions regarding the NTP's recommendations to the Secretary, Department of Health and Human Services, for listing of the nominated substances in the 10th RoC. The NTP will be making final recommendations in 2001 for these nine substances for listing in, or changing the current listing in the Tenth Report.

Background documents provided to the review committees and the public are available on the web in PDF format at http://ntp-staff.niehs.nih.gov/. Hard copies of these documents are also available upon request from Dr. C.W. Jameson at the address that follows.

Comments Solicited for Additional Eleven Substances to be Reviewed in 2000 (10th Report)

A second group of nominations for possible listing in the Tenth Report will be reviewed during the year 2000. These nominations with their pending review actions are provided in the attached table (Table 2).

The NTP solicits public input on these eleven nominations and asks for relevant information concerning their carcinogenesis, as well as current production data, use patterns, or human exposure information. The NTP also invites interested parties to identify any scientific issues related to the possible listing of a specific nomination in the RoC that they feel should be addressed during the reviews. A 60-day comment period will open with the release of a *Federal Register* notice expected to be published in early April.

Comments or questions concerning the review of substances for the 10th Report should be directed to Dr. C. W. Jameson at the address listed below. Publication of the 10th Report is expected in 2002.

9th Edition of the RoC

The 9th Edition of the RoC is scheduled for publication in 2000. The following 24 substances or exposure circumstances were reviewed for possible listing in or delisting from the 9th RoC:

Alcoholic Beverage Consumption
Boot and Shoe Manufacture and Repair
1,3-Butadiene/106-99-0
Cadmium & Cadmium Compounds/7440-43-9
Chloroprene/126-99-8
Diesel Exhaust Particulates
Dyes Metabolized to Benzidine
(Benzidine Dyes as a class)
Environmental Tobacco Smoke
Ethyl Acrylate /140-88-5 **(Delisting)**
Ethylene Oxide/75-21-8
Isoprene/78-79-5

Methyl-t-Butyl Ether/1634-04-4
Nickel Compounds
Phenolphthalein/77-09-8
Saccharin/218-44-9 **(Delisting)**
Silica, Crystalline (Respirable Size)/7631-86-9
Smokeless Tobacco
Strong Inorganic Acid Mists Containing Sulfuric Acid
Tamoxifen/10540-29-1
2,3,7,8- Tetrachlorodibenzo-p-dioxin (TCDD)/1746-01-6
Tetrafluoroethylene/116-14-3
Tobacco Smoking
Trichloroethylene/79-01-6
Solar Radiation and Exposure to Sunlamps and Sunbeds

A list of the recommendations for listing in or delisting from the 9th RoC can be obtained by accessing the NTP Home Page on the web.

8th Edition of the RoC

The most recent RoC (Report on Carcinogens, 8th Edition) was published in 1998 and may be obtained by contacting the NIEHS Environmental Health Information Service (EHIS) at 919-541-3841, Fax 919-541-0273, e-mail at ehis@nih.gov, or subscribe on-line at http://ehis.niehs.nih.gov/.

Preparation and Review Process for the RoC Receives Public Input

On October 21-22, 1999, the NTP held a public meeting in Rockville, MD to obtain the broadest base of input about the *Report on Carcinogens* and to provide all interested stakeholders an opportunity to express their views about the review process and/or the criteria. Comments received at this meeting identified issues primarily associated with procedures for Report preparation, the cancer classifications of substances, and communication during the entire review process.

Public input identified some areas where modifications can be made that will strengthen the review process. This public input, along with comments received over the past several years, will result in some changes (e.g., earlier public release of the RoC background documents; holding the NTP Board of Scientific Counselors RoC Subcommittee meetings in the Washington, DC area; extending the time for public comment at the Subcommittee meetings). The NTP is moving forward in review of nominations for the 10th Report incorporating process changes to enhance stakeholder involvement and to improve communication and public outreach about the RoC. For other areas of concern, the NTP continues to consider suggested changes, and as appropriate, may make additional modifications in the future.

A transcript of the October 1999 meeting is available in hard copy through a written request to: NTP Office of Liaison and Scientific Review, NTP/NIEHS, P.O. Box 12233, MD A3-07, Research Triangle Park, NC 27709 or fax: 919-541-0295 and on-line at the NTP website: http://ntp-staff.niehs.nih.gov/

Additional information about the RoC is found on the NTP web site at http://ntp-staff.niehs.nih.gov/NewHomeRoc/AboutRoC *Or by contacting:*

Dr. C. W. Jameson
Report on Carcinogens, NIEHS
79 Alexander Drive, Bldg. 4401
Room 3118 P.O. Box 12233
Research Triangle Park, NC 27709
phone: (919)541-4096, fax: (919)541-0144, email: jameson@niehs.nih.gov

NTP Center for the Evaluation of Risks to Human Reproduction

Review of Phthlates

The recently established NTP Center for Evaluation of Risks to Human Reproduction provides scientifically-based, uniform assessments of the evidence for reproductive and developmental toxicity of man-made or naturally occurring chemicals or chemical mixtures.

The Center's first Expert Panel was formed in summer 1999 to evaluate the scientific evidence that seven selected phthalate esters (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) may pose a reproductive and/or developmental risk for exposed humans. Phthalates were chosen 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 Expert Panel has met twice and expects to complete its review in the summer 2000.

The Expert Panel's report, once completed, will be published in *Environmental Health Perspectives* and made available on the Center's web site. NTP staff will then prepare an NTP Center Report that will integrate the findings of the expert panel, a summary of public comments, and discussion of any additional, recent studies. The Center report will be transmitted to appropriate regulatory and research agencies and widely available to the public.

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; Sonia Tabacova,, MD, FDA; Rochelle Tyl, PhD, Research Triangle Institute; Paige Williams, PhD, Harvard University*; and Timothy Zacharewski, PhD, Michigan State University*.

* Unable to attend the second Phthalate Expert Panel meeting.

Center Seeks Comments on Candidate Chemicals for Second Review

A second review will be initiated in the latter part of 2000. Candidate chemicals under consideration are:

1-Bromopropane (106-94-5)
2-Bromopropane (75-26-3)
Dimethyl Methyl Phosphonate (DMMP) (756-79-6)
Ethylene glycol (107-21-1)
Glycol ethers
Glyphosate (1071-83-6)
Methanol (67-56-1)
Nicotine (54-11-5)
Phenol (108-95-2)
Thimerosal (54-64-8)
Toluene (108-88-3)

The Center invites public comment on the these chemicals, including toxicology information from completed or ongoing studies, and information on planned studies, as well as current production data, human exposure

information, use patterns, and environmental occurrence. Written comments received will be considered in the review. Please forward comments and chemical information to:

Dr. John Moore, CERHR, 1800 Diagonal Road, Suite 500, Alexandria, VA 22314-2808, Phone: (703) 838-9440.

Public comment and core committee recommendations will be considered in selecting the next substance(s) for review; once selected a request for additional data and the nomination for members of the Expert Panel will be solicited from the public.

Request for Nominations for Future Reviews

Nominations of chemicals for future evaluations are also encouraged. Any individual or organization may nominate. Nominations should include the chemical name, Chemical Abstract Service registry number (if known), reason for the nomination, and references or articles on the chemical, when possible. The nominator's name, address, telephone number and e-mail address should be included with the nomination. Nominations can be made through the Center's web site or by mail to Dr. John Moore at the address listed above.

Further information about the NTP Center for the Evaluation of Risks to Human Reproduction can be obtained through the Center's web site: http://cerhr.niehs.nih.gov *or by contacting: Michael D. Shelby, Ph.D., P.O. Box 12233, Research Triangle Park, NC 27709. Telephone: 919-541-3455*

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

Background

The NTP Interagency Center provides administrative and technical support and serves as a communication and information resource for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM (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. 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.

Recent Validation Review Activities

- The Murine Local Lymph Node Assay (LLNA), a method for assessing the allergic contact dermatitis of chemicals, was reviewed in September 1998, and the final peer review report was made available in February 1999. The peer review panel concluded that the LLNA was a valid alternative to currently accepted guinea pig test methods and that it also provides for the refinement and reduction of animal use. Additional recommendations on the usefulness and limitations of the LLNA are provided in the peer review report: http://iccvam.niehs.nih.gov/llnarep.htm. EPA, FDA, and OSHA announced their acceptance of the LLNA in October 1999.

- The validation status of Corrositex^{R},an *in vitro* method for assessing the dermal corrosivity potential of chemicals, was reviewed by a peer review panel in January 1999. The panel concluded that the method could be used to assess the corrosivity potential of certain chemical classes and could be used in a tiered approach for the testing of some additional chemical classes. When used in this manner, the method provides for the refinement, reduction, and partial replacement of animal use. The final peer review report was published in June 1999 and agencies announced their acceptance in early 2000. Copies may be requested from the Center and it is also on the internet at: http://iccvam.niehs.nih.gov/corprrep.htm.

Future Test Method Activities

- In May 1998, the US EPA requested that ICCVAM evaluate the Frog Embryo Teratogenesis Assay -- *Xenopus* (FETAX), a method proposed for evaluating the developmental toxicity potential of chemicals. NICEATM has recently been assembling available data on FETAX so that ICCVAM and its expert developmental toxicity working group can proceed with further consideration of the method. The NTP has called for data and information from completed, ongoing, or planned studies using or evaluating FETAX which are included in this background document. The background document, which summarizes the initial studies and the performance characteristics of FETAX, will be evaluated by an Expert Panel in a meeting scheduled for May 16 -- 18, 2000 at the Sheraton Imperial Hotel in Research Triangle Park, North Carolina.

  The Expert Panel Meeting is typically convened to evaluate the validation status of methods following the completion of initial development and pre-validation studies. An Expert Panel is asked to recommend additional validation studies that might be helpful in further characterizing the usefulness of a method and to identify any additional research and development efforts that might enhance the effectiveness of a method.

- The NTP Interagency Center recently requested the submission of data and nominations of expert scientists to participate in an Independent Peer Review Evaluation of the Revised Up-and-Down Procedure for Assessing Acute Oral Toxicity. This procedure is an updated version of the OECD Test Guideline 425, Guideline for the Testing of Chemicals, Acute Oral Toxicity: Up-and-Down Procedure, and is proposed as a substitute for the existing OECD Test Guideline 401 for Acute Oral Toxicity. The UDP has the potential to reduce the number of animals required to classify chemicals for acute oral toxicity as compared to Guideline 401. OECD has proposed that Guideline 401 should be deleted since three alternative methods are now available. Prior to deletion of Guideline 401, US agencies have requested that the Interagency Center conduct an independent peer review of the revised UDP to determine the validity of the method as a replacement for Guideline 401.

  The panel meeting is expected to convene on or about July 25. The Center welcomes the submission of data and information from completed, ongoing, or planned studies using or evaluating the UDP.

For further information on any aspects of the Interagency Center please contact:
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 Center for Phototoxicology

A new FDA-NIEHS Phototoxicology Research and Testing Laboratory is now operational and has been designated an NTP Center for Phototoxicology. The Laboratory is designed to allow study of many types of compounds including cosmetic chemicals and additives, sun block additives, tanning enhancers, skin colorants, and tattoo inks with regard to their effects on UV radiation or simulated solar light-induced toxicity and cancer. The exposure of U.S. citizens to UV radiation or sunlight is increasing through more frequent use of tanning booths to augment skin coloration and the trend toward spending leisure/pleasure time in sunlight-oriented activities (e.g., beach, swimming pools). Research and testing activities at the Laboratory should have a significant impact on the quality of information for public health decisions about the interactions of drugs or other compounds with sunlight.

The FDA has had an ongoing interest in phototoxicity and photocarcinogenicity of therapeutics, cosmetics, devices and food supplements and additives and recently developed a basic photobiology research program. Concurrently the NIEHS developed an intramural photobiology research program and through the National

Toxicology Program, (NTP) has considered nominations requiring phototoxicology testing. The laboratory is located at the FDA's National Center for Toxicological Research in Jefferson, Arkansas. Phototoxicology laboratory studies typically use two types of electromagnetic radiation sources. The most widely used light source is fluorescent lamps specially designed to emit radiation in the UV range (280-315 nm) of the electromagnetic spectrum. In addition, an electromagnetic radiation source that closely mimics the spectrum of terrestrial solar light will be used. The simulated solar light is generated using 6.5 kWatt xenon-arc lights and the light is then filtered through Schotts WG320 quartz glass to achieve a spectrum very similar to terrestrial sunlight. Photocarcinogenicity studies will use the SKH-1 hairless mouse as the primary test animal, and as appropriate, additional test animals (e.g., transgenics) will be used. A standing committee (Toxicology Study Selection and Review Committee) will review experimental protocols and progress of studies.

Interest in developing a jointly operated phototoxicology research and testing laboratory was heightened with FDA's nomination of alpha-hydroxy acids to the NTP. These compounds are primarily used as dermatological chemoexfoliants. Use of alpha-hydroxy acid-containing cosmetics is increasing as the beauty-conscious public seeks drugs or cosmetic preparations that will give a more youthful appearance. Two consequences of chemoexfoliation are the increased proliferation of epidermal epithelial cells and deeper penetration of electromagnetic radiation into the skin; the impact of continued use of this type of treatment on skin cancer risk is not known. Through this facility, studies are now underway to allow quantitative determination of the effect of alpha-hydroxy acids and alpha-hydroxy acid treatment on the induction of mouse skin cancer (SKH-1 hairless mouse) by simulated solar light or fluorescent UV radiation.

For additional information please contact
Dr. Paul Howard, National Center for Toxicological Research
Telephone: (870) 543-7672

Upcoming NTP Board Meetings: May 18th and May 24th

Technical Reports Review Subcommittee

The NTP Board of Scientific Counselors Technical Reports Subcommittee is scheduled to meet May 18, 2000 at the Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, 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 reports to be reviewed are:

chloral hydrate
indium phosphide
***p-p'*-dichlorodiphenyl sulfone,**
naphthalene
sodium nitrite

It is anticipated that the meeting will begin at 8:30 am. The peer review is open to the public and time will be allotted for public comment on the technical reports. Prior to the meeting, draft reports will be available on the Internet for public review through the Environmental Health Information Service (EHIS) at http://ehis.niehs.nih.gov. Printed copies can be obtained, as available, from: Central Data Management, MD E1-02, P.O. Box 12233, Research Triangle Park, NC 27709 (919/541-3419), FAX (919/541-3687), email: cdm@niehs.nih.gov.

For additional information, draft agenda, or to register to make public comments contact Dr. Mary Wolfe, NTP Executive Secretary at 919-541-3971 or wolfe@niehs.nih.gov.

NTP Board of Scientific Counselors

A meeting of the NTP Board of Scientific Counselors is scheduled for May 24, 2000 at the Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, Research Triangle Park, North Carolina. The Board, composed of scientists from the public and private sectors, provides primary scientific oversight to the NTP. This one-day meeting is tentatively scheduled to begin at 8:30 am and is open to the public.

A primary topic on the agenda is the NTP Center for the Evaluation of Risks to Human Reproduction including a discussion of its progress, the phthalates review, and its procedures for nomination, selection, and review of chemicals. Also on the agenda will be updates on current areas for NTP toxicological testing and reports about NTP activities including the *Report on Carcinogens* and peer review of NTP Technical Reports. Time will be allotted during the meeting for public comments.

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

Upcoming Meeting: Low Dose Issues for Endocrine Disruptors

The EPA is implementing an Endocrine Disruptor Screening Program as required by the 1996 Food Quality Protection Act. As part of this program, the EPA is in the process of choosing appropriate assays to use for screening those agents and developing standardized, validated protocols for those assays. A critical aspect of the protocol development is dose-setting, especially since in this instance hormonally active agents may cause effects at doses lower than those normally selected for toxicological testing. The EPA has asked the NTP to establish an independent, scientific panel to review the evidence related to low-dose effects and to consider their implications for the development, validation, and interpretation of test protocols.

Comments are being solicited on the planned scope and process for a proposed peer review of studies bearing on the question of whether endocrine disruptors may cause effects at doses lower than are tested using standard toxicological testing procedures. Nominations for peer reviewers, as well as nominations for studies to be reviewed, are also being solicited. Results from the peer review will help the U.S. Environmental Protection Agency and, in particular the EPA's Endocrine Disruptor Screening Program, determine how to address low-dose questions in endocrine disruptor screening, testing, and hazard assessment.

Details regarding the proposed scope and process for the review can be found on the web at: http://ntp-staff.niehs.nih.gov/htdocs/liason/LowDoseEndocrineFr.html.

To submit materials or for further information please contact: James P. Kariya, Office of Science Coordination and Policy (7203), Office of Prevention, Pesticides, and Toxic Substances, Environmental Protection Agency, 401 M St. SW, Washington, DC 20460; telephone number: (202) 260-2916; e-mail address: kariya.jim@epa.gov.

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

As part of the NTP's efforts to expand and improve risk assessment methods and their application, the NIEHS in cooperation with NIOSH, EPA, the Chemical Manufacturers Association, and the United Auto Workers are sponsoring a workshop. The meeting is scheduled for 16-18 August 2000 at the Silver Tree Hotel, Snowmass Village at Aspen, Colorado. The goals for this workshop include developing a national agenda and support for research on risk assessment methods, identifying and overcoming problems with current methods, and developing partnerships for increasing stakeholder and community input.

Inquiries about the workshop should be directed to Estella Lazenby, KEVRIC Company, 8401 Colesville Road, Suite 610, Silver Spring, Maryland 20910 (t: 301-588-6000 ext 239, f: 301-588-2106).

Transgenics Update

The NTP is participating as part of an industry/government consortium to evaluate a number of alternative assays designed to augment or replace the 2-year rodent bioassay. The effort is being coordinated by the International Life Sciences Institute/ Health and Environmental Sciences Institute (ILSI/HESI), and is comprised of approximately 25 pharmaceutical companies and several government agencies. A set of approximately twenty chemicals is being evaluated in five short-term model systems, including three genetically altered mouse models, the newborn mouse assay, and the Syrian hamster embryo cell transformation assay.

The NTP is performing assays on six chemicals in the Tg.AC model by two routes of administration. Information from all studies is expected to be ready for presentation and evaluation at an ILSI/HESI organized workshop to be held in the Washington DC area in November 2000. The findings from this effort will contribute to an NTP evaluation of the genetically altered mouse models by the Interagency Coordinating Committee on the Validation of Alternative Methods, which is scheduled to take place in 2001.

Workshop Summary: "The Role of Human Exposure Assessment in the Prevention of Environmental Disease"

The NIEHS/NTP in cooperation with multiple federal agency and industry partners organized a workshop 22-24 September 1999 that brought together more than 350 scientists and policy-makers from government agencies, academia, industry, and community groups with an interest in exposure assessment issues.

The goals of the Workshop were to describe current opportunities and challenges in exposure assessment research, provide usable information on disease-specific chemical exposures that will enhance integration of exposure assessment with epidemiology and toxicology studies, and highlight approaches for further research and the development of effective prevention and intervention strategies. Plenary session speakers addressed such issues as exposure analysis methodology, exposure-disease relationships, regulatory and legislative issues, gene-environment interactions, disease prevention and intervention, and some current federal initiatives related to exposure assessment. Breakout sessions were based around five broad topics: Aggregate and Cumulative Exposure and Risk Assessment; Disproportionate Exposures and Disease Impact; Assessing Environmental Influence on Children's Health; Integrating Exposure, Dose, Response, and Susceptibility; and Exposure Assessment in Occupational and Environmental Epidemiology. Some of the general themes and recommendations that emerged from the workshop presentation and discussions include:

- Assessing exposure is complex; sources, pathways, timing, mixed and cumulative exposures must be considered.
- There is a need for bridging disciplines such as toxicology, epidemiology, genetics, and exposure analysis as well as agency missions to address knowledge gaps in exposure assessment.
- More resources are needed to develop new and better tools for assessing exposure.
- There is a need to more closely link exposure assessment with research related to disease etiology, disease prevention and environmental genomics.
- Exposure assessment efforts should be in line with public health goals and community concerns.
- The definition of exposure needs to be broadened to include an understanding of social and economic factors that result in increased exposures in the population.

The product of this workshop is a comprehensive report including a description of knowledge gaps and research

needs, and specific recommendations and opportunities for addressing those needs. This research agenda will be designed to increase the available data characterizing human exposures and stimulate hypothesis-driven research necessary for defining exposure-disease relationships, estimating risk, and designing effective disease prevention measures. For additional information about this workshop visit the Meetings & Publications link on the NTP web-site at: http://ntp-server.niehs.nih.gov.

For further information on NTP Exposure Assessment activities contact Dr. Scott Masten, NIEHS/NTP, P. O. Box 12233, Research Triangle Park, North Carolina 27709; by telephone at (919) 541-5710; by FAX at (919) 541-4632; or by email at masten@niehs.nih.gov.

What's New at the Environmental Health Information Service (EHIS) Website?

To maintain the most extensive international online toxicology database, the EHIS continues to add to the NTP online library of technical reports as new items become available. New technical reports and draft technical reports are now accessible by following the NTP Reports link at http://ehis.niehs.nih.gov/. A full listing of NTP reports is now online, showing availability of reports, with links to abstracts and full text of reports.

The EHIS has also recently added two new features to make the web site even more user-friendly. Page numbers for *Environmental Health Perspective* back issues have been added to the Back Issues Online page to make it easier to locate articles online using citation information. Also, a new option has been built into the existing Search page to allow nonsubscribers to filter out subscription-only content. Nonsubscribers can search faster by limiting their searches to the material they can access for free.

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Table 1

Summary of RG1[1], RG2[2] and NTP Board Subcommittee[3] Recommendations for the Agents, Substances, Mixtures or Exposure Circumstances Reviewed in 1999-2000 for Listing in or Delisting from the Report on Carcinogens[4], 10th Edition

NOMINATION / CAS NUMBER	PRIMARY USES OR EXPOSURES	RG1 ACTION	RG2 ACTION	NTP BOARD SUBCOMMITTEE ACTION

Beryllium and Beryllium compounds / 7440-41-7	Used in fiber optics and cellular network communications systems, aerospace, defense and other industry applications.	RG1 unanimously recommended (8/0) listing as *known to be a human carcinogen.*	RG2 recommended (5 yes votes to 4 no votes) listing as *known to be a human carcinogen.*	The Subcommittee unanimously recommended (7/0) listing as *known to be a human carcinogen.*
2,2-bis-(bromomethyl) --1,3-propanediol (Technical Grade) 3296-90-9	Used as a fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam	RG1 unanimously recommended (9/0) listing as reasonably anticipated to be a human carcinogen	RG2 unanimously recommended (8/0) listing as *reasonably anticipated to be a human carcinogen.*	The Subcommittee unanimously recommended (7/0) to list as *reasonably anticipated to be a human carcinogen.*
2,3-Dibromo-1-Propanol/ 96-13-9	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	RG1 unanimously recommended (9/0) listing as *reasonably anticipated to be a human carcinogen.*	RG2 unanimously recommended (9/0) listing as *reasonably anticipated to be a human carcinogen.*	The Subcommittee unanimously recommended (7/0) to list as *reasonably anticipated to be a human carcinogen.*
Dyes metabolized to 3,3'-Dimethylbenzidine	Dyes mainly used for textile industries with other applications in paper, plastics, and rubber industries.	RG1 recommended (5 yes votes to 1 no vote with 1 abstention) to list as *reasonably anticipated to be a human carcinogen.*	RG2 unanimously recommended (9/0) listing as *reasonably anticipated to be a human carcinogen.*	The Subcommittee unanimously recommended (7/0) to list as *reasonably anticipated to be a human carcinogen.*
Dyes metabolized to 3,3'-Dimethoxybenzidine	Dyes mainly used for textile industries with other applications in paper, plastics, and rubber industries.	RG1 unanimously recommended (9/0) listing as *reasonably anticipated to be a human carcinogen.*	RG2 recommended (8 yes votes to 0 no vote with 1 abstention) listing as *reasonably anticipated to be a human carcinogen*	The Subcommittee unanimously recommended (7/0) to list as *reasonably anticipated to be a human carcinogen.*
IQ (2-Amino-3-methylimidazo-[4,5-f]quinoline) / 76180-96-6	Found in cooked meat and fish and in cigarette smoke	RG1 unanimously recommended (7/0) listing *as reasonably*	RG2 unanimously recommended (8/0) listing as *reasonably*	The Subcommittee unanimously recommended (7/0 to list as

		anticipated to be a human carcinogen	*anticipated to be a human carcinogen*	*reasonably anticipated to be a human carcinogen.*
Styrene 7, 8-oxide/ 96-09-3	Used mainly in the preparation of fragrances and in some epoxy resin formulations	RG1 recommended (7 yes votes to 1 no votes) to list as *reasonably anticipated to be a human carcinogen.*	RG2 recommended (6 yes votes to 3 no votes) to list as *reasonably anticipated to be a human carcinogen.*	The Subcommittee recommended (6 yes votes to 0 no votes with 1 abstention) to list as *reasonably anticipated to be a human carcinogen.*
Vinyl Bromide/ 593-60-2	Used primarily in the manufacture of flame retardant synthetic fibers	RG1 unanimously recommended (10/0) listing as *reasonably anticipated to be a human carcinogen*	RG2 unanimously recommended (9/0) listing as reasonably anticipated to be a human carcinogen	The Subcommittee recommended (4 yes votes to 3 no votes) listing as *known to be a human carcinogen.*
Vinyl Fluoride/ 75-02-5	Used in the production of polyvinylfluoride which is used for plastics	RG1 recommended (7 yes votes to 2 no votes) to list as *reasonably anticipated to be a human carcinogen.*	RG2 unanimously recommended (9/0) listing as *reasonably anticipated to be a human carcinogen*	The Subcommittee recommended (4 yes votes to 3 no votes) listing as *known to be a human carcinogen.*

[1] - The NIEHS Review Committee for the Report on Carcinogens (RG1)

[2] - The NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2)

Agencies from the NTP Executive Committee represented on RG2 include: Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA), National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), Occupational Safety and Health Administration (OSHA), National Cancer Institute (NCI), National Center for Environmental Health/CDC (NCEH), and National Institute of Environmental Health Sciences (NIEHS)

[3] - The NTP Board of Scientific Counselors Report on Carcinogens Subcommittee (the External Peer Review Group)

[4] - RoC - Report on Carcinogens

Table 2

Summary for Nominations to be Reviewed in 2000 for Consideration of Listing in or Delisting from the Tenth Report on Carcinogens

NOMINATION / CAS NUMBER	PRIMARY USES OR EXPOSURES	TO BE REVIEWED FOR	BASIS OF NOMINATION

Chloramphenicol (56-75-7)	Used widely as an antibiotic since the 1950s. Veterinary use of chloramphenicol has resulted in the occurrence of residues in animal-derived food.	Listing in the 10th Report	Nominated by RG1[1] based on IARC[2] finding of limited evidence of carcinogenicity in human epidemiology studies and identifying chloramphenicol as a Group 2A- Probable Human Carcinogen (Vol. 50, 1990).
Human Papillomaviruses (HPVs)	HPVs are small, non-enveloped viruses that contain a double-stranded, circular 8 kb DNA genome. HPV infections are common throughout the world, are highly host-specific and, with the exception of some ungulate papillomaviruses, infect only epithelial cells.	Listing in the 10th Report	Nominated by RG1[1] based on IARC[2] finding of sufficient evidence of carcinogenicity in human epidemiology studies and identifying certain human papillomaviruses as a Group 1- Known Human Carcinogen (Vol. 64, 1995).
Lead and Lead Compounds	Widespread uses which have included use in pipes for water distribution, lead-based paints, lead additives in gasoline, and many other applications	Listing in the 10th Report	Nominated by RG1[1] based on recent published data that indicate an excess of cancers in workers exposed to lead and lead compounds.
Methyleugenol (93-15-2)	Flavoring agent used in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, and ice cream. Also used as a fragrance for many perfumes, lotions, detergents and soaps	Listing in the 10th Report	Nominated by RG1[1] based on recent NTP Technical Report (TR 491, 1998) which reported clear evidence of carcinogenic activity of methyleugenol in rats and mice
Nickel and Nickel Compounds including Metallic Nickel & Nickel Alloys	Widely used in commercial applications for over 100 years	Listing in the 10th Report	Action required to complete review of Nickel and Nickel Compounds. This review will be of metallic nickel and nickel alloys. Review of nickel compounds for listing in

			the Report on Carcinogens was completed in 1998.
Estrogens, Steroidal	Estrogens are widely used in oral contraceptives and in post-menopausal therapy for women.	Listing in the 10th Report	Nominated by RG1[1] based on IARC[2] finding of sufficient evidence of carcinogenicity in human epidemiology studies and identifying Estrogens, Steroidal as a Group 1- Known Human Carcinogen (Vol. 72, 1999).
Talc (14807-96-6) (Non-Asbestiform)	Talc (non-asbestiform) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing. Exposure to general population occurs through use of products such as cosmetics.	Listing in the 10th Report	Nominated by RG1[1] based on NTP Technical Report (TR 421, 1993) which reported clear evidence of carcinogenic activity of talc (non-asbestiform) in female rats and also recently published epidemiology studies that suggests that talc exposure among pottery workers has been associated with lung cancer, and ovarian neoplasms in women.
Talc (14807-96-6) Containing Asbestiform Fibers/	Talc (containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing.	Listing in the 10th Report	Nominated by RG1[1] based on IARC[2] finding of sufficient evidence of carcinogenicity in human epidemiology studies and identifying talc (containing asbestiform fibers) as a Group 1- Known Human Carcinogen (Sup 7, 1987)
Trichloroethylene (TCE) (79-01-6)	Trichloroethylene is widely used as a solvent with 80-90% used worldwide for degreasing metals.	Upgrade to Known	Recommended by RG1[1] to be upgraded to a known human carcinogen based on recent published data that indicate an excess of kidney cancers in workers exposed to

			trichloroethylene.
Broad Spectrum UV Radiation	Solar and artificial sources of ultraviolet radiation	Listing in the 10th Report	Review of UVA, UVB and UVC recommended by RG2[3] based or earlier Report on Carcinogens review of solar UV radiation.
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	Listing in the 10th Report	Nominated by the Occupational Safety and Health Administration based on IARC[2] finding of sufficient evidence of carcinogenicity in human epidemiology studies and identifying wood dust as a Group 1- Known Human Carcinogen (Vol. 62, 1995)

[1] - The NIEHS Review Committee for the Report on Carcinogens (RG1)

[2] – International Agency For Research On Cancer (IARC)

[3] - The NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2)

Agencies from the NTP Executive Committee represented on RG2 include: Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA), National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), Occupational Safety and Health Administration (OSHA), National Cancer Institute (NCI), National Center for Environmental Health/CDC (NCEH), and National Institute of Environmental Health Sciences (NIEHS)