July 2000

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

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.

NTP Study Reports

NTP Board of Scientific Counselors Technical Reports Review Subcommittee

A Subcommittee of the NTP Board met May 18, 2000 to review technical reports for the six long-term toxicology and carcinogenicity studies listed below. 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 level of evidence for carcinogenicity for each of the reports is also listed below.

- Chloral Hydrate (TR-502)
  The primary sedative used in children. Exposure by gavage.

Equivocal evidence of carcinogenic activity (pituitary gland) for female mice that were continuously treated for two years.

- Chloral Hydrate (TR-503)
  The primary sedative used in children. Exposure by gavage: *ad libitum* and dietary controlled feeding.

Some evidence of carcinogenic activity (liver) in male mice.

- Indium Phosphide (TR499)
  Used in making semiconductors, lasers, solar cells, and photodiodes. Exposure by inhalation.

Clear evidence of carcinogenic activity (lung and adrenal gland) in male and female rats and clear evidence of carcinogenic activity in male (lung and liver) and female (lung) mice.

- Naphthalene (TR-500)
  Ingredient in moth repellants and toilet bowl deodorants and used as an intermediate in a variety of chemical synthesis processes. Exposure by inhalation.

Clear evidence of carcinogenic activity (nose) in male and female rats.

- Sodium Nitrite (TR 495)
  Color fixative and preservative in meats and fish; also used in a variety of industrial processes. Exposure in drinking water.

No evidence of carcinogenic activity in male rats and male mice, no evidence of carcinogenic activity in female rats, and equivocal evidence of carcinogenic activity (forestomach) in female mice.

- *p,p'*-Dichlorodiphenyl Sulfone (TR 501)
  Starting product in production of polysulfones and polyethersulfones; by-product of pesticide production. Exposure in feed.

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

Draft technical reports or summary of the minutes can be viewed on the NTP web site, http://ntp-server.niehs.nih.gov *or can be obtained by contacting Central Data Management, NIEHS/NTP, P.O. Box 12233 MD E1-02, Research Triangle Park, NC 27709; (919)-541-3419, fax (919)-541-3687 or e-mail:* CDM@niehs.nih.gov.

Completed NTP technical reports can be procured through the Environmental Health Information Service http://ehis.niehs.nih.gov *or by calling (919) 541-3841 or Fax: (919) 541-0763.*

Technical Reports Tentatively Scheduled for Review in 2001

The following are candidate Technical Reports tentatively scheduled for review in 2001.

Spring 2001 Review:

- Acrylonitrile and Methacrylonitrile
  Used in making polymers and plastics
- *o*-Nitrotoluene and *p*-Nitrotoluene
  Used in the manufacture of chemicals including dyes, toluidines, and nitrobenzoic acid
- Citral - Used in lemon flavors and fragrances

Fall 2001 Review:

- Vanadium Pentoxide - Used in light filters and in the semiconductor industry
- Riddelliine - Plant alkaloid found as a contaminant in some foods
- Urethane/Ethanol - By-product of fermentation found in alcoholic beverages
- Dipropylene Glycol - Component of antifreezes and air fresheners

Report on Carcinogens

Prepared by the NTP, the *Report on Carcinogens* (*RoC*) identifies substances -- such as metals, pesticides, drugs, and natural and synthetic chemicals -- and 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 "known" category is reserved for those substances for which there is sufficient evidence of carcinogenicity from studies in humans that indicates a cause and effect relationship between the exposure and human cancer. The "reasonably anticipated" category includes those substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals. Conclusions regarding carcinogenicity in humans or experimental animals are based on expert, scientific judgment, with consideration given to all relevant information.

9th Edition of the Report on Carcinogens

The Department of Health and Human Services released the 9th edition on May 15, 2000. The new and upgraded listings and the delistings in the 9th edition are identified below. The *RoC's* findings are based on three years of study that included three scientific reviews and public comment from scientists, consumers and other interested parties.

- **New to the *9th Report* as "Known":**

•Alcoholic Beverage Consumption
•Dyes metabolized to benzidine (benzidine dyes as a class)
•Environmental Tobacco Smoke
•Smokeless Tobacco
•Solar Radiation and Exposure to Sunlamps and Sunbeds
•Strong Inorganic Acid Mists Containing Sulfuric Acid
•Tamoxifen
•Tobacco Smoking

- **New to the *9th Report* as "Reasonably Anticipated":**

•Chloroprene
•Diesel Exhaust Particulates
•Isoprene
•Phenolphthalein
•Tetrafluoroethylene
•Trichloroethylene

- **Reclassified as a "Known" in the *9th Report*:**

•1, 3-Butadiene
•Cadmium and Cadmium Compounds
•Direct Black 38
•Direct Blue 6
•Ethylene Oxide
•Silica, Crystalline (respirable size)

- **Removed from the *9th Report***:

•Saccharin
•Ethyl Acrylate

♦ **Review for the *9th Report* also Included:**

•Employment in Boot and Shoe Industry
Remains in an appendix.
•Methyl-t-butyl ether
Not recommended for listing.
•Nickel and Nickel Compounds
Deferred listing nickel compounds as a "Known" until completion of review of metallic nickel and nickel alloys.
•2,3,7,8-Tetrachlorodibenzo-p-dioxin
Proposed for upgrade to the "Known" category. The proposed listing is currently in litigation. Depending on the outcome of the litigation an addendum may be published following the Court's ruling.

For more information on how to order a hard copy of the Report or to access it on the Web, visit the NTP Homepage at http://ntp-server.niehs.nih.gov *or contact the National Toxicology Program, Report on Carcinogens, MD EC-14, P.O. Box 12233, Research Triangle Park, NC 27709.*

10th Edition of the Report on Carcinogens

The 10th edition will be published in 2002. Nominations are being reviewed in two groups.

Review of First Group of Nominations

Scientific reviews of the first group of nominations being considered for inclusion in the 10th edition of the *RoC* have been completed. This group of nominations includes the following:

♦ 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 in a fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam.

♦ Beryllium and Beryllium Compounds
Used in fiber optics and cellular network communications systems, aerospace, defense and other industry applications.

♦ Dyes Metabolized to 3,3 Dimethoxybenzidine (Dimethoxybenzidine Dyes as a Class)
Dyes formerly widely used for leather, paper, plastics, rubber, and textile industries.

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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.

A list of the recommendations by the three review groups for listing in or delisting from the *10th RoC* can be obtained by accessing 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. Background documents provided to the review committees and the public are available on the web in PDF at the above URL address. Hard copies of these documents are also available upon request. The NTP will review the recommendations from each of the review committees and consider the public comments received throughout the process in making decisions regarding the NTP recommendations to the Secretary, DHHS for listing of the nominated

substances in the *10th RoC*. The NTP has already solicited public comment to supplement any previously submitted comments or to provide comments for the first time on any substance identified above.

Review of the Second Group of Nominations

Review of the second group of nominations for possible listing in the *10th Report* is underway. These nominations include:

♦ Chloramphenicol

Used widely as an antibiotic since the 1950s. Chloramphenicol is currently used in the United States only to combat serious infections where other antibiotics are either ineffective or contraindicated. To be reviewed for possible listing in the *10th Report*.

♦ Lead and Lead Compounds

Used widely in pipes for water distribution, lead-based paints, lead additives in gasoline, and many other applications. To be reviewed for possible listing in the *10th Report*.

♦ Methyleugenol

Flavoring agent used in jellies, baked goods, nonalcoholic beverages, candy, and ice cream. Also used as a fragrance for many perfumes, and soaps. To be reviewed for possible listing in the *10th Report*.

♦ Nickel (metallic) & Nickel Alloys

Widely used in commercial applications for over 100 years. Action required to complete review of Nickel and Nickel Compounds for possible listing in the *RoC* that began in 1998/99.

♦ Estrogens, Steroidal

Estrogens are widely used in oral contraceptives and in post-menopausal therapy for women. To be reviewed for possible upgrading to a known human carcinogen in the *10th Report*.

♦ Talc (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. To be reviewed for possible listing in the *10th Report*.

♦ Talc (Containing Asbestiform Fibers)

Talc (containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing. To be reviewed for possible listing in the *10th Report*.

♦ Trichloroethylene

Trichloroethylene is widely used as a solvent with 80-90% used worldwide for degreasing metals. To be reviewed for possible upgrading to a known human carcinogen in the *10th Report*.

♦ Broad Spectrum UV Radiation

Solar and artificial sources of ultraviolet radiation. To be reviewed for possible listing in the *10th Report*.

♦ 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. To be reviewed for possible listing in the *10th Report*.

The NTP has solicited public input on these nominations and asks for relevant information anyone may have 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. Comments or questions should be directed to Dr. C. W. Jameson at the address listed below.

December Board Meeting and Opportunity for Public Review and Comment

The second group of nominations will be reviewed in public session by the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee December 13-15, 2000. This review will include an

opportunity for public comment and will be held in the Washington, DC area.

Background documents for these nominations will be available for public review October 1, 2000 and will be accessible from the NTP Home Page at http://ntp-server.niehs.nih.gov. *Hard copies can be obtained by contacting Central Data Management, NIEHS/NTP, P.O. Box 12233 MD E1-02, Research Triangle Park, NC 27709; (919)-541-3419, fax (919)-541-3687 or e-mail:* CDM@niehs.nih.gov.

Additional information regarding the Board meeting will be announced in the near future. Questions regarding the Board meeting can be addressed to the Board Executive Secretary, Dr. Mary Wolfe, at wolfe@niehs.nih.gov *or 919-541-3491.*

Request for Nominations for Future Evaluation for Listing/Delisting

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*. Nominations should contain a rationale for listing or delisting. Appropriate background information and relevant data (*e.g.*, journal articles, NTP Technical Reports, IARC listings, exposure surveys, release inventories, etc.) which support a nomination should be provided or referenced when possible. Anyone may nominate a substance to be considered for listing in or delisting from the *RoC*.

To submit nominations for listing or delisting or for information about the Report on Carcinogens, contact Dr. C. W. Jameson, telephone: (919) 541-4096, fax, (919) 541-0144, e-mail, jameson@niehs.nih.gov.

NTP Center for the Evaluation of Risks to Human Reproduction

The NTP and the NIEHS established the NTP Center for the Evaluation of Risks to Human Reproduction (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.

July 12-13 Review of Phthalates

The third and final meeting of an Expert Panel to complete the evaluation of the following seven phthalate esters will be held July 12-13, 2000 at the Sheraton National Hotel in Arlington, Virginia.

- butyl benzyl phthalate (85-68-7) BBP
- di(2-ethylhexyl) phthalate (117-81-7) DEHP
- di-isodecyl phthalate (26761-40-0, 68515-49-1) DIDP
- di-isononyl phthalate (28553-12-0, 68515-48-0) DINP
- di-n-butyl phthalate (84-74-2) DBP
- di-n-hexyl phthalate (84-75-3) DnHP
- di-n-octyl phthalate (117-84-0) DnOP

Opportunity for Public Review and Input

Expert panel reports to be reviewed at the July 12-13 meeting are available to the public and can be obtained electronically on the NTP website: http://cerhr.niehs.nih.gov or in hardcopy by contacting Ms. Peggy Sheren at CERHR, 1800 Diagonal Road, Suite 500, Alexandria, VA 22314-2808, Phone 703 838 9440, psheren@sciences.com.

Following the July 12-13 meeting and finalization of the Expert Panel Phthalate Reports, public review and comment of the final Expert Panel reports will be solicited. The NTP will then prepare an NTP Center Report, that is based on the expert panel reports, public comments, and any newly available information. The NTP Center Report will include a lay summary of any evidence that exposure may lead to harm and identification of any research needs and gaps. The NTP Center Report will then be transmitted to Federal and State agencies, the scientific community and to the general public. Announcement of the availability of the final phthalate reports will be made as soon as the final reports are complete.

Next Review - Methanol

The CERHR Core Committee, composed of representatives of NTP-participating agencies, reviews chemicals nominated for further study and recommends candidates for further consideration by the NTP. An evaluation of Methanol (67-56-1) is planned for late 2000. Additional information will be announced in the near future. Questions regarding the review can be directed to Dr. Michael Shelby as indicated below.

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

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., NIEHS,* shelby@niehs.nih.gov *or P.O. Box 12233, Research Triangle Park, NC 27709. Telephone: 919-541-3455*

NTP Interagency Center for the Evaluation Of Alternative Toxicological Methods

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) 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) was established in 1997 to facilitate cross-agency coordination and communication on issues relating to the development, 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.

July 25 Peer Review Meeting on the Up-and-Down (UDP) Procedure for Acute Oral Toxicity

An international peer review panel of experts will meet on July 25, 2000, from 8:30 a.m. to 5:30 p.m. at the Sheraton Crystal City Hotel in Arlington, VA. The public is welcome to attend and provide comment during designated public comment sessions. The agenda includes a brief orientation on ICCVAM and the UDP, followed by a peer review of the UDP and supporting information. ICCVAM and NICEATM have organized this independent peer review evaluation of a revised UDP for assessing acute oral toxicity at the request of U.S. EPA. This procedure is a revised version of the Organization for Economic Cooperation and Development (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 traditional OECD Test Guideline 401 for Acute Oral Toxicity. The UDP uses fewer animals to determine acute oral toxicity potential of chemicals 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, U.S. agencies have requested that ICCVAM conduct an independent peer review of the revised UDP to determine the validity of the method as a substitute for Guideline 401.

Background Document Now Available

NICEATM, in conjunction with U.S. EPA and other scientists, recently prepared a Background Review Document that includes the revised UDP protocol and documents supporting the basis and validity of the test method. The Document is available for comment and can be obtained by contacting NICEATM at the address listed below.

A Federal Register notice providing more detail on the meeting is available at: http://iccvam.niehs.nih.gov/udp.htm.

October 17-20 International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity

NICEATM and ICCVAM are convening a scientific workshop to assess the current status of *in vitro* test methods for evaluating the acute systemic toxicity potential of chemicals and to form recommendations for future development and validation studies. The workshop will take place on October 17-20, 2000, at the Hyatt Regency Crystal City Hotel in Arlington, VA. The meeting will be open to the public.

An agenda, registration information, and other details will be distributed in the near future. To receive this information directly, please contact Dr. Stokes as indicated below.

Review of Frog Embryo Teratogenesis Assay -- Xenopus (FETAX): Report Soon Available

An Expert Panel Meeting was held on May 16 - 18, 2000, in Research Triangle Park, NC, to evaluate the Frog Embryo Teratogenesis Assay -- *Xenopus* (FETAX), a screening method proposed for evaluating the developmental toxicity potential of chemicals. The objectives of this meeting included developing consensus on the current validation status of FETAX, providing recommendations for FETAX protocol modifications and further validation studies, recommending current and potential

uses of FETAX, and recommending additional research and further test method development.

The international Expert Panel consisted of 45 scientists in five breakout groups that evaluated the protocol, reliability, performance, environmental applications and future research and development needs. Each working group developed recommendations for improving the test method's intra- and inter-laboratory reproducibility and accuracy. Research and development efforts that might enhance the future usefulness of the assay, including the integration of microarray technology, were also recommended. The final meeting report is currently being prepared. Visit the ICCVAM website: http://iccvam.niehs.nih.gov for updates on when the report will be available, and to access an electronic version. For hard copies of the report please contact Dr. William Stokes at the address listed below.

For further information on any aspects of NICEATM 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 Testing Programs

NTP Requests Input and Nominations for New 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 the testing of chemicals of greatest public health concern. The NTP is soliciting nominations of new 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 subchronic toxicity, chronic toxicity and carcinogenicity, as well as reproductive, developmental, genetic, immunological and neurological toxicity. 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 developed by NTP are 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 to validate new and improved assays for chemical toxicity and test methods and systems that eliminate or minimize the use of laboratory animals.

Significant time and resources are consumed by the selection and testing of a single agent, so each nomination is considered carefully before final selection for NTP testing. Chemicals or other 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 to establish priority for further review and study. The nominator will be informed of the status of their 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. Current testing initiatives are presented below; however, it is important to emphasize that the NTP seeks the broadest participation in the nomination process and nominations need not be limited to the areas listed.

Nominations and inquires regarding nominations on testing initiatives should be addressed to:
Dr. Scott Masten, Office of Chemical Nomination and Selection (B3-10), NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709
E-mail: masten@niehs.nih.gov.
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-server.niehs.nih.gov/NomPage/noms.html.

Current NTP Testing Initiatives

The NTP has a broad mandate to provide toxicological characterizations for chemicals and agents of public health concern and strives to balance the selection of substances for study so that adverse effects from occupational, environmental and consumer exposures are all addressed. Over the history of the NTP, this has resulted in a diverse research and testing program with emphasis on synthetic industrial chemicals, environmental pollutants, agricultural chemicals, pharmaceuticals, consumer product chemicals, constituents of food, food additives, and natural products. Some major NTP testing initiatives already underway and recently discussed with the NTP Board of Scientific Counselors are listed below. It should be realized that this information is presented to give a perspective on the breadth of current NTP research and testing activities and directions and is not meant to limit the solicitation of additional nominations to these areas.

Safe Drinking Water Program
Safe drinking water represents a balance between microbial and chemical risk and is of enormous public health concern, since it is estimated that more than 200 million Americans use treated drinking water. Chlorination of our water supply is a standard treatment technique that reduces mortality and morbidity from infectious disease; however, despite advances in expertise to purify and disinfect our water, chemical contaminants may still be found in finished water. These agents can be grouped into two broad categories, those that occur as a result of the disinfection process (disinfection by-products: DBPs) and those that occur naturally or by contamination (candidate contaminants) in public water systems. One of the most complex issues facing water utilities and the EPA is minimizing the potential for DBP-related health effects while still achieving effective control of waterborne microbial pathogens.

The NTP is playing a critical role in providing data to assess the potential risks from human exposure to the major DBPs

through a collaborative effort with the EPA. The research program includes a systematic, mechanism-based, toxicological evaluation of DBPs that can help provide the EPA data for setting drinking water standards. The study of DBPs is not easy, and their selection for study is based upon their presence in drinking water, their occurrence with different disinfection processes, their chemical structure, and their representation from among the different DPB families: trihalomethanes, haloacetic acids, and haloacetonitriles. The DBPs currently under study include: 3-Chloro-4-(Dichloromethyl)-5-Hydroxy-2(5H)-Furanone(MX), Bromochloroacetic Acid, Bromodichloroacetic Acid, Bromodichloromethane, Chloramine, Chloroform, Dibromoacetic Acid, Dibromoacetonitrile, Dibromochloracetic Acid, Dichloroacetic Acid, Sodium Bromate, Sodium Chlorite, Sodium Chlorate. Research focuses on reproductive toxicity, immunotoxicity, and neurotoxicity as well as carcinogenesis, and research approaches include investigations using transgenic mouse models, standard rodent bioassays, and studies in fish. NTP research is being conducted through agreements with the U.S Army, EPA, and industry. The NTP is also involving the extramural research community through grant support of hypothesis-based mechanistic studies on DBPs and is working closely with the American Water Works Association Research Foundation (AWWARF) sharing protocols and research plans and making them aware of ongoing research activities. Some of the AWWARF's own research awards are being designed to complement activities of the NTP and EPA.

Besides the DBPs, a complex array of candidate contaminants can occur naturally (*e.g.*, arsenic, aluminum), as a result of contamination [*e.g.*, methyl-tertiary butyl ether (MTBE), pesticides, organotins], or with environmental changes (*e.g.*, algae blooms resulting in micotoxins and other toxins). The NIEHS/NIH in collaboration with the EPA is selecting the major contaminants for future study. Both aluminum fluoride and aluminum citrate have been nominated to the NTP for consideration for long-term neurotoxicity studies.

Requests for additional information and questions about this initiative can be directed to Dr. Gary Boorman, NIEHS: boorman@niehs.nih.gov *or P.O. Box 12233 MD B3-08, RTP, NC 27709.*

DNA-Based Products

DNA-based therapies are currently being developed for the treatment of a wide range of human diseases. Examples include plasmid DNA encoding one or more antigenic proteins for vaccines against viral and bacterial pathogens, triplex forming synthetic oligonucleotides to modulate gene expression, and viral vectors for gene therapy. Though DNA-based products show significant promise, by their very nature they all pose a risk of interacting with the host genome or disrupting normal cellular processes in unexpected and unpredictable ways and with potentially adverse consequences. Presently the FDA has only limited authority to require evaluation of non-acute, long-term safety risk associated with these therapies. In addition, the majority of the manufacturers of DNA-based products are generally small biotechnology companies and academic sponsors that lack the resources to perform long-term, large-scale studies on their products. The NTP and FDA are collaborating on an initiative to study the safety of DNA-based products that will address three major safety issues:

- The intracellular persistence and potential for integration into the host genome. Since certain of these products are intended for use in children (*e.g.*, DNA vaccines), there is concern about life-long risk posed by integration.

- Their distribution to the gonads and the potential for integration and germ line transmission. DNA-based products may reach tissues in the body outside their presumably sequestered sites of administration (intradermal or intramuscular); therefore, there is concern about the potential for reproductive toxicity and/or transmission of altered genetic material to subsequent generations.
- The potential for abnormal immune activation. Both viral vectors and DNA vaccines carry genes that stimulate host cells to secrete self and foreign proteins. There is concern about the potential for DNA-based products to promote development of autoimmune disease and disrupt immune homeostasis.

While initial efforts are focusing on DNA-based therapies, the NTP is aware of public concern for other DNA-based products, such as bioengineered foods, and may consider future research in this area.

Requests for additional information and questions about this initiative can be directed to Dr. Richard Irwin, NIEHS: irwin@niehs.nih.gov *or P.O. Box 12233, MD B3-07, RTP, NC 27709.*

Medicinal Herbs (Botanicals)

Medicinal herbs are some of our oldest medicines and their increasing use in recent years is evidence of a public interest in having alternatives to conventional medicine. It is estimated that approximately one-third of the U.S. population uses some form of alternative medicine. The regulation of botanicals in the United States is restrained since passage of the 1994 Dietary Supplement Health and Education Act. Under this Act, proof of their safety is not required prior to herbal products being marketed. Approximately 1500 botanicals are sold as dietary supplements or ethnic traditional medicines. These herbal formulations are not subject to FDA pre-market toxicity testing to assure their safety or efficacy; package inserts are not required to inform consumers of possible adverse effects or possible herb/herb or herb/drug interactions; and there is minimal post-market surveillance for possible adverse or allergic reactions. The 1997 Presidential Commission on Dietary Supplements recommended additional research by Federal agencies on dietary supplements including medicinal herbs.

The NTP has received numerous nominations for study of herbal medicines and other dietary supplements from both the public and Federal agencies. The NTP is currently conducting or planning research on several medicinal herbs (Table 1). These studies focus on characterization of potential adverse health effects including reproductive toxicity, neurotoxicity, and immunotoxicity as well as those associated with acute high dose exposure and chronic exposure to lower doses. In addition, special attention will be given to potential herb/herb or herb/drug interactions and the responses of sensitive subpopulations (*e.g.*, pregnant women, the young, the developing fetus, the elderly, etc).

Requests for additional information and questions about this initiative can be directed to Dr. Tom Burka, NIEHS: burka@niehs.nih.gov *or P.O. Box 12233, MD B3-10, RTP, NC 27709.*

Table 1: Medicinal Herbs (Botanicals) under Consideration by the NTP

Herb or Ingredient	Information
Substances for which studies are ongoing or planned	
Berberine	An alkaloid, active constituent ingredient in Golden Seal.
Goldenseal	Second or third most popular medicinal herb used in this country; traditionally used to treat wounds, digestive problems, and infections. Current uses include as a laxative, tonic, and diuretic.
Comfrey	Herb consumed in teas and as fresh leaves for salads; however, it contains pyrrolizidine alkaloids (*e.g.*, symphatine), which are known to be toxic. Used externally as an anti-inflammatory agent in the treatment of bruises, sprains, and other external wounds.
Echinacea	One of the most commonly used medicinal herb in the United States. Used as a stimulant of the immune system to treat colds, sore throat, and flu.
Milk Thistle Extract	Used to treat depression and several liver conditions including cirrhosis and hepatitis and to increase breast milk production.
Substances being considered for study	
Aloe Vera Gel	Seventh most widely used herb; used as both a dietary supplement and component of cosmetics. The gel has been used for centuries as a treatment for minor burns and is increasingly being used in products for internal consumption (*e.g.*, 'health' drinks).
Ginkgo Biloba Extract	Among the five or six most frequently used medicinal herbs. Ginkgo fruits and seeds have been used medicinally for thousands for years. The extract of green-picked leaves has increasing popularity in the United States. Ginkgo biloba extract promotes vasodilatation and improved blood flow and appears beneficial, particularly for short-term memory loss, headache, and depression.
Ginseng and Gensenosides	Fourth most widely used medicinal herb; gensenosides are thought to be the active ingredients. Ginseng has been used as a treatment for a variety of conditions: hypertension, diabetes, and depression, and intake has also been associated with various adverse health effects.
Kava Kava	Reported to be the fifth most widely used medicinal herb, has psychoactive properties, and is sold as a calmative and antidepressant.
Pulegone	A major terpenoid constituent of the herb, Pennyroyal, and is found in lesser concentrations in other mints. Pennyroyal has been used as a carminative insect repellent, emmenagogue, and abortifacient. Pulegone has well-recognized toxicity to the liver, kidney, and central nervous system.
Thujone	Terpenoid found in a variety of herbs, including sage and tansy, and in high concentrations in wormwood. Suspected as the causative toxic agent associated with drinking absinthe, a liqueur flavored with wormwood extract

Occupational Exposure and Mixtures

The NTP is coordinating an interagency effort between NIEHS and NIOSH to better characterize worker exposures and to use this information both for worker education and to identify occupational health research gaps. This project involves NIOSH-wide participation and should impact the health agenda of both NIOSH and NTP by focusing NTP resources on obtaining '"real world" information about worker practices, complex occupational exposures, and possibly related adverse health effects. Such information is needed to better identify areas for research and to design better laboratory studies on the health effects of chemicals, complex mixtures, and exposure circumstances encountered in the workplace. Current efforts are addressing worker exposure to cellulose inhalation and asphalt fumes including worker practices and exposures and the physical and chemical characteristics of the substances. Future initiatives are proposed for 1-bromopropane, metal working fluids, and welding fumes. NIOSH will work with the NTP in nominating agents for study and designing laboratory studies and will undertake its own research projects under this agreement.

NIOSH is currently planning to conduct a national, cross-sectional, on-site survey of establishments and workers that should provide information for targeting future research. The new survey will include all industry sectors covered by the OSHA and Mine Safety and Health

Administration and will gather nationally representative data on chemical, physical, and biological agents to which workers are potentially exposed, as well as data on exposure controls and health and safety practices.

Requests for additional information and questions about either initiative can be directed to Dr. Mark Toraason, NIOSH: mht1@cdc.gov *or C23, 4676 Columbia Parkway, Cincinnati, OH 45226.*

Phototoxicology Studies and the NTP Center for Phototoxicology

The exposure of U.S. citizens to UV radiation is increasing through more frequent use of tanning booths to augment skin coloration and the trend toward spending leisure and pleasure times in sunlight-oriented activities (*e.g.*, beach, swimming pools). The FDA has an ongoing interest in phototoxicity and photocarcinogenicity of therapeutics, cosmetics, devices, and food supplements/additives and recently developed an inter-agency photobiology research program with the NIEHS. This agreement has resulted in establishment of the FDA-NIEHS Phototoxicology Research and Testing Laboratory and the new NTP Center for Phototoxicology; both are housed at the National Center for Toxicological Research of the FDA in Jefferson, Arkansas. The Center's primary purpose is to conduct mechanistic-based research and photocarcinogenesis studies on compounds of regulatory importance to the FDA. Mechanistic-based studies are concurrently conducted, as needed, to facilitate interpretation of the photocarcinogenesis studies.

The laboratory is designed to allow study of many types of compounds (*e.g.*, cosmetics, tanning enhances, drugs, etc.) and should provide high quality data upon which to base public health decisions about the interactions of drugs or other compounds with sunlight. Solar light is simulated in the animal facilities using 6.5 kWatt xenon-arc lights filtered through Schott quartz glass. The transmitted light is attenuated to achieve a spectrum that closely mimics terrestrial solar light. The facility is also equipped for fluorescent light exposures. Photocarcinogenicity studies will use the SKH-1 hairless mouse as the primary test animal, and as appropriate, additional test animals (*e.g.*, transgenic models) will be used.

The α- and β-hydroxy acids are acidic compounds included in many over-the-counter cosmetics as dermatological chemoexfoliants; their use is increasing as the beauty-conscious public seeks drugs or cosmetic preparations that will give a more youthful appearance. The most widely used α-hydroxy acid is glycolic acid, while the most widely used β- hydroxy acid is salicylic acid. Two possible consequences of chemoexfoliation are increased proliferation of the epidermal epithelial cells and deeper penetration of electromagnetic radiation into the skin. In light of these changes, the impact of continuous use of this type of treatment on the incidence of skin cancer is not known. Studies are now underway to allow quantitative determination of the effect of these compounds on the induction of mouse skin cancer (SKH-1 hairless mouse) by simulated solar light.

Requests for additional information and questions about this initiative and the NTP Center can be directed to Dr. Paul Howard, NCTR: phoward@nctr.fda.gov *or HFT-110, 3900 NCTR Road, Jefferson, AR 72079.*

October 10-12
Endocrine Disruptors Low Dose Peer Review

The U.S. Environmental Protection Agency (EPA) has asked the NTP to establish an independent panel of scientists to review the scientific evidence related to low-dose effects of endocrine disruptors and to consider their implications for the development, validation, and interpretation of test protocols for reproductive and developmental toxicity. If this panel concludes that significant effects may occur at low doses and that the standard dose-setting paradigm is inadequate to detect such effects, then the EPA intends to pursue through a separate forum, the question of how to test for such effects including endpoints to be measured, dose-setting protocols, and appropriate test methods. If the Panel believes that the current data are inconclusive, it will be asked to describe specific research that would resolve the ambiguities. The meeting, which is open to the public, will be held at the Sheraton Imperial Hotel and Convention Center in Research Triangle Park, North Carolina.

Peer Review Goals*
Analyses will focus on interpretation of selected major studies showing or refuting effects at low doses for endocrine disruptors on reproductive and developmental endpoints. The intent is to examine data supporting the presence or absence of low-dose effects in specific studies and then evaluate the likelihood and significance of these and/or other potential low-dose effects for humans. A main topic to be addressed is defining the shape of the dose/response curves for endocrine-active substances in the low-dose region. This analysis and evaluation will be accomplished through the three-day scientific peer review that includes plenary sessions and several breakout sessions.

*The Selection/Organizing Committee for the Low-Dose Peer Review decided not to include dioxin and PCB issues in the October Peer Review. It is likely that a separate Peer Review will be held in the spring of 2001 to consider these chemicals and to integrate information from them with conclusions from the October Peer Review.

Further information about this peer review can be found in Federal Register notices dated January 6, 2000 and April 17, 2000 located on the NTP website at: http://ntp-server.niehs.nih.gov/htdocs/liason/LowDoseEndocrineFR.html *and* http://ntp-server.niehs.nih.gov/htdocs/liason/EndocrineMtgDelayFR.html.
For additional information about this peer review as it becomes available please visit the NTP website at http://ntp-server.niehs.nih.gov or contact The NTP Office of Liaison and Scientific Review at: liaison@starbase.niehs.nih.gov *or fax (919) 541-0295. To make reservations at the Sheraton please call (919) 941-5050.*

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

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 is sponsoring a workshop. The meeting is scheduled for August 16-18, 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).

Environmental Health Information Service (EHIS)

The Environmental Health Information Service (EHIS) adds new technical reports to the NTP's online library. To access these reports, follow 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.

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Upcoming Events

DATE	EVENT	CONTACT
July 12-13, 2000	*Meeting:* NTP-CERHR Final Meeting of the Phthalate Expert Panel Sheraton National Hotel Arlington, VA	Ms. Peggy Sheren, CERHR 1800 Diagonal Road, Suite 500 Alexandria, VA 22314-2808 Phone:703-838-9440 Email: psheren@sciences.com
July 25, 2000	*Meeting:* ICCVAM/NICETAM Peer Review Evaluation of the Revised Up-and-Down Procedure for Acute Oral Toxicity Crystal City Sheraton Hotel Arlington, VA	ICCVAM/NICETAM MD EC-17, PO Box 12233 Research Triangle Park, NC 27709 Phone: 919-541-3398 Fax: 919-541-0947 Email: iccvam@niehs.nih.gov
August 16-18, 2000	*Workshop:* Of Mice, Humans and Models: Future Research Directions for Improving Risk Assessment Methods Silver Tree Hotel, Snowmass Village Aspen, CO	Estella Lazenby, KEVRIC Co. Phone: 301-588-6000 ext. 239 Fax: 301-588-2106
October 10-12, 2000	*Peer Review:* Endocrine Disruptors Low Dose Peer Review Sheraton Imperial Hotel & Convention Center Research Triangle Park, NC	Email: liaison@starbase.niehs.nih.gov Fax: 919-541-0295
October 17-20, 2000	*Workshop:* ICCVAM/NICEATM Workshop on In Vitro Methods for Acute Toxicity Crystal City Hyatt Regency Hotel Arlington, VA	ICCVAM/NICEATM MD EC-17, PO Box 12233 Research Triangle Park, NC 27709 Phone: 919-541-3398 Fax: 919-541-0947 Email: iccvam@niehs.nih.gov
November 28, 2000	*Meeting:* NTP Advisory Committee on Alternative Toxicological Methods Washington, DC Area: TBA	NTP Office of Liaison and Scientific Review MD A3-07, PO Box 12233 Research Triangle Park, NC 27709 Phone: 919-541-3971 Email: wilson9@niehs.nih.gov
December 13-15, 2000	*Meeting:* NTP Board of Scientific Counselors Report on Carcinogens Subcommittee Washington, DC Area: TBA	NTP Office of Liaison and Scientific Review MD A3-07, PO Box 12233 Research Triangle Park, NC 27709 Phone: 919-541-3971 Email: wilson9@niehs.nih.gov

*For further calendar details please visit the web:
http://ntp-server.niehs.nih.gov/Main_Pages/NTP_EVENTS_PG.html