**National Toxicology Program**
**Board of Scientific Counselors**

June 13, 2006

National Institute of Environmental Health Sciences
Research Triangle Park, NC

***Summary Minutes***


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Attachment 1 – Agenda
Attachment 2 – Federal Register Meeting Announcement
Attachment 3 – Committee Roster

# 1. Attendees

**NTP Board of Scientific Counselors**

**Members in attendance:**
Diane Birt, Iowa State University
Christopher Bradfield, University of Wisconsin
Germaine Buck Louis, NIH/NICHD
Kenny Crump, Environ International, Inc.
George Daston, (chair) The Procter and Gamble Company
Prescott Deininger, Tulane University
Nancy Kerkvliet, Oregon State University
Gail McCarver, Medical College of Wisconsin
Charlene McQueen, University of Arizona
Jon Mirsalis, SRI International
Maria Morandi, University of Texas
Harish Sikka, State University of New York at Buffalo
Keith Soper, Merck Research Laboratories
Vernon Walker, Lovelace Respiratory Institute

**Members not in attendance:**
Elizabeth Delzell, University of Alabama
John P. Giesy, Michigan State University
Katharine Hammond, University of California at Berkeley

**NIEHS Staff**
Lutz Birnbaumer
John Bucher
Rajendra Chhabra
Gwen Coleman
Brad Collins
Michael Cunningham
Carolyn Flowers
Paul Foster
Jon Freedman
Raymond Grissom
William Jameson
Grace Kissling
Jo Ann Lewis
Ruth Lunn
Robin Mackar
Joyce Martin
David Malarkey
Scott Masten
Daniel Morgan
Denise Orzeck
John Pritchard
Joe Roycroft
Ann Sassaman
Mike Shelby
Robert Sills
Ray Tice
Molly Vallant
Nigel Walker
Brenda Weis
Samuel Wilson
Kristine Witt
Mary Wolfe

**Other Federal Agency Staff**
William Allaben, FDA
Mark Toraason, NIOSH
Kevin Dreyer, EPA
Paul Howard, FDA

**Public**
Andrew Ballard, BNA
Akihiro Kinoshita, Shiseido Cosmetics
James Blake, RTI International
Susan Borghoff, ILS
Donna Browning, RTI International
Charlie Byers, USG
Bonnie Carson, ILS
Patrick Crockett, Constella Group
James Deyo, Eastman Chemical Company
Reshan Fernando, RTI International
Amy Foscue, Gypsum Association
Claudine Gregorio, ILS
Beom Seok Han, NITR (Korea)
Sanford Garner, Constella Group
Marc Jackson, ILS
Susan Kinney, ILS
Alan Lévesque, ILS
Dawn MacIntyre, ILS
Ivan Rusyn, UNC
Jessica Sanderson, USG
Noriko Shibuya, Shiseido Cosmetics
Glenn Simon, Rhodia
Takahiko Suwa, Shiseido Cosmetics
Kristina Thiagarajan, Oak Ridge National Laboratories

## II. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met on June 13, 2006, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (*Attachment 1*: *Federal Register* meeting announcement; *Attachments 2* and *3*: Agenda and Roster of Members). Dr. George Daston, Chair, welcomed everyone to the meeting and asked the BSC members and attendees to introduce themselves. Dr. Allen Dearry, NTP Interim Associate Director, NIEHS, welcomed and thanked the BSC members for their attendance and service to the NTP.

Dr. Daston introduced Dr. David Schwartz, who became the new director of the NIEHS and the NTP in June 2005.

**Recognition of Dr. Christopher Portier**
Dr. Schwartz presented a plaque to Dr. Christopher Portier for his outstanding service to the NTP while serving as Associate Director from 2001 to 2006. He acknowledged his leadership in formulating the NTP's vision for the future and developing the NTP's roadmap for the 21st century. He complimented Dr. Portier on his development of strong relationships with the NTP's federal partners and with scientists internationally. He recognized two other major accomplishments of Dr. Portier while serving as Associate Director of the NTP, namely, (1) his leadership in developing the first guidelines for evaluating non-cancer endpoints, which the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) uses to assess whether environmental chemicals are

hazards for human reproduction and/or development, and (2) the key role he played in spearheading the High Throughput Screening Initiative and forging the close ties that now exist between the NTP and the Molecular Libraries Initiative at the NIH.
Dr. Schwartz identified Dr. Portier's new role at the NIEHS as Associate Director for Risk Assessment and wished him well in his new endeavor.

**Recognition of Retiring Members**
Dr. Schwartz presented certificates of appreciation to Drs. Diane Birt, George Daston, Charlene McQueen, and Maria Morandi and *in absentia* to Drs. Elizabeth Delzell and John Giesy whose terms on the BSC expire on December 31, 2006. Specifically, he thanked Dr. Diane Birt for her contribution to the writing of the NTP Roadmap for the 21st Century, Dr. Daston for his active role in development of the NTP's Roadmap and his participation on expert panels for the CERHR, Dr. Charlene McQueen for assuming the role of chairperson for the Technical Reports Review Subcommittee and her participation as a member of the High Throughput Screening Working Group for the BSC, and Dr. Maria Morandi for representing the BSC on the Nanotechnology Working Group.

## III. Mainstreaming Environmental Health Sciences: Progress and Challenges, Hopes and Dreams

In his introductory remarks, Dr. David Schwartz said he would like investigators at the NIEHS to focus more on health sciences, which is the mandate of the NIH. His talk was divided into two parts; first he discussed the progress and challenges at the NIEHS and then he conveyed his hopes and dreams for the institute's future including a role that the NTP might play.

**Scientific Accomplishments**
Dr. Schwartz outlined and highlighted research accomplishments at the NIEHS and said NIEHS scientists have made fundamental contributions to public health in the areas of DNA repair and air pollution. They have contributed to the understanding of DNA repair pathways by identifying many of the enzymes and mechanisms involved in this complex process. Defects in DNA repair enzymes result in a number of diseases including cancer and neurodegenerative diseases as well as aging. There are two clear opportunities for the NIEHS to pursue, namely, (1) identifying susceptible populations because of polymorphisms in their repair and associated genes and (2) understanding the basic biology of this process that could contribute to the identification of therapeutic agents targeted to aid in the DNA repair process.

With regard to air pollution, he said a number of genetic loci have been identified as being involved in asthma causation, with different genes being affected depending on the type of insult. Using endotoxin as the insult, his group has shown that people who have a specific polymorphism in one of the affected genes have a lower risk of developing

atherosclerosis or dying from myocardial infarction, which may be due to lower levels of C-reactive protein.

**Progress in Program Development**

Two approaches are being used to implement the NIEHS strategic plan: (1) an integrative research approach to understanding complex human diseases and (2) recruiting and training the next generation of environmental scientists. Dr. William Martin, Director of the Office of Translational Research, will focus on strengthening integrative research through implementation of an extramural DISCOVERS center program and interdisciplinary RO1s and will oversee the new Intramural Director's Challenge program. Dr. Perry Blackshear will head a clinical research unit, which will be established at NIEHS.

The NIEHS is planning three programs targeted toward the recruitment and training of future scientists. These include a R25 program for high school and undergraduate students, T32 and K12 grants for training and career development of seasoned investigators, and the ONES program that will be awarded to new investigators attempting to link environmental exposure to a disease outcome. The investigator's previous accomplishments will be more heavily weighted than preliminary data on the topic of the grant.

Dr. Schwartz plans to increase the involvement of researchers in global environmental health programs and expand community-based research. A project is now underway that focuses on the exposure of residents to air pollutants and molds as the result of Hurricane Katrina. Other studies will focus on populations throughout the world that are exposed to high levels of indoor pollutants.

**Genes and Environment Initiative**

Dr. Schwartz briefly outlined the Genes and Environment Initiative (GEI), a Secretarial initiative in the FY 2007 budget. From 2007- 2010, $40 million/year has been earmarked for NIEHS including $26 million for human genetic case-control studies and $14 million for the Environmental Biology Program (EBP). The GEI has been designed to develop approaches to enhance the understanding of diseases caused by gene environment interactions. As an example, he noted the excellent work of Dr. Gerald Wogan from MIT who unraveled the etiology of hepatic carcinoma in humans. Dr. Wogan showed that aflatoxin and hepatitis B virus interact synergistically in causing liver cancer, and he identified biomarkers of exposure such as aflatoxin mercapturic acid conjugates, DNA aflatoxin-N7 guanine adducts, and p53 mutations in lymphocytes.

The EBP will focus on evaluating how the environment impacts health and involves the development of sensor technology and methodologies for measuring biomarkers of personal exposure. The initiative will be coordinated across NIH and centrally managed with defined goals and deliverables. Studies within the EBP will include the monitoring of diet and activity level using biological sensors and foster the development of technology to measure biomarkers of exposure. The program has three main aims: (1) to assess genetic vulnerability as the result of polymorphisms, (2) to develop environmental

sensors to improve the reliability of measures of exposure, and (3) to develop technologies to monitor biomarkers.

One project within the EBP is the airway biology program, which will focus on biomarkers of response in a number of mouse strains following exposure to ozone, cigarette smoke, allergens, and lipopolysaccharide. This approach will be used to identify susceptibility genes and morbidity factors to aid in our understanding of the complex phenotypes involved in asthma causation in humans.

In closing, he thanked the staff at the Institute for their advice and guidance relating to these initiatives and programs.

**BSC Discussion**
Dr. Toraason said the studies on the hazards of indoor air pollution would provide a great opportunity for interactions between NIEHS and NIOSH noting NIOSH's extensive experience in assessing exposures. He was pleased that the NIEHS plans to study individual susceptibility to pollutants.

Dr. Buck Louis said an initiative on reproductive outcomes would be welcome. She is especially interested in epigenomic changes during development. She suggested that the experiments be designed so that measurements are taken at different time points after exposure to evaluate changes in exposure indicators over time.

Dr. Daston was intrigued with the finding that endotoxin-induced damage is a predisposition factor for other inflammatory diseases. Dr. Schwartz responded that regulation of the process might be occurring at the cell's surface. He said a number of common pathways and mechanisms, including inflammation, oxidative stress, and mitochondrial dysfunction, could possibly be linkages between a number of diseases.

Dr. Sikka asked whether the mechanism underlying the interaction between components of a chemical mixture is being considered, and Dr. Schwartz replied that when biomarkers of exposure and biomarkers of response to a class of agents are identified then exposure to more than one agent in the class would be studied.

**Host Susceptibility Initiative (HSI)**
Dr. Schwartz asked for questions on the Host Susceptibility Initiative (HSI) being headed by Dr. John Pritchard. One objective of the HSI is to focus on areas in which the NTP and the broader scientific community might interact. The NTP and the NIEHS have supported the genotyping of 16 strains of mice by Perlegen and the company has identified 8 million SNPs. The HSI presents an opportunity for the NTP to expose different mouse strains to a broad array of environmental agents to understand how genetics contribute to health outcomes and to identify the genes that underlie phenotypic diversity. These genetic differences might help explain why an agent causes disease in some individuals and not others.

**BSC Discussion**
Dr. Daston asked if the NTP would collaborate with the Genome Research Institute that is investigating polymorphisms in humans. Dr. Schwartz responded that murine studies would lead to focused human studies and that only a few genes in mice have, to date, been found to be phenotypically important in humans.

Dr. Toraason asked if one could nominate a hypothesis for testing such as the identification of specific genes or a pathway that may play a role in a specific disease. Dr. Schwartz thought this was a unique suggestion and replied that results from the HTS assays where 1400 chemicals with some toxicity data are being tested might be used as a means for identifying those agents for priority testing in the HSI.

## IV. NTP Update

Dr. Dearry briefly highlighted some recent NTP activities and provided a status update on others. He began his report by mentioning the NTP Roadmap, which had been developed with the intent of reducing the use of long-term rodent assays and investigating the use of shorter term approaches to assess the toxicity of substances. The NTP held three workshops to initiate implementation of the roadmap, and two of these workshops would be discussed at this meeting. A fourth workshop, Biomarkers for Toxicology Studies, is planned for September 2006. The objective of this workshop is to identify biomarkers for lung and cardiac function and lipid and carbohydrate metabolism and determine their utility to the NTP testing program as a means for characterizing endpoints of environmentally induced diseases or biological processes related to disease etiology.

A recent workshop, Hormonally Induced Reproductive Tumors: Relevance of Rodent Bioassays, was held May 22-24, 2006, in Raleigh, NC. The goal of this workshop was to determine the adequacy and relevance of rodent models to assess human disease of the ovary, mammary gland, prostate, and testis. Dr. Dearry noted that Dr. Paul Foster would report on this workshop to the BSC.

The NTP sponsored a High Throughput Screening (HTS) Assays Workshop on December 14-15, 2005. The objective of the workshop was to obtain information about HTS techniques and address the potential utility of this technology for toxicology and the NTP. In August 2005, the NIEHS/NTP became a formal participant in the NIH Chemical Genomics Center (NCGC) that is focusing on the use of HTS technology to identify small molecules that can be optimized as chemical probes to study the functions of genes, cells, and biochemical pathways.

Dr. Dearry said Dr. Pritchard would make a presentation on the HSI, which Dr. Schwartz touched on briefly during his talk. The NTP hopes that this initiative will be useful for determining the relationship between genetic susceptibility and phenotypic response.

## A. Activities at NTP Centers

Dr. Dearry outlined meetings and reports completed or ongoing in two NTP Centers.

### *1. NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)*

- Di (2-ethylhexyl)phthalate (DEHP)

The CERHR convened an expert panel to re-evaluate the reproductive and developmental toxicities of DEHP. The expert panel confirmed that exposure to DEHP may pose a hazard to human development especially if exposure is to infants under one year of age.

- Genistein and Soy Formula

An expert panel met in March 2006 and concluded that there is negligible concern that genistein poses a risk to human development or reproduction and that there are insufficient human or animal data to reach a conclusion for soy formula. A summary of the meeting with the expert panel's conclusions is available on the CERHR website.

- Hydroxyurea and Bisphenol A

CERHR will be holding future expert panels meetings to evaluate the potential reproductive and/or developmental hazards to humans associated with exposure to hydroxyurea, which is used to treat sickle cell anemia, and bisphenol A, a precursor of a number of resins.

### *2. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)*

- The NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) convened a peer review panel on May 23, 2006, in Bethesda, MD. The panel evaluated the usefulness of data from two cytotoxicity assays that measure neutral red uptake to estimate the acute oral toxicity potential of test substances. The ICCVAM held a peer review of four test methods for ocular toxicity on May 11-13, 2006, at the NIH.

## B. Awards

Dr. Dearry outlined a number of awards that had been bestowed on NTP scientists at the annual meeting of the Society of Toxicology (SOT). Captain William Stokes, Director of NICEATM at the NIEHS, received the *Enhancement of Animal Welfare Award* for his contributions to reducing the use of experimental animals for research.

The Risk Assessment Specialty Section at SOT selected the paper "Dose-additive Carcinogenicity of a Defined Mixture of 'Dioxin-like Compounds'" as the winner of the best paper demonstrating the application of risk assessment for 2005. Dr. Nigel Walker, NIEHS, is the senior author.

Dr. Julia M. Gohlke, a postdoctoral fellow in the Environmental Toxicology Program at the NIEHS, won a Biological Modeling Special Section (BMSS) student poster award for her presentation "Elucidation of a Gene Regulatory Network for Forebrain Development Using Bioinformatics Approaches for the Analysis of Compiled Microarray Datasets." Dr. Gohlke was honored at the SOT BMSS reception on March 8.

# V. Roadmap Activities

## A. High Throughput Screening (HTS) Assays

### *1. HTS Assays Workshop*

Dr. Charlene McQueen a member of the NTP BSC HTS Working Group, said the purpose of the workshop was to communicate the needs of the NTP to the HTS community and educate the NTP about HTS. The plenary session at the workshop included informational presentations on the conduct of HTS assays, data handling, and the potential use of data collected from these assays by regulators. Next, the participants were divided into four breakout groups to discuss specific aspects of HTS technology. Since the NTP developed collaboration with the NCGC, a part of the NIH Molecular Libraries Initiative (MLI), some of the discussion during the plenary sessions and in the breakout groups related to this interaction.

Breakout Group 1 discussed specific targets for HTS assays, with a focus on those targets and assays that might be useful in predicting carcinogenicity. The group provided general guidance on the principles to use in selecting pathways and targets for study and recommended that the NTP preferentially consider testing a range of concentrations for each test substance to obtain concentration-response relationships. This group also proposed that the cell-based HTS assays use physiologically relevant primary cell lines that can biotransform chemicals and avoid the use of transformed cell lines, if possible.

Breakout Group 2 discussed study design and analytical methods. They concurred with Breakout Group 1 regarding the need for concentration-response studies and the use of metabolically competent primary cells. They concluded that the HTS assays must be reproducible, include concurrent controls with strong and weak responses in each plate, and minimize false negative responses. To interpret the results of most cell-based HTS assays, compounds must be tested at noncytotoxic concentrations. Although the HTS community has used dimethyl sulfoxide (DMSO) as the universal solvent, other solvents should be investigated because many environmental substances are relatively insoluble in DMSO. This breakout group stressed the importance of obtaining comprehensive chemoinformatics on the substances being tested and noted that it is difficult to test volatiles in HTS assays.

Breakout Group 3 discussed data handling. One approach is to make all HTS data publicly available in PubChem, a database of normalized data established to support the MLI. However, the group suggested that the NTP would likely need to establish its own database for HTS results to maintain information on internal controls, historical controls, and plate-to-plate variation. Also, it was considered critical that the NTP use a standard

machine language format to input HTS data to enable linkage to the current NTP toxicology database so that data can be easily mined for relationships and linkages between HTS and standard toxicological test results.

Breakout Group 4 was comprised mainly of representatives from federal regulatory agencies who discussed the potential usefulness of HTS data in making regulatory decisions on the toxicity of substances. This group concluded that HTS data presently cannot be used to make regulatory decisions, but might be used to prioritize substances for more robust testing. They also pointed out that regulators would need to become knowledgeable about HTS assays and their limitations before HTS results could be used in regulatory decision-making. They suggested that outreach programs to train regulators on the use and interpretation of HTS data would be essential. Breakout group 4 also proposed a need for criteria to evaluate HTS assays including their relevance, reliability, repeatability, sensitivity, and specificity. They said the selected assays should be accepted widely.

**BSC Discussion**

Dr Diane Birt asked whether the testing of complex mixtures was discussed, and Dr. McQueen replied that it is premature to consider mixtures until all the other parameters for the assays are worked out.

Dr. Daston said he appreciated the potency problems between testing environmental agents versus substances tested in the pharmaceutical arena. Compounds with lower potency are more likely to lead to higher false negative rates, and he endorsed testing over a large dose range to address this potential problem.

Dr. Samuel Wilson asked about the barriers to regulators accepting data from HTS assays. Dr. McQueen responded that there is a need to educate the regulators early in the use of this technology. Dr. Toraason said NIOSH would wait until such methods are scientifically accepted before considering the usefulness of HTS data. Dr. Daston replied that he anticipates NICEATM would evaluate the validity of any HTS assays proposed for regulatory purposes.

Dr. Mirsalis said in the late 1970s it was thought that *in vitro* genetic toxicology testing would replace *in vivo* studies. Subsequent research showed a 60-70% concordance between *in vitro* data and *in vivo* rodent data, and a 60-70% concordance between rodent and human data. He said it would be unlikely that a higher concordance between HTS and *in vivo* rodent data would be obtained and he hoped that scientists would not discard HTS assays due to a similar concordance. Dr. McQueen replied that the NTP does not expect that HTS will replace *in vivo* testing, but rather that this technology will prioritize chemicals or classes of chemicals for testing in animals. Dr. Daston concurred that HTS is proposed as a screen for prioritizing chemicals for further testing. He noted that in the past, exposure drove the prioritization of chemicals for testing, whereas there might be many compounds produced in smaller quantities that are more toxic and need to be tested.

Dr. Kerkvliet said the first tier of HTS assays needs to be sensitive and predictive and the cells used in these assays must respond to substances that alter different signaling pathways. She asked whether co-culturing of more than one cell line was discussed and Dr. McQueen responded that currently only one cell line is being used in each assay system.

Dr. Bradfield asked if NIH is planning to fund scientists to submit new technologies to the NCGC that could be applied to the HTS format, and Dr. McQueen responded that such a request would be made public soon.

### *2. Status of the NTP HTS Initiative*

Dr. Raymond Tice discussed the progress of the NTP HTS Initiative. A major step has been development of collaboration between the NTP and the NCGC. Dr. Portier initiated this collaboration in mid 2005 following discussions between Dr. Schwartz and Dr. Francis Collins (NIH/National Human Genome Research Institute).

The NTP Roadmap identified three main goals for its HTS initiative namely (i) to identify the mechanism of action of compounds, (ii) to develop predictive models of *in vivo* biological response, and (iii) to prioritize substances for further in-depth toxicological evaluation.

The NTP selected and shipped NCGC 1408 substances in DMSO for testing. Due to the configuration of the 1536-well microtiter plate used for HTS at the NCGC, 1408 is the number of different substances tested per plate and the other wells are used for negative and positive controls. The 1408 substances were selected because either NTP tested them in various toxicological assays or public toxicological data are available. The list includes 55 substances in duplicate to evaluate assay reproducibility. Each substance will be tested at 12-15 concentrations over a range of 5 logarithms starting at about 50 μM to obtain a concentration response curve. The intent of the NCGC is to test these substances in multiple HTS assays using stable human and comparable rodent cells lines as well primary cell lines with metabolic competency.

At the NCGC, HTS assays must meet at least two criteria. First, the duration of any cell-based assay must not be longer than 48 hours from the time the cells are added to the wells to the time the final sample is collected for analysis to avoid the loss of signal due to evaporation of the small amounts of medium used per well. Second, the assay should not involve more than six robotic manipulations. Based on these criteria, the NTP identified six commercially available assays and provided them to the NCGC. Two of these assays measure cytotoxicity, three measure different caspase activities, and one measures the activity of a membrane glycoprotein involved in drug resistance. For its first trial, the NCGC optimized one cytotoxicity assay (based on measuring ATP levels) and collected concentration-response data on the 1408 NTP substances using six human cell lines including a transformed foreskin fibroblast cell line (BJ), a lung fibroblast cell line (MRC-5), a neuroblastoma cell line (SK-N-SH), a hepatoma cell line (HepG2), an acute T-cell leukemia cell line (Jurkat), and a transformed embryonic kidney cell line (HEK293). Dr. Tice noted that some substances were cytotoxic in all cell lines while

others were active in one cell line only. The normalized values for each test substance concentration, information on the shape of the concentration-response curves, the IC50 values (the concentration causing a 50% reduction in ATP levels calculated using the Hill equation), and chemoinformatics information (e.g., structures provided by Dr. Ann Richard from the EPA Distributed Structure-Searchable Toxicity Public Database) have been loaded into PubChem, a public database for the presentation of MLI HTS data. Information on HTS protocols and assays can be retrieved from PubChem also.

Dr. Jon Freedman is testing these same 1408 substances in his developmental and reproductive assays using *Caenorhabditis elegans*. The 1408 substances may also be tested in a zebrafish embryo assay.

In support of the NTP HTS Initiative, an NIEHS HTS faculty was formed in late 2005. This faculty has established collaboration with the EPA Chemical Prioritization Community of Practice (CPCP), which is interested in using HTS assays to obtain mechanistic information and for priority setting. The two groups meet every other month to coordinate HTS-related activities such as identifying toxicity targets, additional assays suitable for HTS, and compounds of mutual interest to send to the NCGC for testing and developing informatics related to data handling and mining.

**BSC Discussion**

Dr. Daston said he is delighted that the NIEHS and EPA have begun this interaction and hopes it will extend beyond the EPA facility in Research Triangle Park to the rest of EPA personnel involved in bioinformatics. He hopes the BSC will be kept appraised of the progress and consulted regarding future assays and chemicals for testing.

Dr. Sikka said it is likely that the many different classes of compounds being tested will have different modes of action and he hopes that the assays will be sensitive enough to detect these differences. Dr. Tice responded by saying that he and his colleagues share the same concern and that they would make every attempt to ensure that sensitive and reproducible assays are used. Dr. Sikka said it is important that the NTP formulates the right questions and develops a means by which the program can mine the data to get as much information as possible.

Dr. Toraason remarked that HTS data would only be useful if they can be applied to public health questions. Dr. Tice replied that an NTP goal is to evaluate HTS assays critically for their ability to provide information relevant for understanding toxic effects in humans; however, the success of this approach cannot be fully evaluated until a large number of compounds has been tested in a significant number of assays using a variety of human and rodent cell lines.

Dr. Bradfield said the NTP should state the hypothesis before initiating testing. It is likely that the data will under predict highly toxic compounds and over predict compounds that are non-toxic. Dr. Tice replied that a number of different hypotheses could be evaluated using HTS. One example is the extent to which data from *in vitro* cytotoxicity assays might be used to predict acute oral toxicity in rodents and humans.

## B. Nanotechnology Working Group (NWG) Public Meeting

Dr. Maria Morandi, a member of the BSC on the working group, reported on the March 15, 2006 meeting in Washington, DC. The NWG is a technical advisory body established (1) to provide a structured and formal mechanism for bringing stakeholders together to learn about NTP nanotechnology research related to public health, address issues related to that research, and promote dissemination of those discussions to other federal agencies, nanotechnology stakeholders, and the public and (2) to provide advice and comments to NTP on its proposed studies. The NWG consists of representatives from non-profit public and environmental organizations, academia, and industry. Dr. Steve Roberts, University of Florida, serves as Chair.

Presentations about research endeavors on nanotechnology were made by representatives from the National Institute for Standards and Technology (NIST), National Cancer Institute, EPA, National Environmental and Health Implications (NEHI) Working Group, NTP, and NIEHS. NIST is involved in nanoparticle characterization and standardization of samples submitted by the scientific community. About 15% of its budget has been directed to this effort. The NCI Nanotechnology Characterization Laboratory located in Frederick, Maryland focuses on the application of nanotechnology for diagnostic and therapeutic efforts and studies the toxicity of nanoparticles with different surface functional groups. The EPA, which has budgeted $9 million for FY2005-06, has written a white paper on nanotechnology and is offering Science to Achieve Results (STAR) grants. The EPA is also working with the Organization of Economic Co-operation and Development (OECD) and other European groups to develop a tiered testing protocol for nanomaterials. Dr. Celia Mertzbacher representing the Office of Science and Technology presented an update from the NEHI Working Group on a document on research needs for nanotechnology. NEHI coordinates the nanotechnology activities among federal agencies and decides on important future research issues for agencies to address. Dr. Nigel Walker outlined NTP's goals, the classes of materials that will be studied, the experimental strategy, and impediments to progress relating to obtaining enough purified compound for study. Dr. Sally Tinkle from the NIEHS, Division of Extramural Research and Training discussed the second interagency research solicitation, collaborative activities between NIH institutes, and recent NIEHS meetings and workshops.

## C. Hormonally Induced Reproductive Tumors: Relevance of Rodent Bioassays Workshop

Dr. Paul Foster discussed the third NTP Roadmap workshop held on May 22-24, 2006, in Raleigh, North Carolina. The workshop's topic was chosen because the NTP is encountering more substances that produce tumors via hormonally mediated mechanisms and is uncertain how to evaluate their relevance to human health. Tumors of endocrine tissues (e.g., breast and prostate) are some of the most commonly encountered tumors in human populations. Some regulatory agencies have asked whether reproductive tumors observed in animals develop through mechanisms that are applicable to humans. For example, the induction of breast tumors in rats after atrazine exposure seems to occur via a rodent-specific mechanism; therefore, the relevance of this tumor to human health is questionable.

Background presentations on the first day of the workshop covered clinical and epidemiological information on human tumorigenesis in the ovary, breast, testis, and prostate. The usefulness of rodent models for studying hormonally mediated carcinogenesis in these tissues and the mechanisms by which these tumors are produced were also discussed.

On the second day, the invited attendees and members of the public participated in four breakout groups, one for each of the four target tissues. The charge to the breakout groups was to determine the adequacy and relevance to human disease outcomes of rodent models to study these hormonally induced reproductive tumors.

On the morning of the third day, the breakout group chairs presented summaries of the discussions. For the ovary, the breakout group attendees agreed that the rodent models are not useful indicators of human response. Certain transgenic and *in vitro* models may be more predictive, but they need further evaluation. For the mammary gland, the breakout group concluded that the rat is a better model for this tumor type than the mouse and that there is not enough information to evaluate the false positive and false negative data that have been obtained in rodents. The breakout group on the prostate concluded that current NTP models and most other transgenic models are not useful to study prostate tumors because they are rarely recorded in rodents. For the testis, the breakout group said the rodent model is sensitive for detecting Leydig cell tumors, but not germ cell tumors, which is the tumor type most frequently encountered in humans. This group also noted a significant disadvantage of using the F344 rat for the identification of testicular tumors due to its insensitivity to other hormonally mediated tumor types and high background tumor rate particularly leukemia, which complicates the interpretation of subtle pathological changes in many tissues.

Workshop participants made the following suggestions regarding future activities:

- Add interim necropsies to distinguish between chemically induced tumors and high background values for some tissues.
- Make tissues available for extramural scientists to study the mode of action of a chemical.
- Add additional endocrine responsive endpoints, such as periodic vaginal smears and a whole mount of the mammary gland, to the study protocols.
- Be flexible in the design of studies, but keep some parameters constant between studies for comparative purposes.
- Use different models and windows of exposure to detect effects particularly when the prostate is the suspected target site.
- Evaluate the importance of developmental programming in hormonally dependent tissues that might lead to pre-neoplastic events and tumors, especially if exposure is *in utero* or early in neonatal development.
- Consider the use of an $F_1$ cohort from NTP reproduction studies in the Sprague Dawley rat for chronic bioassays. Such an approach was used in a recent report on genistein.
- Differentiate between hormonally induced versus hormonally mediated pre-neoplastic events and tumors.

A fourth workshop, Biomarkers for Toxicology Studies will be held on September 20-21, 2006, at the NIEHS. NTP staff will then synthesize the input from all the NTP Roadmap workshops and present this information to the BSC at a future meeting.

**BSC Discussion**
Dr. Vernon Walker, who chaired the workshop, agreed that the workshop was interesting. He said Dr. Bucher had stated at the workshop his disappointment that no biomarkers to understand the development of hormonally induced tumors were presented or available. Dr. Walker added that genetic changes are not as easy to identify in tumors in reproductive organs as in tumors in other tissues, and the study of biomarkers for hormonally induced tumors is in its infancy. Previous studies attempting to ascertain hormonally derived tumors using Sprague Dawley rats has not progressed well, but an approach to studying the F1 generation of exposed adults might be informative.

Dr. Daston said the information from forthcoming cancer studies on β-estradiol, nonylphenol, and ethinyl estradiol might provide useful information to support the utility of a perinatal exposure dosing regime of compounds that might induce tumors via a hormonally mediated mechanism.

## VI. Concept Review

Ms. Jo Ann Lewis, Office of Acquisitions in the Division of Extramural Research and Training, provided guidance to the BSC for review of the concept. She said the BSC should evaluate the value and scientific relevance of the proposed activity; the availability of technology; the extent to which practical, scientific, or clinical uses are identified for the anticipated results; and the adequacy of the methodology for performing the activity and obtaining meaningful results. Discussions should not cover details of the project or request for proposals, specific technical approaches, or data questions.

**NTP/NIEHS Inhalation Facility Support Contract**

Dr. Daniel Morgan informed the BSC that the review of the concept is necessary because it has been five years since the last review and the contract will be re-competed with a change in the statement of work when the present contract expires in January 2007. The new contract will be for four years with three two-year extensions. The purpose of the contract is to provide inhalation support for the NTP and for intramural investigators in the Division of Intramural Research, NIEHS. The contract will be used to investigate mechanisms of toxicity, evaluate dosimetry, and develop inhalation exposure technology and models of respiratory disease. He outlined other requirements including a location close to NIEHS and dedication of the facility to NIEHS' requirements. The contract is needed because the measurement of exposure through inhalation is technically difficult and requires specially designed air handling capabilities for gases and vapors, aerosol generation, monitoring equipment, exposure chambers, and considerable engineering expertise.

The statement of work (SOW) contains three main tasks, namely to: (1) provide space for the operation of an inhalation facility, (2) maintain an animal facility, and (3) conduct studies. Proposed changes to the previous SOW include a significant increase in space for housing and maintenance of a large number of genetically modified mice, an increase in the number of rooms to perform inhalation exposures, capacity to perform different types of exposures in different rooms, an increase in animal maintenance personnel to allow the more skilled personnel to undertake necropsies and other animal procedures, and the procurement of animals and supplies by the contractor rather than by the government. These changes will streamline animal ordering, increase animal holding and exposure capacity, increase space for necropsies, reduce scheduling conflicts, and increase quality and quantity of work.

**BSC Discussion**
Dr. Walker said it is important to continue the pharmacokinetic and dose-response studies and have ready access to the facilities where exposure will occur. He is concerned about the increased number of studies and questioned whether the contractor would have the requisite technology. He asked whether gaseous and particulate exposures were the norm and whether primary and secondary stressors are included in the exposure regimens. Dr. Morgan replied that exposure is usually to gases, vapors, and liquid aerosols with an emphasis on small and short-term studies. He said the contractor is expected to be familiar with special techniques such as administering a challenge before or after exposure to the gas. Dr. Walker asked if the present contractor is aware of the high cost of genetically modified mouse models and Dr. Morgan replied that they are cognizant of these costs. Dr. Walker said in the near future the Institutional Animal Care and Use Committee will require different exposure chambers for mice and rats, and this requirement should be considered in projecting the cost.

Dr. Mirsalis asked whether the large outlay in cost of the facilities would be borne by the government or whether the contractor would provide the facilities. Dr. Morgan responded that it is the responsibility of the contractor to provide the facility, and the Government will provide most of the exposure equipment.

The Chair called for a motion; Dr. Mirsalis proposed that the NIEHS continue the support of this activity through a contract and Dr. McQueen seconded the motion. It passed unanimously with 13 yes votes and 0 no votes.

## VII. NTP BSC Technical Reports Review Subcommittee

Dr. Charlene McQueen, Chair of the Subcommittee, summarized the actions on the draft NTP Technical Reports reviewed at the meeting on September 27-28, 2005. The Subcommittee reviewed reports on dibromoacetic acid, divinylbenzene, methyl isobutyl ketone, diisopropyldicarbodiimide, and methylimidazole using conventional F344 rat and $B6C3F_1$ mouse models. Dr. McQueen outlined the neoplastic lesions found in these studies. The findings on the photocarcinogenicity of glycolic or salicylic acid in SKH-1 mice exposed to simulated solar light (SSL) were also presented. A photoprotective affect of salicylic acid was observed, but glycolic acid did not alter the latency of SSL to

cause dermal carcinomas. Draft reports were also reviewed on dichloroacetic acid, bromodichloromethane, sodium bromate, and diisopropylcarbodiimide tested in p53 and Tg.AC genetically modified mouse models.

Dr. McQueen also mentioned the draft reports reviewed the previous day including a multigenerational study of genistein and three draft NTP Technical Reports on genistein, α-methylstyrene, and methylene blue trihydrate. She said the outcomes of these reports would be presented to the BSC at its next meeting.

**BSC Discussion**
Dr. Kerkvliet asked whether the exposure duration was shorter for the studies with the p53 mice compared to the conventional 2-year bioassay, and Dr. McQueen replied that the p53 mice were exposed for 6 or 9 months.

Dr. Keith Soper proposed and Dr. Jon Mirsalis seconded a motion for the BSC to vote *en bloc* to accept the Subcommittee's recommendations on the draft NTP Technical Reports. The motion passed unanimously with 13 yes votes and 0 no votes.

## VIII. NTP Study Nominations and ICCEC Recommendations

Dr. Scott Masten briefly outlined the review and selection process for substances nominated for study by the NTP. He noted that the process includes review by multiple advisory groups and opportunities for public comment. Following a review by the Interagency Committee for Chemical Evaluation and Coordination (ICCEC), the NTP announces preliminary study recommendations for each nomination in a Federal Register notice and solicits public comments. Next, the BSC followed by the NTP Executive Committee reviews the nominations and study recommendations. Once a nomination is selected, studies are initiated as time and resources permit.

Dr. Masten said 10 new nominations are currently under review; 8 are recommended for study, and 2 for deferral until further information is available.

**BSC Discussion**
Prior to the meeting, the NTP asked individual BSC members to serve as lead discussants for specific nominations.

*Arbutin*
The BSC questioned the rationale for studying arbutin in rodents as the metabolism may differ in rodents and humans. Hydroquinone (HQ), a rodent carcinogen, is formed from the cleavage of the glycosidic moiety in humans but less efficiently in rodents. Dr. Masten said the Cosmetic, Toiletry and Fragrance Association (CTFA) provided a human dermal study where HQ was found in urine, although the study did not rule out the possibility that HQ could have originated from sources other than topically applied arbutin. Some members of the BSC questioned whether metabolism studies should precede the more expensive toxicity studies. The question arose as to whether toxicity studies should be undertaken at all. Dr. McQueen said metabolism studies would

indicate whether similarities or differences exist in the metabolism of arbutin in humans and rodents. If rodents differ from humans, other models should be sought. Dr. Allaben explained that the FDA has limited ability to regulate these products, as no pre-market approval is needed; thus the FDA turns to the NTP to undertake studies on dietary supplements. Dr. Sikka asked if data are available in other species besides humans and rats, and Dr. Masten said there is little information on any other species. Dr. Masten explained that the reason for undertaking studies with arbutin is not solely to investigate HQ formation, but rather that there are limited safety data and widespread consumer use.

Dr. Daston summarized the discussion by stating that the BSC believes that there needs to be a more logical framework as to which studies to undertake and a rationale for each study. He suggested that the NTP carefully define the sequence of studies that would be undertaken. Dr. Dearry said the BSC's role is to comment on whether the proposed studies are a worthwhile endeavor rather than to prioritize studies.

*Phenoxyethyl acrylate*
The BSC agreed that studies on phenoxyethyl acrylate should be deferred pending further evaluation of toxicity data that would be made available by the industry sponsor through the Extended High Production Volume (EHPV) program. EHPV is a voluntary industry program whereby exposure data are made available publicly. Dr. Masten responded to a question regarding the types of tests performed by industry through the EHPV program by stating that the toxicology studies are usually of short-term duration of 4-8 weeks.

*Trifluoromethylbenzene*
Dr. Masten said although toxicity data on trifluoromethylbenzene (TFMB) are lacking, TFMB is replacing chlorinated solvents in some cleaning applications. Since the chlorinated analog benzotrichloride is a multi-site rodent carcinogen, there is concern that TFMB may also be a carcinogen. However, toxicity data on TFMB are limited and it is presently being tested in the OECD Screening Information Data Set (SIDS) program.

Dr. Soper said TFMB is a chemically stable compound, which is thought to bioaccumulate in the environment. Dr. Kerkvliet asked whether a study is necessary since the chlorinated isomer is a known carcinogen and Dr. Masten responded that carcinogenicity could not be predicted based solely on structure-activity relationships. The BSC agreed with the recommendation for deferral pending review of (1) the forthcoming Toxic Substances Control Act Inventory Update Rule on production data and (2) the OECD SIDS program's output.

*Ceric oxide (Microscale and nanoscale forms)*
Ceric oxide is used in microelectronics polishing, as a catalyst in petroleum refining, and as a diesel fuel additive to reduce harmful emissions. Using nose-only exposure, a variety of lung effects were observed in a subchronic inhalation study of microscale ceric oxide undertaken by Rhodia.

Dr. Bradfield asked if there had been any characterization of particle size in the subchronic study. Dr. Glenn Simon from Rhodia replied that if nanoscale particles were

present they would have been in very low concentrations due to the agglomeration of ceric oxide in the exposure chambers. Dr. Simon said he supports a study to evaluate the toxicity of nanoscale versus microscale particles of ceric oxide and considers the possible difference in kinetics as an important parameter in designing studies.

Dr. Buck Louis was concerned that if ceric oxide were incorporated into fuels, a larger percentage of the population would be exposed. She said ceric oxide is an additive in ophthalmic solutions, which would support the recommendation for dermal studies.

Dr. Morandi said ceric oxide has been used as an additive to diesel fuel for buses in the United Kingdom and Europe for more than 10 years and asked why Rhodia had not registered it in the United States. Dr. Simon responded that Rhodia applied for registration of several cerium products as fuel additives, but the EPA turned down the application because there was a concern regarding the release of cerium in the United States.

The BSC agreed with the recommendation for toxicological characterization including chemical disposition and toxicokinetics studies, and comparative inhalation toxicity and dermal penetration studies of both the microscale and nanoscale forms.

*Gypsum, natural and synthetic forms*
Gypsum (calcium sulfate dihydrate) is a naturally occurring fibrous or non-fibrous mineral that is not persistent *in vivo*. Since non-specific lung effects have been reported with other particulates, there is concern that it might be a respiratory hazard. There was widespread human exposure to gypsum after the attack on the World Trade Center (WTC); however, there is only very weak evidence that it can cause pulmonary toxicity, although there is a lack of well-conducted epidemiology studies.

The BSC agreed with the recommendation that gypsum be tested in short-term pulmonary toxicity studies, but they considered it to be of relatively low priority. Dr. Morandi said it appears to be very soluble in body fluids and there is no evidence that it is a health hazard. Dr. Crump agreed with Dr. Morandi and said it is of low toxicity even in its fibrous form and is a nuisance dust with a short half-life. He asked why the NTP wants to compare intratracheal and inhalation exposure routes. Dr. Masten responded that the intratracheal route is easier and cheaper and could be used for more in-depth kinetic studies if lung deposition is similar between the two routes. If a long-term study were warranted, the inhalation route would be used. The BSC differed in its views on whether comparative intratracheal and inhalation studies are necessary.

Dr. Mirsalis said one of the manufacturers claims that it has employee medical monitoring data collected over 20 years. If the company will provide the data, this information would be far more useful than any animal study. If these human data are not available, the NTP should undertake a minimal set of animal studies.

**Public Comment**
Dr. Byers, USG Corporation, said the company has been manufacturing sheetrock and various types of gypsum since 1902. The company has funded human monitoring studies of miners and manufacturing workers for 25 years. Although annual physicals of these workers have not found an excess of lung disease or fibrosis, Dr. Byers does not have the authority to release this medical information. The company also has not found an excess of lung tumors in rodents exposed by inhalation. He said WTC dust was highly alkaline compared to natural and synthetic gypsum.

Dr. Allaben inquired why employees have annual X-rays and why the results on the workers are not compared to an unexposed group. Dr. Byers did not respond directly to Dr. Allaben, but said the company performs industrial hygiene testing for gypsum dust every two years and attempts to keep the level of dust close to $2mg/m^3$ in the facility.

Dr. Mirsalis said the animal study sponsored by USG was a single intratracheal exposure followed by an unexposed period of 26 weeks before sacrifice. The NTP should review this study before undertaking any studies in animals.

*Flame retardants*
The Consumer Product Safety Commission (CPSC) nominated the functional class of flame retardants for testing due to possible risks to consumers exposed to furniture, bedding, and other products sprayed with these chemicals. There are also potential risks to workers involved in manufacturing these chemicals and to the general public due to environmental release after disposal. The CPSC staff and the National Research Council (NRC) have conducted risk assessments and/or toxicity reviews on 16 flame retardant chemicals or chemical classes. Of these, the CPSC nominated 11 flame retardant chemicals for testing because more data are needed to better characterize potential risks. The 11 flame retardant chemicals are: antimony trioxide, decabromodiphenyl oxide, a mixture of four isomers of tris(chloropropyl)phosphate), phosphonic acid, (3-((hydroxymethyl)amino)-3-oxopropyl)-dimethyl ester, tris(hydroxymethyl)phosphine oxide, and aromatic phosphates.

*a. Antimony trioxide*
Antimony trioxide (ATO) was previously recommended for cardiac toxicity, chronic toxicity, and carcinogenicity studies via inhalation, but is now recommended for chronic oral toxicity studies.

Dr. McQueen asked why chronic inhalation studies were requested since there are several reports of inhalation studies in rats. Dr. Masten responded that these studies are considered inadequate for assessing potential carcinogenicity. Dr. McQueen then asked if NTP would investigate whether nanoparticles are released from the burning of antimony trioxide, and Dr. Masten said the NTP likely would not undertake such a study but would seek this information from other sources.

Dr. Morandi and Dr. McQueen said they support the nomination for oral studies, but Dr. Kerkvliet asked about the justification of using the oral route since the BSC previously

approved inhalation studies. Dr. Masten said the inhalation studies have not started yet, and the NTP could conduct short-term exposure studies via both routes and a longer-term exposure study via the inhalation or oral route.

Dr. Sikka asked whether dermal studies are appropriate, and Dr. Masten replied that this would be reasonable, but the oral route of exposure is preferred for investigating systemic effects.

Dr. McCarver suggested that studies with ATO should be via the dermal and oral routes in combination with other flame retardants to mimic human exposure.

The BSC agreed with chronic oral toxicity studies and said if nanoscale particles are released during flame retardant applications, this form should be considered for study.

**Public Comment**
Dr. James Deyo, Eastman Chemical Company, representing the International Antimony Oxide Industry Association (IAOIA), supported the nomination because of human exposure in occupational settings and non-occupational exposures from food and drinking water, and because there is not an adequate two-year study. There was minimal toxicity in a 90-day study when 2% ATO was added to the diet. ATO was positive in an *in vitro* clastogenic study, but negative *in vivo*. He reported on three long-term inhalation studies in which conflicting results were obtained even though the same concentration was used in two experiments. Dr. Deyo suggested that new studies are needed with animals exposed by inhalation and the oral route. Dose setting is important to avoid particle overload, and new studies should include retention kinetics and measures of inflammation and cell proliferation in the lung.

In response to a question from the BSC, Dr. Deyo said particle size was not well characterized in the first study where tumors were found, but a respirable-sized particle was used in the subsequent two studies where particle loading was observed in macrophages.

Dr. Daston summarized the discussion by saying that the IAOIA agrees with the BSC's recommendations.

*b. Decabromodiphenyl oxide*
Decabromodiphenyl oxide is persistent in the environment and there is concern that it may undergo dehalogenation to more bioavailable congeners. There is extensive toxicity information available, but there is a need for neurotoxicity studies following developmental exposures. If a developmental neurotoxicity study, which is being planned by industry to satisfy European Union (EU) regulatory requirements, is implemented, it will be unnecessary for the NTP to duplicate the effort.

Dr. McCarver said there is increasing use of decabromodiphenyl oxide and the conduct of such a study is important. Consideration should be given to the vehicle for exposure and the timing of administration. She asked Dr. Masten if the NTP participated in the design

of the industry study and he said no, but he believes the parties involved are cognizant of these factors and the importance of testing a highly pure substance.

The BSC agreed with the recommendation to undertake developmental neurotoxicity studies with exposure via the oral route if an adequate private sector study is not undertaken.

*c. Tris(chloropropyl)phosphate), mixture of four isomers*
Dr. Walker said tris(chloroethyl)phosphate (TCEP) has been used as a flame retardant, but has been replaced by tris(chloropropyl)phosphate (TCPP) in some applications because TCEP induces kidney tumors in F344 rats and in two strains of mice. Both TCPP and TCEP are clastogenic *in vitro*, and since TCEP is a non-genotoxic carcinogen, it seems reasonable to test TCPP. He questioned using the oral route of exposure, even though both isomers are minor contaminants in surface water, because volatilization from carpeting and other indoor products is more likely to impact a larger population. Dr. Masten responded that the NTP typically selects oral exposure regimens unless there is a compelling reason to use another route.

The majority of the BSC agreed with the recommendation that TCPP be tested in oral subchronic and chronic toxicity studies using the commercial mixture or one of the four major isomers found in various proportions in the commercial mixture.

*d. Phosphonic acid, (3-((hydroxymethyl)amino)-3-oxopropyl)-, dimethyl ester*
Although phosphonic acid, (3-((hydroxymethyl)amino)-3-oxopropyl)-, dimethyl ester (PA) is covalently bound to fabrics, it may be released over time. There is limited toxicity data on PA and the BSC concurred with the recommendation for oral subchronic and chronic toxicity studies and for dermal absorption studies.

*e. Tris(hydroxymethyl)phosphine oxide*
Tris(hydroxymethyl)phosphine oxide (THPO) is a metabolite and possible degradation product of the parent compound tris(hydroxymethyl)phosphine chloride (THPC), a reactive flame retardant used on cellulosic fibers. Exposure to THPC is unlikely, as it is bound covalently to the fibers. TPHC was not carcinogenic in NTP 2-year gavage studies although a number of non-neoplastic findings were documented.

Dr. Sikka said it seems unlikely that THPO would be released from fibers placed in water and doubted whether it is bioavailable. He asked if NTP has any data on the aqueous extraction of TPHO or other potential breakdown products from the fabrics and, if so, whether they have been identified. Dr. Masten replied that CPSC would like to have this kind of information.

Dr. Crump questioned whether it is necessary to test several similar flame retardants in subchronic and chronic studies especially if they are covalently bound to fabrics and, thus exposure is likely to be low. He said that it would be very useful for the NTP to conduct studies to assess exposure to flame retardants.

The BSC agreed with the recommendation that THPO be tested for oral subchronic and chronic toxicity studies and dermal absorption studies.

*f. Aromatic phosphates*
The class of chemicals known as aromatic phosphates includes *tert* butylphenyl diphenyl phosphate, 2-ethylhexyl diphenyl phosphate, isodecyl diphenyl phosphate, phenol, isopropylated, phosphate (3:1), tricresyl phosphate (TCP), and triphenyl phosphate. Some commercial flame retardant formulations contain mixtures of several different aromatic phosphates. Neurotoxicity and reproductive toxicity have been demonstrated for some of the chemicals in this class. The NTP tested TCP and there was no evidence of carcinogenicity.

Dr. Kerkvliet asked whether it might be more informative to study a mixture and compare this data to what is known about TCP or other individual chemicals in the class. Dr. Masten replied that industry has performed studies on commercial mixtures, but little is known about the individual compounds, so this type of data would be useful to the CPSC.

The BSC agreed with the recommendation that selected aromatic phosphates be tested in subchronic and chronic toxicity studies and in neurotoxicity and/or developmental neurotoxicity studies using the oral route of exposure. However, before this endeavor is initiated, the NTP needs to coordinate with the U.S. EPA because additional testing might be required of manufacturers.

*tert-Butylacrylamide*
The BSC agreed with the recommendation that *tert*-butylacrylamide be studied for metabolism and disposition, subchronic toxicity, and mammalian genotoxicity, with the extent of these studies being dependent on any additional information that might be supplied by the industry sponsor through the EHPV Program. Dr. Mirsalis agreed with the recommendation and said a 90-day subchronic toxicity study with an *in vivo* micronucleus endpoint should be undertaken. He suggested that an assessment of neurotoxicity be included in the 90-day study and said *in vitro* genotoxicity studies would be of little value.

*Diazonaphthoquinone derivatives*
The BSC agreed with the recommendation for *in vitro* genotoxicity, immunotoxicity, phototoxicity, and dermal absorption studies. Dr. Kerkvliet said immunotoxicity studies are appropriate given the potential that these compounds are sensitizers; however, she was not aware of suitable *in vitro* approaches to assess this endpoint. Dr. Mirsalis noted the possibility of environmental contamination from past use and the potential for occurrence in drinking water. He agreed with the concern for immunotoxicity and suggested consideration of the local lymph node assay. He further commented that an *in vivo* micronucleus study is warranted.

*3-Dimethylaminopropyl methacrylamide*
The BSC agreed with the recommendation that metabolism and disposition, genotoxicity, and subchronic toxicity studies be undertaken for 3-dimethylaminopropyl methacrylamide, but that the priority for testing is low. The NTP should review study data for related chemicals and consider any additional information that might be supplied by the industry sponsor through the EHPV Program. Although there is little information on this chemical, Dr. Walker noted that there appears to be some potential for exposure to consumers and effects on the spleen and testis were observed in a single short-term toxicity study. Dr. Mirsalis suggested that metabolism studies be undertaken first to aid in prioritizing any further toxicity studies.

*N-Methyl-3-oxobutanamide*
The BSC agreed with the recommendation that N-methyl-3-oxobutanamide be tested for *in vitro* and *in vivo* genotoxicity and the studies should include structurally related diketene compounds and selected N-phenyl derivatives, which are used as pigments in cosmetics in the studies.

## IX. Host Susceptibility Initiative

Dr. John Pritchard said the initiative is still being planned, but it would focus on gene environment interaction, individual susceptibility, and their relationship to disease. The initiative will leverage the types of studies NTP is presently doing and determine whether the generated data could contribute to the identification of specific genes involved in disease causation. Initially, the NTP will select mouse strains for testing, identify endpoints from NTP standard testing approaches, perform tests on the selected strains, and communicate the findings to NIEHS Division of Intramural Research (DIR) scientists and the scientific community at large. The NTP will meet with four mouse geneticists to discuss how many and which strains to use, whether different strains are needed for different end points, the length of the studies, and what has to be factored into the experimental design so that appropriate statistical analyses can be performed.

Ideally each endpoint selected should be important to a critical biological system, have a clear link to the human disease of interest, and be able to be tested in an appropriate mouse strain. Multi-strain testing will then be performed by contract under the direction of a NTP staff scientist. It is envisioned that study design for the multi-strain assessment will be assigned to the scientist who designed the original study since it is anticipated that the chemicals selected for evaluation will be based on prior NTP studies. The NTP will use a team approach and scientists with expertise in chemistry, pathology, pharmacokinetics, and bioinformatics will be consulted. Those studies that identify clear differences in strain susceptibility will be reported directly to DIR scientists and extramural scientists to pursue translation of the findings as a means for providing an increased understanding of the genetic basis for the toxicity and disease responses.

**BSC Discussion**
Dr. Daston asked whether the large amount of data from the single nucleotide polymorphism (SNP) mapping study would be available to the public. Dr. Bucher

responded that this information would be entered into GeneBank and would be on the Perlegen website. He said this database would be a resource for selecting the right strains for testing.

Dr. Allaben said he hoped the NTP interagency partners would be involved in the discussions on strain selection. Dr. Dearry said Dr. Bucher mentioned the program at the last NTP Executive Committee meeting and he welcomes participation from FDA and other agency partners.

Dr. Buck Louis said it is important to involve all the stakeholders early in the process and if NTP wants to have cooperation with DIR scientists and statisticians, they need to be involved in the planning discussion with any outside advisory group. Dr. Pritchard concurred and said the advisory group could speak knowledgably about the issues concerning strain selection and use, but that the final decisions regarding all aspects of study design would be made by NTP scientists with the continuing input of NTP member agencies, as well as other interested groups.

Dr. Kerkvliet said she was excited and supportive of this initiative and it would dovetail well with the HTS initiative.

Dr. Morandi asked how the choice of the murine strains would relate to what is known from human genetics. Dr. Pritchard replied that Dr. Schwartz's reference to asthma on the study of exposure to environmental agents as a means of identifying genes would be used as a probe to link findings in rodents with clinical data. Dr. Morandi added that there is a large difference in the incidence of asthma in different human populations in the United States, and the genetic information from these populations might be useful in studying susceptibility. Dr. Pritchard said the endpoints chosen would depend on information the NTP has from previous studies as well as human clinical data. Dr. Bucher said the exposure biology program has mouse, human and non-human primate components, and would seek biomarkers in tissues from these species exposed to the same pollutants.

Dr. McQueen recalled that a breakout group from the strains and stocks workshop dissuaded the NTP from using multiple strains in their bioassay testing program, but possibly information from this initiative might aid the NTP in choosing additional strains for bioassays. Dr. Bucher replied that multiple stains would not be used routinely in the NTP testing program; however, if a specific result indicates that multiple strains should be used to test a particular chemical, the NTP would do so.

Dr. Soper said the sequencing of numerous strains may reveal an interesting pattern of SNPs, but these data are not informative about which part of the genome to study.

Dr. Daston summarized the discussion and said it is reasonable to use the SNPs database from the 15 strains, but informatics need to be used to correlate these differences with toxicity outcomes.

Dr. Dearry thanked the BSC members for their participation and the very important input they provided to the NTP at this meeting.

The meeting was adjourned at 4:45PM.

**NTP Board of Scientific Counselors Meeting**
**Agenda**

Rodbell Auditorium, Rall Building
National Institute of Environmental Health Sciences
Research Triangle Park, NC
June 13, 2006

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| | | |
|---|---|---|
| 8:30 AM | **Introductions** | Dr. George Daston, Procter and Gamble, Chair |
| 8:40 | **Welcome and NIEHS' Activities**<br>• Recognition of Dr. Christopher Portier<br>• Recognition of Retiring Members<br>• Introduction of Dr. Allen Dearry, Interim Associate Director, NTP<br>• NIEHS' Strategic Plan: New Frontiers in Environmental Sciences and Human Health<br>• Exposure Biology Program | Dr. David Schwartz, NIEHS |
| 9:30 | **NIEHS/NTP Update**<br>• Public Comments<br>• Board Discussion | Dr. Allen Dearry, NIEHS |
| 9:45 | **Roadmap Activities**<br>• High Throughput Screening Assays (HTS)<br>o Working Group activities<br>o Status of NTP HTS Initiative | <br><br>Dr. Charlene McQueen University of Arizona<br>Dr. Raymond Tice, NIEHS |
| 10:30 | **BREAK** | |
| 11:00 | **Roadmap Activities (continued)**<br>• Nanotechnology Public Meeting, March 15, 2006<br>• Hormonally-Induced Reproductive Tumors: Relevance of Rodent Bioassays Workshop | <br>Dr. Maria Morandi, University of Texas Health Sciences Center<br>Dr. Paul Foster, NIEHS |
| 11:30 | **Concept Review**<br>NTP/NIEHS Inhalation Facility Support Contract (**ACTION**)<br>• Public Comments<br>• Board Discussion | Dr. Daniel Morgan, NIEHS |
| 12:00 PM | **LUNCH** | |

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|---|---|---|
| 1:00 PM | **Technical Reports Review Subcommittee**<br>• Report of September 27-28, 2005 Meeting **(ACTION)**<br>• Public Comments<br>• Board Discussion | Dr. Charlene McQueen<br>University of Arizona |
| 1:30 | **NTP Study Nominations and Recommendations**<br>• Public Comments<br>• Board Discussion | Dr. Scott Masten, NIEHS |
| 3:00 | **BREAK** | |
| 3:30 | **NTP Study Nominations and Recommendations**<br>• Public Comments<br>• Board Discussion | Dr. Scott Masten, NIEHS |
| 4:00 | **Host Susceptibility Initiative**<br>• Public Comments<br>• Board Discussion | Dr. John Pritchard, NIEHS |
| 4:30PM | **ADJOURN** | |

| Type of respondents | Estimated number of respondents | Estimated number of responses per respondent | Average burden hours per response | Estimated total annual burden hours requested |
|---|---|---|---|---|
| **Collection and submission of materials** | | | | |
| Individuals at academic institutions | 910 | 1 | 0.50 | 455 |
| Annualized totals | 1820 | | | 1128 |

The annualized cost to respondents is estimated at $31,978.86, $6,189.46 for survey completion, and $12,894.70 for the review of course information and collection and submission of materials, respectively.

There are no Capital Costs to report. There are no Operating or Maintenance Costs to report.

*Request for Comments:* Written comments and/or suggestions from the public and affected agencies are invited on the following points: (1) Whether the proposed collection of information is necessary for the proper performance of the function of the agency, including whether the information will have practical utility; (2) The accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions; (3) Ways to enhance the quality, utility, and clarity of the information to be collected; and (4) Ways to minimize the burden of the collection of information on those who are to respond, including the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology.

**FOR FURTHER INFORMATION CONTACT:** To request more information on the proposed project or to obtain a copy of the data collection plans and instruments, contact Dr. Paul M. Coates, Director, Office of Dietary Supplements, National Institutes of Health, Suite 3B01, 6100 Executive Boulevard, Bethesda, MD 20892–7517; or fax your request to 301–480–1845; or e-mail *ods@nih.gov*. Dr. Coates can be contacted by telephone at 301–435–2920.

*Comments Due Date:* Comments regarding this information collection are best assured of having their full effect if received within 60 days of the date of this publication.

Dated: April 13, 2006.

**Paul M. Coates,**

*Director, Office of Dietary Supplements, National Institutes of Health.*

[FR Doc. E6–5922 Filed 4–19–06; 8:45 am]

BILLING CODE 4140–01–P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### National Toxicology Program (NTP); Liaison and Scientific Review Office; Meeting of the NTP Board of Scientific Counselors

**AGENCY:** National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).

**ACTION:** Meeting announcement and request for comments

**SUMMARY:** Pursuant to Public Law 92–463, notice is hereby given of a meeting of the NTP Board of Scientific Counselors (NTP BSC). The NTP BSC is composed of scientists from the public and private sectors and provides primary scientific oversight to the Director for the NTP and evaluates the scientific merit of the NTP's intramural and collaborative programs.

**DATES:** The NTP BSC meeting will be held on June 13, 2006. In order to facilitate planning for this meeting, persons wishing to make an oral presentation are asked to notify the Executive Secretary for the NTP BSC by May 31, 2006 (see **FOR FURTHER INFORMATION CONTACT** below). Written comments should also be received by May 31, 2006, to enable review by the NTP BSC and NIEHS/NTP staff prior to the meeting. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, should contact 919–541–2475 (voice), 919–541–4644 TTY (text telephone), through the Federal TTY Relay System at 800–877–8339, or by e-mail to *niehsoeeo@niehs.nih.gov*. Requests should be made at least 7 days in advance of the event.

**ADDRESSES:** The NTP BSC meeting will be held in the Rodbell Auditorium, Rall Building at the National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709.

**FOR FURTHER INFORMATION CONTACT:** Public comments and any other correspondence should be submitted to Dr. Barbara Shane, Executive Secretary for the NTP Board (NTP Liaison and Scientific Review Office, NIEHS, P.O. Box 12233, MD A3–01, Research Triangle Park, NC 27709; telephone: 919–541–4253, fax: 919–541–0295; or e-mail: *shane@niehs.nih.gov*).

**SUPPLEMENTARY INFORMATION:**

#### Preliminary Agenda Topics and Availability of Meeting Materials

Preliminary agenda topics are as follows:

- NIEHS Strategic Plan.
- Update of NTP Activities.
- NTP BSC's Technical Report Review Subcommittee Report.
- NTP Testing Nominations.

A copy of the preliminary agenda, committee roster, and any additional information, when available, will be posted on the NTP Web site or may be requested in hardcopy from the Executive Secretary for the NTP BSC (see **FOR FURTHER INFORMATION CONTACT** above). Following the meeting, summary minutes will be prepared and made available on the NTP Web site.

#### Attendance and Registration

The meeting is scheduled for June 13, 2006, from 8:30 a.m. to adjournment and is open to the public with attendance limited only by the space available. Individuals who plan to attend are encouraged to register online at the NTP Web site by May 31, 2006, to facilitate access to the NIEHS campus. Please note that a photo ID is required to access the NIEHS campus. The NTP is making plans to videocast the meeting through the Internet at *http://www.niehs.nih.gov/external/video.htm*.

#### Request for Comments

Time is allotted during the meeting for the public to present comment to the NTP BSC and NTP staff on the agenda topics. Each organization is allowed one time slot per agenda topic. At least 7 minutes will be allotted to each speaker, and if time permits, may be extended to 10 minutes. Registration for oral comments will also be available on-site, although time allowed for presentation by on-site registrants may be less than that for pre-registered speakers and will be determined by the number of persons who register at the meeting.

Persons registering to make oral comments are asked, if possible, to send a copy of their statement to the Executive Secretary for the NTP BSC (see **FOR FURTHER INFORMATION CONTACT** above) by May 31, 2006, to enable review by the NTP BSC and NIEHS/NTP staff prior to the meeting. Written statements can supplement and may expand the oral presentation. If registering on-site and reading from written text, please bring 40 copies of the statement for distribution to the NTP BSC and NIEHS/NTP staff and to supplement the record. Written comments received in response to this notice will be posted on the NTP Web site. Persons submitting written comments should include their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any) with the document. Please note that this meeting provides a second opportunity for the public to provide comment on testing recommendations for substances nominated to the NTP. Comments submitted to the NTP in response to the April 2006 **Federal Register** notice on this topic (Volume 71, Number 69, pages 18341–18344) will be considered at the NTP BSC meeting and do not need to be resubmitted.

### Background Information on the NTP Board of Scientific Counselors

The NTP BSC is a technical advisory body comprised of scientists from the public and private sectors who provide primary scientific oversight to the overall program and its centers. Specifically, the NTP BSC advises the NTP on matters of scientific program content, both present and future, and conducts periodic review of the program for the purposes of determining and advising on the scientific merit of its activities and their overall scientific quality. Its members are selected from recognized authorities knowledgeable in fields, such as toxicology, pharmacology, pathology, biochemistry, epidemiology, risk assessment, carcinogenesis, mutagenesis, molecular biology, behavioral toxicology and neurotoxicology, immunotoxicology, reproductive toxicology or teratology, and biostatistics. Members serve overlapping terms of up to four years. NTP BSC meetings are held annually or biannually.

Dated: April 11, 2006.

**Samuel H. Wilson,**

*Deputy Director, National Institute of Environmental Health Sciences and National Toxicology Program.*

[FR Doc. E6–5924 Filed 4–19–06; 8:45 am]

BILLING CODE 4140–01–P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Substance Abuse and Mental Health Services Administration

### Revision of Final Fiscal Year (FY) 2006 State Allotment of Community Mental Health Services (CMHS) Block Grant (BG)

**AGENCY:** Substance Abuse and Mental Health Services Administration (SAMHSA).

**ACTION:** Public notice.

**SUMMARY:** SAMHSA has revised the final FY 2006 calculations for the CMHS BG 50 States and Washington, DC after it has been discerned that the July 1, 2003 population estimates used in the calculation involved multiple counting of persons who reported more than one race. This notice describes the background and rationale for revising the calculations and presents a revised set of State-specific final FY 2006 CMHS BG allotment figures, showing the differences in the two sets of calculations.

**FOR FURTHER INFORMATION CONTACT:** Joe Gfroerer, Office of Applied Studies/SAMHSA, 1 Choke Cherry Road, Room 7–1015, Rockville, MD 20857, (240) 276–1262.

### Background

Under Public Law 102–321, the Secretary of the U.S. Department of Health and Human Services (DHHS), acting through the Director of SAMHSA's Center for Mental Health Services, determines the allotments for States and territories for the CMHS BG and disburses federal funds to eligible States and territories. Public Law 102–321 contains the eligibility criteria for receipt of funds under the CMHS BG, and provides the formulae and methods for determining State and territory allotments. The Office of Applied Studies (OAS) at SAMHSA is responsible for acquisition and compilation of required source data and the computation of BG allotment amounts for States and territories. The preliminary and final FY 2006 CMHS BG allotment calculations were performed in accordance with SAMHSA procedures established during 1995 that were documented in the **Federal Register** notice published on June 26, 1996. The law requires that the CMHS BG calculations use the most recent State-level data for resident population by age (18–24, 25–44, 45–64, and 65 or over) and for the cost-of-services index and the fiscal capacity index.

### Rationale for Revising Final FY 2006 CMHS BG Calculations

SAMHSA used the July 1, 2003 population estimates file (SC–EST2003–race5.txt; released by the Census Bureau on September 30, 2004) that was available on the cut-off date of October 1, 2004 for both preliminary and final FY 2006 CMHS BG allotment calculations. The file included a 5-category, mutually-nonexclusive race variable that allowed multiple counting of persons who reported more than one race. Internal reviews have indicated that though calculations for determining State allotments were done correctly, the file (SC–EST2003–race6.csv; released by the Census Bureau on September 30, 2004) containing a 6-category, race6.csv; released by the Census Bureau on September 30, 2004) containing a 6-category, mutually-exclusive (i.e., no multiple counting) race variable would have been more appropriate for use in the calculations. An examination of these two data files has indicated that multiple counting of persons was particularly higher for Hawaii (26.3%), Alaska (5.0%), California (2.5%), Colorado (1.9%), Nevada (2.6%), Oklahoma (4.2%), Oregon (2.5%) and Washington (3.1%), compared to the national average (1.6%).

### Revised Final FY 2006 CMHS Allotments

Taking into consideration both the multiple-counting problem with the population estimates source data used and the procedural requirement for using source data for the FY 2006 CMHS BG allotment determinations that were released on or before October 1, 2004, SAMHSA has revised the final FY 2006 CMHS BG allotments. Revised final State allotments for FY 2006 were determined by replacing the 5-category-race-based population estimates with the 6-category-race-based population estimates. A comparison of the revised final FY 2006 CMHS BG State allotments with current allotments is shown in the following Table. The attachment shows FY 2005 final allotments, current and revised FY 2006 CMHS BG allotments, and the difference in these allotments in dollars and percent. The revised allotments are lower for Alaska, California, Colorado, Hawaii, Montana, Nevada, New York, Oklahoma, Oregon, Washington, and the District of Columbia, while the revised allotments for all other States increased by small amounts. The allotments for all territories would remain unchanged with the revision, as would the

# NATIONAL TOXICOLOGY PROGRAM
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## June 13, 2006

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*** Not in attendance