

**National Toxicology Program
Board of Scientific Counselors**

December 1, 2006

National Institute of Environmental Health Sciences
Research Triangle Park, NC

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I. Attendees

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met on December 1, 2006, at the National Institute for Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. The following individuals attended the meeting.

NTP Board of Scientific Counselors

Diane Birt, Iowa State University
Christopher Bradfield, University of Wisconsin
Germaine Buck Louis, National Institute of Child Health and Human Development
Kenny Crump, Environ International, Inc.
George Daston (chair), The Procter and Gamble Company
Prescott Deininger, Tulane University
John Giesy, University of Saskatchewan
Katharine Hammond, University of California at Berkeley
Nancy Kerkvliet, Oregon State University
Gail McCarver, Medical College of Wisconsin
Charlene McQueen, University of Arizona
Maria Morandi, University of Texas
Harish Sikka, State University of New York at Buffalo
Vernon Walker, Lovelace Respiratory Institute

NTP Board of Scientific Counselors members not in attendance

Elizabeth Delzell, University of Alabama
Jon Mirsalis, SRI International
Keith Soper, Merck Research Laboratories

NIEHS Staff

Jack Bishop	Denise Orzeck
John Bucher	John Pritchard
Christine Bruske	Joseph Roycroft
Rajendra Chhabra	David Schwartz
Michael Cunningham	Michael Shelby
Allen Dearry	Cynthia Smith
Paul Foster	Diane Spencer
Jon Friedman	Stanley Stasiewicz
John French	Matthew Stout
Marc Hollander	Raymond Tice
Tommy Hardee	Gregory Travlos
Michelle Hooth	Nigel Walker
William Jameson	Michael Waters
Jo Ann Lewis	Samuel Wilson
Ruth Lunn	Kristine Witt
Joe Lui	Mary Wolfe
Robin Mackar	Michael Wyde

Scott Masten

Other Federal Agency Staff

William Allaben, FDA/National Center for Toxicological Research

Mark Toraason, National Institute for Occupational Safety and Health

Public

Randy Allen, Hyperion Corporation

Susan Borghoff, ILS

Donna Browning, RTI International

Jeffrey Charles, ILS

Irma Grossi, RTI International

Milton Hejtmancik, Battelle

Christopher Johnson, RTI International

Andrew Joseph, MR Path

Gloria Jahnke, Sciences International

Susan Kinney, ILS

Jim Mathews, RTI International

Leslie Recio, ILS

Ivan Rusyn, University of North Carolina

II. Introductions and Welcome

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, director of the NIEHS and the NTP.

III. Accomplishments at the NIEHS and NTP

A. Presentation

In his introductory remarks, Dr. Schwartz thanked the BSC for their involvement in the NTP. He outlined a number of training programs and future endeavors for the NIEHS and the NTP.

Training Programs

The following training programs have been implemented.

- The Short Term Educational Experiences for Research (STEER) Program will train high school and undergraduate students to undertake research in environmental sciences during the summer.
- The T32 program will educate physician scientists in environmental sciences. For example, a joint program has been developed with the National Human Genome Research Institute (NHGRI) whereby academicians will be co-mentored in two disciplines such as environmental sciences and genetics.
- NIEHS will provide a supplement to RO1 grants to train minority and foreign students for 2 years to undertake global environmental research.

- The K12 grant is a training grant to mentor physician scientists early in their careers. Presently 17% of scientists funded by NIEHS are physician scientists and one of Dr. Schwartz's goals is to increase this to 25-30%.
- The Outstanding New Environmental Scientist Awards (ONES) program is a supplement to a RO1 grant for scientists who received their first independent grant; eight were awarded this year. The supplement is for the purchase of equipment or supplies for the investigator's laboratory.

Basic Research

One of Dr. Schwartz's highest priorities is to allocate and maximize funding for RO1 grants; in 2006 21% of the grants submitted to NIEHS were funded. The institute funded 17% of the grants submitted to the epigenetics program and proposals for an RO1 on comparative genomics have been received for review.

Translational Research

Dr. William Martin, Director of the Office of Translational Research, is directing two programs – (1) the Disease Investigation through Specialized Clinically-Oriented Ventures in Environmental Research (DISCOVER) program, in which extramural basic and applied researchers are funded to focus on a clinical problem with an environmental sciences component and (2) the Director's Challenge, in which basic and applied intramural scientists cooperate on an environmental science problem. One Director's Challenge award was made in 2006.

HEAL (Head off Environmental Asthma in Louisiana) Program

This program is focused on studying the potential exposure of children to microbial contamination following their relocation to New Orleans after Hurricane Katrina. The program is patterned after the Inner City Asthma study with a standard-of-care group and an environmental intervention group to ascertain whether exposure to this contamination either exacerbates or causes the symptoms of asthma. The program is a combined public-private partnership funded by the Merck Children's Asthma program and the NIH National Center on Minority Health Disparities. The program will be implemented by the Louisiana Department of Public Health in New Orleans and Tulane University.

Future Endeavors

a. Genes and Environment Initiative

Dr. Brenda Weis will present information during the meeting on the Genes and Environment Initiative (GEI), which is focused on exposure biology and biological responses. NIEHS will receive \$88 million over four years for the GEI and five RFAs will be funded.

b. Clinical Research Unit

Funds have been appropriated to build a modular clinical research unit at NIEHS that will open in the summer of 2007. This facility will provide basic scientists an opportunity to interact with physician scientists and applied scientists in the NTP to address whether basic mechanisms identified by NIEHS scientists are relevant to the pathogenesis of a variety of diseases.

c. Workshop on Global Environmental Health

A workshop on the Global Environmental Health Initiative will be held mid January 2007. Invited participants will be asked to identify a clear direction for the study of global environmental health issues and health problems caused by environmental exposures.

NTP Accomplishments

The NTP has begun implementation of the NTP Roadmap and is collaborating with the Molecular Libraries Initiative (MLI), part of the NIH Roadmap, on high throughput screening (HTS) assays. The NTP sent chemicals with known toxicity to NIH for testing in *in vitro* toxicity assays. The NTP is presently analyzing this data to ascertain if data from HTS assays might be used to prioritize chemicals for testing in 2-year bioassays.

Dr. John Pritchard, NIEHS, is leading the Host Susceptibility Initiative (HSI), which will focus on determining genetic regulators that could affect the toxicity of an agent. The HSI will study the responses to toxicants of up to 15 mouse strains with known genomic sequences. The NTP has partnered with NIEHS in the Airway Disease Project, part of the GEI, to study how genetic differences influence biological mediators in airway disease.

Dr. Schwartz said Dr. Samuel Wilson is chairing the search committee for a permanent Associate Director for the NTP. It is hoped that this position will be filled by mid to late spring.

B. BSC Discussion

Dr. Daston asked if the NIEHS would be involved in studying other diseases besides respiratory diseases and Dr. Schwartz said respiratory diseases were chosen because of in-house expertise. The GEI program has limited funding and \$4M has been earmarked for the Airway Disease Project.

Dr. Daston commended NTP for implementing the additional activities relating to the roadmap and asked how NTP would allocate its resources between its traditional activities and these new initiatives. He felt that any change in direction that affects the availability of data for use by other federal agencies, might be controversial. Dr. Schwartz said in the near term initiation of these new programs would be limited until a permanent NTP Associate Director is hired. He said the HTS and HSI programs need to play a larger part in the NTP research and testing program, and the NTP must focus on streamlining the animal testing program to integrate it with these new programs. Once the priorities for these programs are set, they will be presented to the BSC and public for comment.

Dr. Wilson said Dr. Schwartz and he are working closely with NTP management to develop a consensus as to how these programmatic changes might be made and communicated to the public.

Dr. Mark Toraason mentioned NIOSH's Research to Practice (R2P) program that requires scientists at the inception of research projects to define how their completed work will impact the health of workers. He then asked how the NTP would use information on individual susceptibility to an environmental hazard so that it would reduce adverse effects in a population. Dr. Schwartz responded that NIEHS is putting discovery into practice through environmental justice programs and community outreach. The HEAL program, which addresses how microbial contamination affects airway disease, is an example. Scientific information from this study should enable physician scientists to suggest an intervention program, which could be implemented by the CDC, NIOSH, and state health departments.

Dr. Daston thanked Dr. Schwartz for his presentation and congratulated him on his strategic accomplishments.

IV. NTP Update

A. Presentation

Dr. Dearry briefly highlighted some recent NTP activities and provided a status update on others. He outlined the broad array of substances the NTP is testing including herbals and dietary supplements, nanoscale materials, photoactive compounds, and polybrominated flame-retardants. He said the number of studies started and completed during FY06 is similar to that for FY05 and FY04. He summarized the findings for genistein, tested in both a multigenerational study and a 2-year bioassay. There were small minor toxic effects in the pups from the F₀ and F₁ generations given the highest doses, but the data suggested no carryover of effects from one generation to another. A study on gestational administration of azidothymidine (AZT) to mice showed that the offspring developed bronchiolar alveolar neoplasms later in life.

Regulatory agencies use data and information from many NTP reports, although it is difficult for NTP to track their usage. He reported that the NTP-CERHR Monographs on three phthalates: butyl benzyl phthalate (BBP), di-*n*-butyl phthalate (DBP), and di-*n*-hexyl phthalate (DnHP) supported their addition to the California Proposition 65 list of reproductive toxicants. Also, seven phthalates were included in deliberations by EPA to the list of chemicals in the Voluntary Children's Chemical Environmental Program. The WHO used the NTP technical reports on dioxin and polychlorinated biphenyls to re-evaluate the use of the Toxic Equivalency Factor approach for dioxin cancer risk assessment.

He briefly mentioned four workshops carried out as part of the NTP Roadmap. Reports on three of the workshops were presented previously to the BSC and recommendations from the fourth, Biomarkers for Toxicology Studies, would be presented later that day.

He gave a brief update on the proposed review process for nominations to the 12th Report on Carcinogens (RoC). He said that there would be public peer review meetings of the draft background documents by *ad hoc* scientific expert panels, as well as a peer review of the draft substance profiles by the BSC to provide greater transparency and increased

expert review. The RoC process has been approved by NIEHS' federal partners and reviewed by the public. The NTP plans to submit the amended process to the Office of Management and Budget (OMB) through the Department of Health and Human Services. OMB will have 30 days to review and respond to NTP.

1. Activities at NTP Centers

A. Presentation

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

- **Center for Evaluation of Risks to Human Reproduction (CERHR)**
Expert panel meetings were held in March 2006 on soy formula and genistein and the draft NTP briefs are available for public comment through December 8, 2006. Draft expert panel reports on hydroxyurea and bisphenol A are available for public comment through December 15, 2006. Expert panel meetings will be held on January 24-26, 2007 and March 5-7, 2007 for hydroxyurea and bisphenol A, respectively.
- **NTP Interagency Center for Evaluation of Alternative Toxicological Methods (NICEATM)**
 - A workshop was held in November 2006 on the use of the mouse LD₅₀ assay for botulinum toxin testing. The *in vitro* methods are promising, but development and validation are still needed.
 - Test method recommendations on acute oral systemic toxicity proposed by a peer review panel in May 2006 will be forwarded to federal agencies. The *in vitro* cytotoxicity test methods are not sufficiently accurate to predict regulatory hazard categories, but may determine starting doses for *in vivo* protocols.
 - Test method recommendations from two peer review panels held in 2005 on ocular toxicity testing will be forwarded to federal agencies. Several of the *in vitro* methods may be appropriate alternatives to *in vivo* ocular testing.
 - He said NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) are developing a 5-year plan for publication in November 2007 and soliciting public comments on elements for the plan through their website.

B. BSC Discussion

Dr. Germaine Buck Louis was concerned about the relatively low number of reproductive studies that the NTP is undertaking. She said human epidemiology studies have identified potential reproductive toxicants and she hopes NTP might study their mechanisms of action. Dr. Dearry responded that the NTP is conducting a number of

multigenerational reproductive studies. Dr. John Bucher said the number of current studies is low because there has been a delay in finalizing the contract to conduct these studies, which also will focus on developmental neurotoxicity and immunotoxicity.

Dr. Vernon Walker pointed out that the NTP has also been involved in studies on p53 mutations in lung tumors of offspring exposed transplacentally to AZT and lamivudine and made seminal findings that up to four different mutations in the p53 gene are found in lung tumors of these exposed animals. A second study by NTP scientists has shown a 10-fold increase in the incidence of micronuclei in mother and child pairs who received AZT during gestation. These studies indicate that although AZT treatment prevents transmission of HIV to babies whose mothers are infected, this treatment may have negative side effects that were not known previously. These findings have spurred an interest in finding other nucleoside analogues that are as effective, but have fewer adverse effects.

Dr. Daston encouraged the NTP to increase their partnerships with the European Partnership on Animal Alternatives, as Europe will be phasing out the use of animals for testing of personal care products between 2009 and 2013. He said the NTP should partner with the Registration, Evaluation, and Authorization of Chemicals (REACH) program and work with EPA who is also studying perfluoroalkylacids (PFOAs). He is pleased that the NTP is monitoring the use of its publications for public health, as this is an excellent indication of the relevance of the NTP program. Dr. Dearry responded that it is a challenge to track the use of NTP publications. Dr. Wolfe, NIEHS, said the NTP reviews the EPA IRIS database and other federal databases, but often it is difficult to know when an agency uses NTP data. Dr. Dearry said NICEATM and ICCVAM are partnering with the European Center for the Validation of Alternative Methods (ECVAM) on the use of *in vitro* assays with respect to REACH and that Dr. Melnick, NIEHS, who is directing the study on the PFOAs, is serving on the EPA Scientific Advisory Board examining PFOAs.

Dr. William Allaben said an example of translational research that has had an enormous effect on public health is the finding that alpha-hydroxy acids do not increase the risk of cancer when used daily as exfoliating compounds. These were NTP studies conducted at the FDA National Center for Toxicological Research.

2. NTP Retreat

A. Presentation

Dr. Dearry summarized the salient outcomes from the NTP retreat held on October 18 - 19, 2006.

The objectives of the retreat were to:

- Make decisions to aid the NTP in implementing its Roadmap for the 21st Century.
- Evaluate the current position of the program for meeting the NTP Roadmap's objectives.
- Implement the outcomes of various NTP Roadmap workshops and initiatives.

- Assess where the program can incorporate workshop findings and recommendations into current activities, studies, and designs.
- Evaluate the impact to the program of making changes to current practices as a means for increasing its effectiveness and efficiency.

Six topics were discussed at the retreat including pathology review, animal strains and host susceptibility, reproductive tumors and *in utero* exposures, high throughput screening, biomarkers, and the NTP process for nominations and study design. The outcomes of the discussion are summarized below.

- **Pathology Review**
Due to the large number of tissues examined in a 2-year bioassay and a 90-day study, it is recommended that digital images for pathology working groups be used to implement virtual or electronic conferences. Presently, there are four levels of review of pathology data. It was suggested that consideration be given to redundancies in the process that could be removed without affecting the quality of the data assessment. It was also suggested that an enhanced pathology review be undertaken for noncancer toxicity studies.
- **Strains and Host Susceptibility Initiative**
The breakout group recommended that the NTP curtail the use of the F344 rat due to changes in its phenotype over time, its reproductive problems, and the high background tumor incidence. Instead, the program should use the Wistar Han or another appropriate strain. The use of the B6C3F₁ mouse should be continued as it still provides a good spectrum of tumor susceptibility. Multiple mouse strains will be needed to examine genetic diversity in the HSI and possibly additional mouse strains could be used in future two-year studies.
- **Reproductive Tumors and *in utero* Exposures**
The F344 rat is an inappropriate model for certain types of tumors in reproductive organs and thus a different rat strain such as the Sprague Dawley should be used. NTP should place more emphasis on developmental programming by incorporating *in utero* perinatal dosing into the study design, as this exposure regimen is optimal for the development of tumors in the brain and germ cells and other endocrine sensitive organs.
- **High Throughput Screening**
Before initiating extensive testing of NTP nominations, NTP should consider evaluating them in HTS assays as a means of setting priorities for further *in vivo* toxicology testing. However, using HTS assays for prioritization has limitations. First, HTS technology must be evaluated based on the predictive capacity of a battery of HTS assays for a given endpoint, and then this data must be compared to and correlated with data from conventional *in vivo* assays. For data management and analysis, it will be necessary to mine data for predictive relationships within or between classes of compounds.

- **Biomarkers**

Different biomarkers for the lung, heart, and lipid and carbohydrate metabolism were recommended. These recommendations were similar to those from the workshop (see below): namely to monitor cytokines in bronchioalveolar lavage (BAL), serum troponin or B-type natriuretic peptide for changes in heart tissue, and serum fructosamine for detection of insulin resistance. Measurement of fructosamine will need to be validated in relation to nutritional status.

- **NTP Process and Study Design**

The NTP needs to improve the criteria for determining the public health impact of a proposed nomination instead of using the current agent-oriented criteria. A proactive campaign to identify sets or themes of nominations of high public health significance is needed. There needs to be better integration of different disciplines and coordination of the scientific activities across multiple staff and studies or projects. One suggestion was to review NTP activities by research topic and current directions instead of an agent-by-agent review. There is a need to develop a process for consistent electronic data collection using similar formats across different types of studies, as present information technology tools are disconnected and data are not currently stored in easily accessible formats. It is essential that the NTP recruit additional personnel with the relevant expertise to ensure sufficient breadth, depth, and knowledge to implement its new programs.

- **Next Steps**

In the near future, the NTP plans to

- Enhance its capacity for digital imaging and electronic exchange for pathology review.
- Assemble an advisory group(s) to handle the logistics of changing the rat strain and beginning the host susceptibility studies.
- Use an *in utero* and perinatal dosing regimen for relevant studies.
- Enhance data analysis from the HTS initiative through its interaction with the NIH Chemical Genomics Center.
- Validate methods for troponin, inflammation markers in BAL, and fructosamine.
- Convene a group to evaluate and modify the nomination process.

BSC Discussion

Dr. Allaben asked whether NTP's federal partners would be members of the implementation groups and Dr. Dearry replied that they are invited to participate. The group discussing the change in the rat strain has met once, but the nominations group is still in the planning mode.

Dr. Daston said he is pleased that the nomination process will be more transparent in the future.

Dr. Walker said he routinely uses echocardiograms to monitor cardiomyopathy in animals treated with AZT and similar drugs and has found this technology to be useful.

He asked whether this technique, which uses non-invasive probes, was discussed at the biomarkers meeting. Dr. Gregory Travlos responded that there was some discussion about ultrasound but the consensus was that it is not ready for routine use. Dr. Allaben said the NTP is partnering with the FDA to use a digital imaging system in their next scheduled pathology working group review.

Dr. Harish Sikka asked why hepatic biomarkers were not considered at the workshop. Dr. Travlos said the workshop focused on three organ systems as the NTP wanted input on biomarkers from organs not routinely measured. The NTP regularly measures hepatocellular injury and cholestasis in its studies.

V. Roadmap Activities

1. Biomarkers for Toxicology Studies Workshop

A. Presentation

Dr. Gail McCarver reported on the fourth NTP Roadmap workshop held on September 20-22, 2006, at NIEHS. The charge to the workshop's participants was to identify biomarkers and evaluate their utility for inclusion in rodent toxicology studies to better characterize endpoints of environmentally induced human diseases or biological processes related to human disease etiology. The workshop focused on the lung, heart, and lipid or carbohydrate biomarkers. The speakers in the plenary session outlined the characteristics of an ideal marker and pointed out that monitoring a rodent biomarker that is homologous with a human marker would be the most useful. The breakout groups were asked to identify key noninvasive biomarkers for tissue injury or metabolic function.

The lung breakout group recommended biomarkers from lung bronchiolar lavage samples as the most important with evaluation of histopathology and immunohistochemistry also being useful. Imaging techniques were discussed but not recommended.

The heart breakout group recommended monitoring troponin levels because they are used as an early marker of cardiac damage in humans. A second potential biomarker is the B-type natriuretic peptide (BNP), which measures changes in blood pressure. Alpha-macroglobulin in the rat is considered a good biomarker as it represents C-reactive protein in humans.

The breakout group evaluating lipid or carbohydrate biomarkers recommended monitoring plasma cholesterol and triglycerides. They also suggested insulin as a measure of glucose intolerance or fructosamine, which is a better measure of glucose intolerance than is glucose. Other biomarkers identified were body composition, hepatic lipid levels, and sterol regulatory element binding protein although the latter would need validation for rodents.

B. BSC Discussion

Dr. Daston asked Dr. Travlos if he wanted to comment on the NTP's progress since the workshop. Dr. Travlos replied that NTP had acquired one instrument to measure troponin, and a second to measure pulmonary cytokines in bronchiolar lavage and insulin in serum. NTP would validate a method for fructosamine and for α -macroglobulin, a homolog for C reactive protein which is a marker of inflammation in humans.

Dr. Charlene McQueen said there is a quantitative grading system to assess fatty acid accumulation in the liver and suggested the NTP use this assay. Dr. Travlos said the NTP does not plan to pursue biomarker discovery at the present time.

Dr. Gail McCarver asked about collecting and storing tissues for future analysis of gene expression, and Dr. Bucher responded that it would not be productive or cost effective to collect tissues for genomics without having a hypothesis to test. He said it is technically difficult to freeze tissues rapidly for RNA and DNA analysis while simultaneously harvesting tissues for routine evaluations.

2. Directions of the NTP High Throughput Screening (HTS) Initiative

A. Presentation

Dr. Raymond Tice discussed the progress of the NTP HTS initiative. He identified its goals and summarized points from his previous presentation to the BSC on June 13, 2006. He discussed in detail NTP's interactions with the NIH Chemical Genomics Center (NCGC), one of the testing centers of the NIH Molecular Libraries Initiative (MLI). NTP sent NCGC a set of 1408 compounds that included 1206 compounds tested in various NTP tests, 147 compounds identified by ICCVAM/NICEATM for the validation of alternative test methods, and 55 duplicate compounds to assess assay reliability. The 1408 compounds have been tested in an ATP-based cytotoxicity assay using 7 human cell lines and 5 rodent cell lines. The data will be loaded into PubChem, an NIH-sponsored, publicly accessible database, after their accuracy is verified. The NCGC has standardized the protocols for a caspase 3/caspase 7 assay and the lactic dehydrogenase cytotoxicity test for one human and one rodent cell line. The NCGC is also testing the NTP 1408 chemicals in as many as 56 additional in-house HTS assays and the NTP is investigating whether other MLI centers might also test the 1408 compounds.

Dr. Tice presented a preliminary evaluation where IC_{50} data for the ATP cytotoxicity assay were compared with results from various NTP assays (e.g., genetic toxicity, cancer bioassays), as well as *in vivo* toxicity data (e.g., acute oral toxicity) collected from publicly accessible databases. A weak correlation was found between the IC_{50} data for *in vitro* cytotoxicity and acute oral LD_{50} data for various species.

NTP has identified the next set of 1408 compounds to submit to the NCGC for testing. This set will include structurally related compounds that cover a wide activity range, compounds that require metabolic activation, and compounds that have been tested for a specific toxicological endpoint of interest (e.g., immunotoxicity).

Dr. Tice next summarized the status of collaboration between NTP HTS staff and the EPA Chemical Prioritization Community of Practice (CPCP) to identify HTS assays of common interest, additional compounds for testing, and common approaches for bio- and chem-informatics. In closing, Dr. Tice emphasized the importance of making the NTP HTS data publicly accessible via PubChem, integrating these data with other databases (e.g., NTP toxicology databases), and having tools available to mine data across multiple databases to identify patterns of HTS assay responses indicative of *in vivo* toxicity.

B. BSC Discussion

Dr. McQueen asked whether metabolically competent cells are being used in the HTS assays or if the reaction mixture could be supplemented with S9, which might be less expensive than using primary cells. Dr. Tice replied that adding an S9 mix would not be practical because of the long exposures used for most of the cell-based assays. Ultimately, the NCGC plans to test compounds in primary hepatocytes or cell lines that have been engineered to be metabolically competent. Dr. McQueen suggested that it might be possible to compare the different cell lines based on gene expression.

Dr. Buck Louis applauded Dr. Tice's efforts and noted that there was limited discussion about the statistical methods being used. Dr. Tice said NTP is evaluating the responses from individual assays to identify the most appropriate approaches to use to analyze the dose-response data while also working closely with bioinformatics experts at EPA, the NCGC, and in the private/academia sectors to evaluate patterns of response potentially indicative of *in vivo* toxicity.

Dr. Christopher Bradfield asked Dr. Tice how the NTP plans to evaluate the progress of the HTS initiative. Dr. Tice said he expects any evaluation of the initiative's success to be iterative with additional analyses being conducted as related sets of HTS assays are completed. Success will depend on the ability of the HTS assays to prioritize compounds correctly relative to their toxicological activity or provide mechanistic data that helps explain the ability of a compound to be active in one or more toxicological assays. Unfortunately, it is not possible *a priori* to state how many HTS assays will be needed for a particular toxicological endpoint. Furthermore, failure to predict one type of *in vivo* toxicity would not preclude success for a different toxicity. Dr. Tice said the NTP has decided to focus specifically on immunotoxicity. He has assembled a group of scientists knowledgeable in the field to develop a hypothesis and identify the most appropriate immunotoxicity assays.

Dr. Wilson responded to Dr. Bradfield's statement by saying that the analysis of the assays is incredibly complex, but open-ended. He suggested that the NTP provide a framework for the assessment of progress made on these assays. To date, it has been a successful proof of principal, but now the NTP needs to conceptualize how to move ahead. As with any project, it will be necessary to establish discrete goals and work towards a time line to evaluate relationships. The NTP must obtain consensus with all the participants regarding the timeline.

Dr. Buck Louis asked why the correlation between the IC₅₀ for *in vitro* cytotoxicity and acute oral LD₅₀ data for rodents is so low and what kind of *a priori* decision criteria would be used to identify an acceptable correlation. Dr. Tice replied that the relatively poor correlation is because *in vitro* cytotoxicity tests generally underpredict the toxicity of highly toxic compounds and overpredict the toxicity of weakly toxic compounds. The former occurs because these compounds likely act via a mechanism not measurable in the cell lines used, while the latter might involve aspects of adsorption, distribution, metabolism, and excretion (ADME) also not evaluated *in vitro*. The European Centre for the Validation of Alternative Methods (ECVAM) has a program known as “A-Cute-Tox” whose purpose is to develop a battery of *in vitro* assays capable of better predicting acute oral toxicity in rodents and humans. This program includes development of assays that identify organ-specific toxicity as well as those that will account for ADME. Dr. Tice added that the *in vitro* assays identified for this battery would need to be added to the HTS battery to provide additional information.

Dr. Daston said he hopes the process and goals for further testing will be agreed upon soon.

Dr. Dearry concluded the discussion by saying NTP is developing a hypothesis for testing and assembling a scientific advisory committee for the HTS program. He asked the BSC members to contact him if they are interested in serving on this committee.

2. Testing of NTP HTS chemicals in *Caenorhabditis elegans*

A. Presentation

Dr. Jonathan Freedman outlined the five tasks for the program, which are to:

- Develop methods to measure the toxicity of developmental and neurological toxicants by monitoring growth, size, reproduction and movement.
- Expose *C. elegans* to at least 200 known or suspected developmental and/or neurological toxicants and determine changes in phenotypic characteristics.
- Create and/or obtain green fluorescent protein-based, stress-responsive transgenic *C. elegans* for improving sensitivity and specificity of toxicity screens.
- Use *C. elegans* microarray analysis to test a subset of chemicals tested earlier.
- Adapt methods for high throughput analysis using RNA interference.

He outlined the experimental protocol, showed that growth and feeding of the worms are inhibited by known toxicants including cadmium and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and explained how the EC₅₀ is calculated. He listed the green fluorescent protein (GFP)-based transgenic nematodes engineered by his laboratory based on key steps in conserved pathways. He said microarray studies with cadmium, MNNG, diquat, and fumonisin have been completed. He described the abnormal movement of worms exposed to aldicarb and sodium arsenite. He summarized the data on the first 1408 NTP chemicals tested in two runs. There were 61 positive responses in both replicates and 182 positive responses in one replicate.

He discussed the analytical challenge of storing and analyzing such large amounts of data and said the goal is to model nematode growth using a 4-dimensional distribution. His laboratory is attempting to develop statistical algorithms to classify nematodes into discrete growth phases and to develop a statistical method to allow rapid analysis of the data. Three manuscripts have been accepted for publication. He said EPA chemicals, including pesticides, marine toxicants, ionic liquids and nanomaterials, would be tested in the future. He briefly mentioned the difficulty in taking medium throughput screening technology to a high throughput screening level.

He posed a question about the future of “worm toxicology” at the NIEHS as to whether it is a research and development or testing activity and whether NIEHS/NTP should develop a contract for routine screening of chemicals.

B. BSC Discussion

Dr. Daston asked if the data from the *C. elegans* studies are posted on PubChem and Dr. Freedman responded that he plans to post the data before the related manuscripts are published.

Dr. Buck Louis applauded Dr. Freedman’s efforts and noted that there was limited discussion about the statistical methods. She said both this project and the HTS initiative lend themselves to the development of new statistical methods. She asked whether Dr. Freedman is working with the biometry branch at NIEHS and he said yes. He said Dr. Christopher Portier, NIEHS, is advising and helping him develop statistical modeling tools.

Dr. Bradfield said with *C. elegans* there is a 15% hit rate indicating that the false positive rate is high. Dr. Freedman said the assessment is more complicated because of the stringency he places on defining a positive response (at least an 80% depression). He said a 30-50% reduction in a response is classified as equivocal. As a result there is a large variability between replicates, which is basically a statistical problem.

VI. Concept Review- NIEHS/NTP Host Susceptibility Program

A. Presentation

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.

Dr. John French said Dr. John Pritchard presented an outline of the initiative at the last BSC meeting in June 2006. An extramural group of experts on mouse genomics met with NIEHS/NTP scientists in July 2006 to discuss the results of the sequencing of 15 mouse strains and the HSI was discussed at the NTP retreat in October. The purpose of

this research and development contract is to provide NTP the capacity to use multiple isogenic mouse strains to study the genetic basis for variation in quantitative measures of chemical-induced toxicity *in vivo*.

The aims of the study are to:

- Use the significant genetic diversity within different laboratory and/or wild-derived (isogenic) mouse strains to model and predict potential population-level ranges of response to toxicant exposure.
- Identify and understand the functional characterization of specific genes and their allelic variants that are associated with individual differences in response to toxicant exposure.
- Use comparative genetic analysis of susceptibility genes discovered in individual strains of mice to identify risks in susceptible human populations harboring genetic variations in orthologous genes and pathways.

He said this is a new initiative to leverage NTP expertise and data to gain insight into critical genes and basic disease processes contributing to an individual's response to environmental exposures. It is intended to foster greater use of NTP data for understanding complex human disease and ultimately to increase the understanding of gene-environment interactions leading to: (1) identification of new biomarkers for detection of exposure and/or effect of environmental agents and (2) new candidate genes and signaling pathways for clinical intervention.

He said a non-Good Laboratory Practices research contract would be required in order to meet study-dependent, non-standard methodologies and techniques. He said a two-pronged approach would be used in which NTP scientists would perform part of the study in-house via contract and part would involve research partnerships with the Division of Intramural Research (DIR) or extramural scientists. The NTP would measure the toxicity of a selected chemical in the isogenic mouse strains to determine the quantitative responses due to genetic variation in the strains. These outcomes would then be investigated further using research partnerships to perform haplotype-phenotype association analysis, quantitative gene analysis, and functional genomic studies leading to the identification of biomarkers of exposure and effect as well as targets for translational research.

B. BSC Discussion

Dr. Prescott Deininger, lead discussant, asked whether the concept would develop end points and, if so, how they would be chosen or whether it would be hypothesis driven. Dr. French replied that this is both a discovery and hypothesis contract to determine the genetic basis of a biological phenotype, correlate phenotype to haplotype, and attempt to link a specific gene or pathway to an outcome using functional genomics.

Dr. Walker asked if the BSC is being asked to agree to a concept based on a broad outline without any specific details and he wondered if the BSC would know more before the contract is advertised. Dr. Dearry said NTP is asking the BSC to approve the concept on a global level. Although an initial study may be performed, a subsequent contract might

not be implemented. An expert panel will advise the NTP on whether subsequent studies are warranted based on the data generated. The organ system and chemical of interest have not been defined.

Dr. Deininger asked if the endpoint is to find differences between strains, and Dr. French replied that NTP hopes that linking a biomarker of toxicity with a genetic marker could be used to make a haplotype association.

Dr. Dearry said NTP's role would be to test a chemical in the 15 isogenic strains and populate a database with the phenotypic response to that chemical. Subsequent studies on haplotypes and QTLs and microarrays would be undertaken by DIR scientists or through a contractual arrangement.

Dr. McCarver said the questions are whether the data collected would be useful enough for the NTP to proceed to the next step and whether the animal data could be related to the human. Dr. French responded that the intent is to link the findings in isogenic strains of mice with orthologous genes in humans that show the same or similar allelic variation.

Dr. Daston asked for a vote on the concept. Dr. McQueen proposed that the BSC approve the concept and Dr. Deininger seconded; there were 12 yes votes, 0 no votes, and 1 abstention. Dr. John Giesy did not feel he had the expertise to vote on the topic.

VII. NTP/NIEHS Genes and Environment Initiative: Exposure Biology Program

A. Presentation

Dr. Brenda Weis said the Genes and Environment Initiative (GEI), which aims to accelerate the understanding of genetic and environmental contributions to health and disease, consists of two components: a genetics program and the Exposure Biology Program (EBP). The genetics program will identify gene variants in people with or without disease and the EBP will develop technologies to measure environmental exposure at the point of human contact and identify biomarkers of exposure and response to environmental chemicals/biologicals, dietary factors, psychosocial stressors, and addictive substances. The EBP will provide new devices and assays to build upon existing research programs, which typically assess human exposure using single ambient exposure measurements and questionnaires. The new monitors will be more specific, personalized, portable, deployable, and take real time quantitative measurements of exposure and dietary intake. Biomarker development will focus on defining markers of response for common pathogenic mechanisms such as inflammation, oxidative stress, apoptosis, and DNA damage and repair that are disrupted by a variety of exogenous exposures and are associated with multiple human diseases. It will be important to have the same level of precision for the genetic and exposure data to assess their impacts on disease causation. New NIH appropriations for the genetics program and EBP are \$26M and \$14M per year, respectively. The NIEHS will commit additional funds to the EBP making the total support for the EBP \$88M for four years.

One EBP project is the Environmental Airway Disease Project (EADP), whose aim is to further our understanding of the genetic and environmental contributions to human airway disease through the development of new assays and integrated panels of biomarkers that reflect critical biologic processes in disease pathogenesis. The EADP is focusing on three respiratory diseases, namely asthma, chronic obstructive pulmonary disease (COPD), and bronchitis, because they are major public health burdens and researchers at the NIEHS have expertise in the fundamental mechanisms of airway injury that involve innate immunity and oxidative damage. This project will identify markers to LPS, cigarette smoke, ozone, and cockroach allergens in 15 genetically divergent murine strains sequenced recently by Perlegen for the NIEHS. NIEHS will compare these markers to markers in archival tissues from mice and humans exposed to these pollutants. It is hoped that molecular markers will reflect changes in DNA and RNA adducts, proteins, and metabolites and that these molecular changes can be linked to pulmonary function and the release of cytokines and chemokines. Dr. Weis described the study design and said the new and archived tissues will be shared with researchers to run other analyses.

She said five RFAs released by October 2006 would be funded by the end of July 2007. The RFAs solicit the development and delivery of field deployable sensors that can be used in population-based studies to measure environmental exposure to chemicals/biologics, dietary factors, physical activity, psychosocial stressors, and addictive substances. Multiple biomarkers (or biomarker panels) will be needed to characterize the entire response to these stressors. Molecular signatures will be defined by changes in gene expression, proteins or metabolites, or other molecular events such as protein-protein interactions.

Examples of biosensors are lab-on-chip and micro fluidics platforms, molecular imaging technologies, and molecular probes. The research topics of interest for the biomarker RFAs are

- The development of single or multiple biomarkers of response to environmental stressors.
- Comparison of patterns of response across species including humans.
- Comparison of panels of biomarkers progressing from invasive to noninvasive specimens.
- Comparison of biomarkers following acute versus chronic exposure.

B. BSC Discussion

Dr. Crump said he is glad the NIEHS is making an effort to study exposure, which is an important component to understanding health outcomes from environmental pollutants. He asked whether the two-pronged approach to building devices and measuring exposure can be controlled or whether it must be linked with external exposures. Dr. Weis said the NIEHS hopes to partner with the EPA who has expertise in measuring ambient environmental exposures.

Dr. Daston said the NIEHS must understand the variability in biomarker response even when exposure is fixed.

Dr. Kerkvliet asked how this information would help our understanding of disease causation, as people are exposed to many substances throughout their lifetime. Dr. Weis agreed that it is not easy to relate a specific environmental exposure as a causative or modifying factor, but these studies will be a positive step forward particularly in a clinical setting for populations at risk.

Dr. Crump said there are other groups such as the Urban Air Center and the Health Effects Institute developing devices and NIEHS should consider the possibility of coordinating their efforts. Dr. Weis replied that a workshop was held in October where representatives from these groups attended, and there was support from the attendees for NIEHS to pursue the development of these devices.

Dr. Toraason said measuring biomarkers is only the initial step; the problem is determining when a threshold is reached and disease is initiated. He said it is essential that animal studies be included in the program as it will be the only way to determine the threshold. Dr. Weis replied that using animal models to pursue biomarkers of exposure and response is an important aspect of the EBP.

VIII. NTP BSC Technical Reports Review Subcommittee Meetings

1. Meeting held on June 12, 2006

A. Presentation

Dr. McQueen, Chair of the Subcommittee, summarized the actions on the NTP Draft Technical Reports reviewed at the meeting on June 12, 2006. The Subcommittee reviewed reports on α -methylstyrene and methylene blue trihydrate using conventional F344 rat and B6C3F₁ mouse models. There was some evidence of carcinogenic activity of α -methylstyrene in male F344/N rats with clear evidence of carcinogenic activity in female B6C3F₁ mice, but only equivocal evidence in male B6C3F₁ mice. With methylene blue trihydrate, there was some evidence of carcinogenic activity in male F344/N rats and male B6C3F₁ mice and equivocal evidence of carcinogenic activity in female B6C3F₁ mice.

Generations of pups from a multigenerational continuous breeding study with genistein in Sprague Dawley rats showed minor effects. Offspring from the F₁ and F₃ generations exposed *in utero* and during lactation to genistein, were either exposed to genistein or a control diet until 2 years of age. There was some evidence of increased mammary gland adenomas and adenocarcinomas in F₁ females fed genistein for 2 years, and equivocal evidence of increased pituitary gland neoplasms in F₁ females if feeding of genistein ended at 20 weeks of age.

B. BSC Discussion

Dr. McQueen proposed and Dr. Walker seconded a motion for the BSC to vote *en bloc* to accept the Subcommittee's recommendations on the NTP Draft Technical Reports. The motion passed unanimously with 13 yes votes, 0 no votes, and 0 abstentions.

2. Meeting held on August 28, 2006

A. Presentation

Dr. McQueen, Chair of the Subcommittee, summarized the actions on the NTP Draft Technical Reports reviewed at the meeting on August 28, 2006. The Subcommittee reviewed NTP draft reports on allyl bromide and dicyclohexylcarbodiimide in p53 and Tg.AC models.

- Squamous cell papillomas of the vulvae were noted in Tg.AC female mice receiving allyl bromide.
- Squamous cell papillomas of the skin were observed in Tg.AC female mice receiving dicyclohexylcarbodiimide.

Draft reports on benzene, glycidol, and phenolphthalein were reviewed using the p16^{Ink4a}/p19^{Arf} mouse.

- Benzene caused malignant lymphomas in male mice.
- Glycidol caused histiocytic sarcomas in male mice. There was some evidence of increased alveolar bronchiolar adenomas in female mice receiving glycidol.

The Subcommittee discussed the future use of genetically modified models (GMM) in NTP cancer hazard identification. The Subcommittee agreed with the NTP's proposal to utilize them as needed when

- *There is compelling prior evidence that suggests that a particular agent or class of agents could be adequately studied in a particular model.*
- or
- *There is insufficient test agent available to employ conventional 2-year or lifetime exposure cancer models.*
- or
- *Studying the effects of mixtures of agents if the response of the particular model chosen is known for at least one component of the mixture.*

The NTP proposes to continue to develop and/or refine GMMs for the study of agents, when appropriate. The NTP concludes that there is insufficient evidence to support the routine replacement of the 2-year mouse bioassay with GMMs.

Dr. McQueen said that the NTP plans to review draft technical reports on cresol, cumene, formamide, isoeugenol, propargyl alcohol, sodium dichromate dihydrate tested in conventional rats and mice and review a multigenerational study of ethinyl estradiol in Sprague Dawley rats at its next NTP BSC Technical Reports Review Subcommittee meeting in 2007.

B. BSC Discussion

Dr. Kerkvliet asked whether other end points of toxicity besides tumors were observed in the GMMs. Dr. Bucher responded that the doses used in the GMM studies were not overtly toxic and the objective of using GMMs is their responsiveness in less than 2 years. The concordance of data in GMMs and conventional mice is quite good, but NTP's concern is the non-responsiveness of GMMs to known human carcinogens.

Possibly second-generation models with two or more genetic alterations may be more sensitive.

Dr. Katharine Hammond asked whether the GMMs were particularly sensitive to a specific class of chemicals. Dr. Walker responded that one class being tested at the FDA National Center for Toxicological Research is nucleoside analogues, which are usually administered as mixtures to patients. It seems appropriate to test the various combinations of this class of drugs for carcinogenicity in the GMMs with shorter times to tumor. Dr. Bucher said the Tg.AC mouse is highly responsive to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and thus the carcinogenicity of polychlorinated biphenyls (PCB's) is presently being tested in this strain. He said the NTP believes that these models are still valuable, but not as a substitute for the conventional bioassay.

Dr. Allaben said the FDA accepts data on drugs tested in a 2-year rat study and a GMM mouse study. Dr. Bucher said the development and use of GMMs might be appropriate in the HSI initiative.

Dr. Deininger proposed and Dr. McQueen 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, 0 no votes, and 0 abstentions.

Dr. Deininger proposed and Dr. Walker seconded the motion for the BSC to accept the recommendations regarding the subsequent use of GMM's as outlined above. The motion passed unanimously with 13 yes votes and 0 no votes and 0 abstentions.

IX. CERHR Nomination and Selection Process

A. Presentation

Dr. Michael Shelby, director of the Center for the Evaluation of Risks to Human Reproduction (CERHR), said CERHR's main activities are to (1) convene expert panels to evaluate selected chemicals for effects on human reproduction and development, (2) maintain a website for information and communication, and (3) respond to individual inquiries on reproductive health issues. CERHR produces three products: CERHR expert panel reports compiled by experts on a specific nomination, NTP Briefs which include the NTP's conclusions about any reproductive hazards associated with the substance evaluated, and NTP-CERHR monographs which contain the above documents as well as any public comments on the expert panel reports. He summarized the status of the monographs including those produced, ones presently under review, and ones for which the draft expert panel report will be available soon. He outlined the six steps of the nomination and selection process.

Substances are nominated via the NTP or CERHR websites.

- The CERHR Core Committee, consisting of representatives of NTP-participating agencies, reviews preliminary dossiers on nominated substances at quarterly meetings.
- CERHR then prepares full dossiers on substances of interest.

- The CERHR Core Committee reviews the full dossiers and recommends/selects substances for expert panel evaluation.
- The recommended substances are sent to the NTP Associate Director for review and approval.
- CERHR announces the approved substances in the Federal Register and invites public comments.

Substances are selected for evaluation based on (1) their potential for human exposure, (2) the extent of data from reproductive and developmental toxicity studies, (3) their production volume, and (4) public concern. He provided an example using bisphenol A for which production is greater than 10 million pounds per year. It is found in the food supply, there is extensive literature with 65 developmental toxicity, 37 reproductive toxicity, and 43 exposure studies in the literature, and there is public concern particularly relating to low dose effects.

Recently the National Institute for Occupational Safety and Health nominated lead for review as there is some evidence that it can cause spontaneous abortions and reduced birth weight at levels < 20 µg/dL in blood while a blood lead level of 40 µg/dL is permitted in occupationally exposed workers including pregnant women. Production of lead is greater than several hundred thousand tons/year, everyone is exposed, there is extensive scientific literature, and there is a longstanding concern for neurotoxicity from exposure to lead.

Dr. Shelby asked the BSC for their thoughts regarding whether the BSC should have an advisory role in the selection of chemicals for CERHR expert panel evaluations.

B. BSC Discussion

Dr. Buck Louis said she was pleased with the format of the process: the range of nominations to CERHR is broad, the multi-step process has established criteria, and the process facilitates discussion from the time of nomination to publication of the monograph. She questioned the recent increase in the time interval between receiving a nomination to publication of a monograph. Dr. Shelby responded that it used to take six months from the time of the expert panel meeting until publication of the monograph, but recently an extra step to peer review the NTP Briefs has slowed down the process. Dr. McCarver asked how the timeframe for completing a report in the testing program compares with the time frame for producing a monograph. Dr. Dearry responded that CERHR is much more efficient than the testing program, but that there are more steps to finalizing a report from the testing program.

Dr. Buck Louis asked if there could be a formal approach to measure the use of monographs by federal and state agencies. Dr. Shelby responded that Dr. Wolfe had mentioned earlier in the meeting that this was an extremely difficult task. He said the NTP knows that various government agencies such as the Consumer Product Safety Commission, EPA, FDA, and California EPA utilize the documents, but use by other agencies is more difficult to determine. He was surprised when the U.S. Bureau of Reclamation contacted him recently asking about the NTP-CERHR Monograph on

Acrylamide. The Bureau is using this document in a hazard assessment of the use of polyacrylamide to prevent water seepage from irrigation canals. Dr. Shelby added that a report documenting no adverse effects for a substance could be as important as one documenting adverse effects.

Dr. McCarver asked what percentage of nominations CERHR reviews, and Dr. Shelby said CERHR had received about 420 nominations in about 9 years and 17 monographs have been published with 4 more in various stages of preparation. The main reasons for the low ratio of monographs: nominations are an inadequate database on reproductive effects, a low exposure level to humans, and the lack of information on a chemical's use in the United States. She asked if there could be a crossover from CERHR to the NTP testing program whereby specific research needs on a nomination could be addressed by the testing program. Dr. Bucher said such a linkage potentially exists as Dr. Paul Foster who is deputy director for CERHR also directs reproductive studies through the testing program. Dr. Katharine Hammond added that it might be useful to determine whether NTP's partners could supply the data. Dr. Shelby thought these good suggestions to consider.

Dr. John Giesy asked whether CERHR writes an opinion as to why a nomination was not selected for evaluation. Dr. Shelby said the reasons for not selecting a substance for evaluation are recorded in the summary of the Core Committee meeting. CERHR acknowledges the receipt of nominations, but does not inform nominators of its decisions, and no nominator has ever asked CERHR for its decision. Dr. Gail McCarver said the downside to not publishing a report on the Core Committee meeting outlining data needs is that external scientists are not aware of these data needs and whether they might consider addressing them.

Dr. Walker asked for clarification on several issues: at what point in the process would NTP want input from the BSC, how would the BSC receive the information for review, would the BSC vote on the nominations, and would the committee's involvement lend legitimacy to the program. Dr. Dearth responded that the NTP Director and he have asked for more external review of the scope of the entire NTP program, not just CERHR. The BSC would provide an opinion on whether an evaluation is warranted for the substances recommended by the CERHR Core Committee. The BSC would receive a dossier with background information and the review could occur before the Core Committee makes a decision on nominations to recommend to the NTP Associate Director. Through an announcement in the Federal Register, the BSC meeting would also provide an opportunity for the public to provide comments on the nominated substances.

Dr. Shelby raised another issue within CERHR for the BSC's consideration: how to consider nominations with small data sets. For example, he referred to the case with PFOAs for which there is a fair amount of data overall, but not enough on reproductive outcomes to convene an expert panel. Other examples are diethylphthalate and dimethylphthalate for which reproductive data are limited despite extensive human exposure. Dr. Buck Louis suggested that CERHR solicit unpublished data on nominations through Environmental Health Perspectives. This mechanism would be

most appropriate for the less well-studied compounds including those with smaller datasets.

Dr. McQueen suggested that the BSC use the same approach for CERHR nominations currently used for nominations to the testing program. Dr. Daston thought this a reasonable first-approach that could be modified if it proves unsuitable. Dr. Shelby agreed that more attention could be given to non-selected nominations by soliciting information on missing data and the BSC might recommend studies that could be undertaken.

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

The meeting was adjourned at 4:45PM.