National Toxicology Program
Board of Scientific Counselors

October 26, 2004

NIEHS, Research Triangle Park, NC

Summary Minutes

I. Attendees

Members:
Diane Birt
Aaron Blair
Kim Boekelheide
Hillary Carpenter
Harvey Checkoway
George Daston
Elizabeth Delzell
Thomas Gasiewicz (chair)
John Giesy
Shuk-Mei Ho
Margaret Karagas
Charlene McQueen
Maria Morandi
Barbara Pence
James Popp
Stephen Roberts
Richard Storer
Cheryl Lyn Walker
Bruce Weir

Members Absent:
Larry Andrews
Gail Charnley
Samuel Cohen
Michael Elwell
Howard Frumkin
Irva Hertz-Picciotto
James Klaunig
Walter Piegorsch
Mary Anna Thrall
Mary Vore

***ad hoc* Attendee:**
Joseph Ibrahim

NIEHS Attendees:
Allan Benton
Lutz Birnbaumer
John Bucher
Rajendra Chhabra
Brad Collins
Adriana Doi
Jonathan Freedman
Retha Newbold
Ken Olden
Chris Portier
William Schrader
Barbara Shane
Cynthia Smith
Jennifer Smith

Melissa Gentry
Dori Germolec
Gloria Jahnke
Bill Jameson
Beby Jayaram
Grace Kissling
Ruth Lunn
Diane Spencer
William Stokes
Fernando Suarez
Molly Vallant
Nigel Walker
Mary Wolfe

Agency Attendees:
William Allaben, NCTR/FDA
Mark Toraason, NIOSH

Public Attendees:
Pamela Blackshear, ILS
Reshan Fernando, RTI International
Tom Goldsworthy, ILS
Charles Hebert, Southern Research Institute
Jon Lodge, RTI International
Alexa McCarron, RTI International
Catherine Price, RTI International
Les Reco, ILS
Charles Sparacins, RTI International

II. Introduction and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors ("the Board") met on October 26, 2004, in the Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. (*Attachment 1*: *Federal Register* meeting announcement; *Attachments 2* and *3*: Agenda and Roster of Members). Dr. Thomas Gasiewicz welcomed everyone to the meeting and asked the Board members and attendees to introduce themselves. Dr. Christopher Portier, Director of the Environmental Toxicology Program (ETP), and Associate Director, NTP, NIEHS, welcomed and thanked the Board members for their efforts. He expressed Dr. Kenneth Olden's regrets for being unable to attend most of the meeting. He recognized Dr. Carpenter who was retiring from the Board and thanked him for his participation since 2000. He noted that the NTP benefits from having a member from a state health department.

III. NTP Update

A. Changes in Personnel

Dr. Portier told the Board that Dr. David Schwartz, a physician from Duke University, would replace Dr. Olden on April 4, 2005, as Director of NIEHS. He said Dr. Schwartz would attend the next Board meetin and the members would have an opportunity to meet him.

B. Recent NTP Meetings

1. Vision

A NTP retreat for August 10-12, 2004, was held to discuss the vision for the 21st century and a draft roadmap for its implementation.

2. Report on Carcinogens

The 11th Report on Carcinogens is planned for release by the end of the year. Dr. Portier congratulated Dr. Jameson and his staff for their efforts in preparing this report.

3. ICCVAM / NICEATM

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) that provides oversight for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) met on October 20, 2004, in Research Triangle Park, NC. ICCVAM is tasked with advancing the development and validation of alternative tests that refine, reduce and/or replace the use of animals. Presentations were made on alternative toxicological methods to test for ocular and skin irritancy and on the NTP roadmap. The SACATM offered advice to Dr. Portier regarding the roadmap.

4. Technical Reports Review Subcommittee

The next Technical Reports Review Subcommittee of the Board meeting is scheduled for December 9-10 at the NIEHS. The draft of NTP technical reports scheduled for review are azido-thymidine (AZT) administered transplacentally, three studies of polychlorinated biphenyls (PCB 153, a mixture of PCB 126 and PCB 153 and a mixture of PCB 118 and PCB 153), two water disinfection by-products (bromodichloromethane and sodium chlorate), and benzophenone.

5. Center for the Evaluation of Risk to Human Reproduction

The Center for the Evaluation of Risk to Human Reproduction will convene an expert panel to review the potential reproductive and/or developmental toxicity of amphetamines and of methylphenidate on January 10-12, 2005, in Alexandria, Virginia.

C. Other Issues

1. NTP Website

Dr. Portier encouraged the Board to visit the updated NTP website that is being revised to make access to data from NTP studies easier. In addition, the databases have been augmented with data not previously available on the website. He thanked Dr. William Eastin for his efforts in upgrading the website and the staff in the NTP Liaison and Scientific Review office for testing the new website and offering suggestions for its improvement.

2. NIEHS Center for Rodent Genetics

The NIEHS/NTP has implemented a contract to build a haplotype map of 15 mouse strains. These maps will be informative as the NTP considers whether to use different mouse models with different exposure scenarios.

IV. NTP Roadmap

Dr. Portier reminded the Board that almost a year ago he presented a vision for the NTP for the 21st century. Three working groups were convened to individually advise the NTP on the vision and a framework for its implementation. These working groups presented their reports at the June 2004 meeting of the Board. The Board working group, chaired by Dr. Samuel Cohen, presented their insightful thoughts on the future directions of the program. The NIEHS working group, chaired by Dr. Michelle Hooth, undertook a detailed review of the NTP's activities and provided important organizational and scientific changes for the program. An interagency group headed by Dr. John Bucher, focused on the needs of federal agencies, their concerns regarding resources, long term planning and interagency cooperation. The NTP held a satellite meeting on March 25, 2004, following the Annual Meeting of the Society of Toxicology, where a number of prominent toxicologists addressed the Board Working Group giving their views on the NTP's vision and future of toxicology. Based on these inputs, Dr. Portier drafted a roadmap that was discussed and revised at a retreat on August 9-11, 2004 in Greensboro, NC. Participants were divided into four breakout groups that included NIEHS staff and representatives from SACATM, the Board, federal agencies, industry and academia. The breakout groups were assigned two tasks: (1) rewriting of a specific section of the roadmap to clarify the direction of the program and (2) development of an activity matrix for one of four major areas of the roadmap to include the time frame for undertaking activities recommended for that area. He said the groups did an excellent job rewriting the sections of the document. The four breakout groups addressed the following activities of the roadmap: (1) high throughput screening (HTS), (2) bioassay review and design, (3) medium throughput screening including genomics, proteomics and metabonomics ("omics") and (4) data analysis and interpretation. Members of the Board who attended chaired the breakout groups (Dr. George Daston - HTS group, Dr. James Popp - MTS and "omics" group, Dr. Stephen Roberts - bioassay review and design group, and Dr. Hillary Carpenter - data analysis group). NIEHS/NTP staff served as rapporteurs.

Dr. Portier presented the roadmap for the NTP for the 21st century that will help to guide the program for the next 5-10 years. He said presently the NTP receives nominations for study that undergo a review by the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC), the Board and the NTP Executive Committee and this is an opportunity for public comment. The NTP sets priorities for testing for carcinogenesis, reproductive toxicity, and immunotoxicity. If an adverse effect is obtained in any of these studies, the program attempts to determine the mechanism(s) of the toxic effect and assess whether the finding(s) are relevant in humans.

In contrast, the roadmap outlines a different approach to the testing of compounds for their toxicity. It involves the development of broad-based, targeted, screening assays by which the toxicity (and mechanism) of a chemical can be evaluated before it is studied in chronic assays. It also provides for an evaluation of the mechanism of the toxic response for classes of compounds.

Dr. Portier conveyed the recommendations of each breakout group. The HTS group said it was a laudable goal for NTP to consider implementing HTS assays. It suggested cataloging the available, relevant and appropriate assays to determine which assays would be most suitable and how easily they might be acquired. The HTS Group suggested that (1) the NTP hold a workshop in 2005 on HTS assays, (2) the NTP form an advisory group to guide the selection of assays, and (3) the NTP hold a second workshop to discuss the use and interpretation of data from mechanistic assays in guiding the program on decisions and/or further testing. Subsequent activity would be the screening of ± 600 agents previously tested in the bioassay and in 2007 initiate activities to determine if the data collected are meaningful and useful or whether the battery of tests should be amended. The HTS Group suggested that the NTP seek guidance from groups such as pharmaceutical companies, because of their exhaustive experience with HTS assays.

The bioassay review and design group (the "BRD Group") was supportive of the NTP continuing studies such as those on individual dioxin and PCB congeners and their mixtures to determine potential additive effects and Dr. Portier concurred. The BRD Group was encouraged by the NTP's use of digital pathology to evaluate slides and tissues through the Internet. Dr. Portier said a goal is digital scanning of an intact animal. The group suggested that a workshop be held in 2005 to discuss the relevance of the strains and species currently used in the two-year bioassay and whether NTP might consider alternative strategies. In addition, they suggested that the NTP examine the usefulness of the subchronic and clinical pathology studies. The group suggested that the NTP strengthen its toxicokinetics program and proposed creation of an interagency consortium to guide NTP in the design and development of physiologically based pharmacokinetic (PBPK) models. The BRD Group also suggested that the NTP evaluate the timing and duration of exposure noting that there is a paucity of information about the risk of early and late life exposure; NTP could contribute to providing data during these life cycle stages. Finally, the BRD Group suggested that the NTP consider re-examining slides from earlier bioassays to determine whether the use of newer technologies might change the pathology call for carcinogenicity.

The MTS and "omics" breakout group (the "MTS Group") debated the goals and objectives of using HTS and MTS assays. The group opined that screening assays for toxicity could involve the use of invertebrates and lower vertebrates such as *Caenorhabditis elegans*, zebrafish and possibly *Drosophila spp*. and thought that the program has not spent sufficient time and resources on investigating these models. They suggested development of a database on studies using these organisms and holding a workshop to define the criteria for selecting the most appropriate models. The MTS group felt that undertaking a concerted effort on MTS and "omics" might enable the NTP to be routinely using these assays by 2008.

The data analysis group ("DA group") had the most difficult task since the NTP is uncertain of the type of data that might be collected by implementing new testing initiatives. This group felt that a key issue is that information technology needs to handle the volumes of data likely to be generated from HTS, MTS and "omics". They felt current capabilities would be overwhelming. The DA group recommended holding a workshop (2007) to define the software required to analyze and interpret the data of the selected HTS and MTS and "omic" assays. The program

must continue to interact with decision-makers at federal agencies and be cognizant of their needs. The group also discussed the proposed organization of the NTP Office of Nominations. Dr. Portier said that the office needs to be expanded to coordinate, track and disseminate information on the nominations.

Dr. Portier closed by noting that the roadmap is aggressive and scientifically challenging but he is hopeful that it will strengthen the science of toxicology and the utility of the NTP for the future.

Board Discussion

Cost of new initiatives and resources

Dr. Aaron Blair asked how many chemicals would be tested in HTS and what the cost would be. Dr. Portier responded that the NTP estimates it will spend less than $3-5 million on the testing of 2,000 compounds using 10-20 assays/year. This is less than the $25 million/year that NIH plans to spend on HTS to test 100,000 compounds in 20 assays/year. Dr. Blair asked about the resources that would be needed for these new initiatives compared to what is being spent on present activities. Dr. Portier responded that the program has always invested in a number of proposed research areas. For example, the program spent $10-12 million/year on transgenic animals, *in vitro* assays and immunotoxicology assays without affecting its normal activities. He believes HTS assays will cost about $1/well for simple assays and up to $50/well for more complicated assays and depending on the number of doses and replicates. The project using *C. elegans* has produced useful results in two years and less than $1 million has been spent per year. He envisages the start-up cost for assays with zebrafish will be similar to *C. elegans*. He said the NTP is contributing $2 million / year to "omics" studies in the National Center for Toxicogenomics at NIEHS, where chemicals of interest to the NTP are being examined. He said the data analysis for these new tests are likely to be difficult and time consuming, but not necessarily costly, and the cost for meetings and workshops will not impact the budget greatly.

High throughput screening assays

Dr. Daston said the development and use of HTS assays is a timely and laudable goal for NTP, because there is a wealth of information on mechanisms that was unknown when the apical tests were designed. The difference between the approach used by pharmaceutical companies and the NTP is that the former chooses a single well-defined target, develops a suitable HTS assay and screens 10^5 to 10^6 compounds while the NTP's goal is the development and use of assays to assess the effect on multiple targets of toxicity with the screening of fewer chemicals of interest. An initial challenge will be the selection of assays covering a reasonable fraction of the mechanisms of interest and their integration with the apical tests to determine whether concordance exists. A second challenge will be whether the data collected are sufficient to determine whether any long-term study is warranted. The determination of mechanistic data is long overdue and presently only half of the information on a chemical is being used for risk evaluation. Dr. Daston envisioned the adoption of HTS will make testing more efficient.

Dr. Gasiewicz asked Dr. Portier if he could give an example of a group of compounds or an endpoint where HTS could be used relatively soon. Dr. Portier responded that the HTS breakout group recommended that NTP convene a workshop to discuss potential assays, but one group of

assays that comes to mind are those that measure mutagenicity. The program has tested over 2,000 compounds in the *Salmonella* assay and many in the micronucleus assay; strategically, these assays would seem to be ones to target for HTS.

Dr. Mark Toraason said the acceptance of the assays by the scientific community is extremely important. He asked how the NTP would monitor their acceptability. Dr. Portier replied that he would ask the Board or working groups of the Board and interagency scientists to review the selected assays before implementing studies. Dr. Portier suggested that the NTP would likely form an interagency coordination committee to provide input and guidance. He said validation of the endpoint(s) being measured would be necessary to ensure the assays are being performed correctly and used appropriately.

Dr. Daston asked if the program was considering nuclear receptor binding assays, and Dr. Portier responded that assays measuring androgen receptor binding are presently being funded through the ICCVAM process. He said the program would be cautious in its choice of endpoints and selection of assays.

Dr. Blair agreed that information from HTS would improve decision-making, but was unclear about how the NTP would select which mechanism to evaluate. He felt the range of options is enormous, such that the NTP will need to set priorities for its limited resources.

Dr. Barbara Pence asked if a defined approach for dosing cells for HTS would be used and Dr. Portier responded that the workshop on HTS will address the question of methodology. She emphasized that the range of concentrations to be used is important because a response at a high concentration might not be relevant. She suggested that the program consider using physiological concentrations that can be achieved pharmacologically. Dr. Portier said the design and range of concentrations would be discussed at the workshop.

Medium throughput screening (MTS) assays and "omics

Dr. Gasiewicz asked whether *C. elegans* or zebrafish models are envisioned to replace mammalian systems. Dr. Portier said the data from the MTS would be compared to the responses observed in HTS assays and depending on the results in two types of assays, the chemical or one or two members of the class might be tested further in a mammalian system. He reiterated that the use of HTS and MTS assays would not reduce the reliance on mammalian systems to evaluate the toxicology of chemicals. The real value of data from the HTS and MTS assays would be to define classes for testing based on mechanism.

Nominations

Dr. Diane Birt asked if the NTP Office of Nominations would be more efficient if it were integrated with other agencies such as the EPA. Dr. Portier responded that the ICCEC has members from 7 or 8 agencies including EPA that review nominations, and the ICCEC would remain as an integral part of the process for review of nominations for testing.

Dr. Shuk-Mei Ho asked whether computational biology or molecular modeling would be used before testing a chemical in HTS. Dr. Portier responded that one of the changes in the nominations office would be the inclusion of a theoretical chemist to work on molecular

modeling, structure-activity relationships, computational models, and the use of predictive tools to provide guidance on priorities for testing. He believes part of these activities might be accomplished by partnering with structural chemists at the FDA's National Center for Toxicological Research (NCTR) and a new computational group at the EPA in Research Triangle Park.

Databases

Dr. Cheryl Walker asked how Dr. Portier would facilitate the mining of the new databases that will be constructed and whether the data would be accessible retrospectively. Dr. Portier responded that he realizes that combining the data from the different endpoints and their subsequent interpretation will be difficult. He hopes to initiate an interagency consortium to explore how this might be accomplished. He is also hopeful that extramural funding for computational analysis will increase over time. One advantage of the NTP database is its quality and accessibility to the public. The NCI bioassay data on 400 chemicals was unavailable until recently when the NTP incorporated it into the present NTP bioassay database.

Genetic variability

Dr. Gasiewicz asked whether polymorphisms would be considered in the testing program and Dr. Portier replied that genetic variability in the human population would be addressed. Presently, the NTP is funding a contract to develop a haplotype map of 15 mouse strains to understand the genetic variability among the strains and the role of genetic variation in responses to toxic materials. Genetic maps have been constructed on human cell lines and functional toxicology studies have been performed on these cell lines in an attempt to relate responses to genetic variability. Dr. Popp said the MTS group endorsed the long-term goal of investigating the role of genetic variation in toxicology.

Dr. Daston said genetic variability adds another layer of complexity to the studies but it will be important in the future. The understanding of the toxicity of a chemical is an iterative process and the main function of the HTS and MTS assays is to speed-up the process of characterizing a chemical's hazard. The roadmap initiatives will be successful if they can shorten the time required to identify chemical hazards and if the screening programs are informative regarding susceptibilities of populations.

Dr. Margaret Karagas asked if the program plans to exploit molecular epidemiology resources in MTS or "omics" studies, and Dr. Portier responded that, whenever possible, human tissues would be used. However, with current restrictions on the use of human tissues it might be difficult. Dr. Portier agreed that this aspect is critical and will be considered as the program evaluates the myriad of HTS and MTS assays.

Communication

Dr. Popp said the current version of the roadmap is much improved compared to the original, because now the reader has an understanding of how mechanistic studies will be incorporated into the program. Communication of goals and their acceptability by stakeholders are of the utmost importance. He emphasized the importance of communication between the NTP and the scientific and regulatory communities that use NTP data.

Dr. Bucher replied that the NTP is aware of its need to take a leadership role in the evaluation and adoption of new scientific methodologies by the scientific and regulatory communities. Recently, the program has become more reliant on mechanistic endpoints in several areas, including the use of mechanistic information in the listing of chemicals in the Report on Carcinogens and the use of transgenic animals in carcinogen hazard identification. Communication approaches used previously, such as public workshops and seminars, will be adopted in implementing the roadmap.

Dr. Carpenter echoed Dr. Popp's sentiment regarding communication and complimented the program for the roadmap's evolution. He said the Board working group emphasized communication in its report because the vision proposes a significant paradigm change for governmental agencies. He would like reassurance that communication and education will be stressed. Dr. Portier responded that the NTP is committed to both education and communication.

Dr. Portier thanked Drs. Mary Wolfe and John Bucher for their contributions to the revision of the vision and roadmap.

V. Concept Reviews

Mr. Allan Benton, chief of grant reviews from the Division of Extramural Research and Training, NIEHS, outlined the guidelines for discussion of concept reviews. He said the discussion would be public and the general concept could be discussed without specific detail. Otherwise the concept would have to be discussed in a closed meeting. If the session were closed, any Board members and their affiliated institution would not be permitted to respond to a Request for Proposals.

A. Potential for Environmental and Therapeutic Agents to Induce Immunotoxicity

Dr. Dori Germolec, NIEHS, outlined the purpose of the concept to develop and validate methods to determine whether chemicals modulate the immune system. She said under the current contract, compounds are evaluated in a tiered panel of assays. If a chemical is found to modulate the immune system, the molecular mechanism(s) by which this occurs is investigated. She said this contract had been an extremely successful NTP activity and the information collected has had a major impact on immunotoxicity testing.

The contract is re-competed every five years and Virginia Commonwealth University has had the contract since 1985. Besides testing nominated agents for their effects on the immune system, the contractor conducts studies on the molecular mechanism(s) of action of compounds that alter immune function. Presently, the contractor measures immunomodulation of compounds in F344 rats and B6C3F1 mice following exposure via the dermal, intraperitoneal, oral, or inhalation routes or following inclusion of the compound in the feed or drinking water. The contractor performs range-finding studies on four chemicals each year. Tissue weights are measured and assays that screen for immunopathology, cell and humoral mediated immunity, non-specific immunity, and lymphocyte cell quantification are undertaken. Under the current contract, 18 chemicals were tested in range-finding studies. If a compound is positive in the range-finding studies, it undergoes additional testing in assays to evaluate hemopoietic stem cells and host

resistance. Five chemicals were tested in the past five years in this in-depth battery. The hypersensitivity of six chemicals was tested in four assays, namely, the local lymph node assay, the mouse ear swelling test, and tests for cell quantification and cytokine mRNAs. Suitable assays for autoimmune diseases, which reflect human diseases, are under development, because no reliable tests exist. Three mouse models have been used to quantify autoantibodies, serum immunoglobulin levels, urinary protein and glucose levels following exposure to cadmium, genistein and *Echinacea*. A database of all data collected in immune function tests is being compiled. Within the past five years, the contractor has published over 25 peer-reviewed publications as well as numerous reports for the NTP.

The new contract will be for three years with five additional, optional years and a number of task options. The contract will extend the histopathological studies to routinely include the histopathology of lymphoid tissues. Tissues will be collected routinely for genomics studies to assess whether there is a correlation between altered immune function and gene expression. The modulation of gene expression within a specific pathway will be determined rather than evaluating gene expression of tissue-specific arrays. It is hoped that this approach will determine whether gene fingerprinting can be used to screen for immunomodulating compounds. Developmental studies will be included as a defined task, and will entail the evaluation of currently used test methods, the identification of new endpoints to assess development of the immune system during gestation, and the determination of whether alterations in the immune system in young animals persist into adulthood. Two options will allow for the testing of additional compounds, the conduct of mechanistic studies, and the development of new technologies. In summary, the statement of work is similar to the present contract, but with the inclusion of additional endpoints in routine evaluations and with a task for developmental immunotoxicity. The contract also will focus on (1) the use of genomics for screening; (2) the evaluation of the immunomodulatory potential of agents of public health concern with emphasis on susceptible populations such as neonates and the elderly, disease endpoints, and autoimmune diseases; and (3) studies to determine how cellular and molecular events are associated with modulation of immune function.

Board Discussion

Dr. Daston asked Dr. Germolec whether she has evaluated which assays are the most effective, which ones are redundant, and whether the NTP has modified the battery of tests based on this analysis. Dr. Germolec responded that in the early 1990s the NTP performed a risk assessment comparing the sensitivity and predictability of individual immune function tests and combinations of tests and found that the antibody-forming assay is the most predictive. This observation was not unexpected, since this assay tests for a deficiency in one of a number of required elements for the normal functioning of the immune system. This assay was 75% predictive while a combination of this test with another test was 90-100% predictive. The NTP will repeat this evaluation once the database (noted above) that contains the results from all immune function tests is assembled.

Dr. Gasiewicz asked about long-term developmental endpoints the contractor would target since alterations in some endpoints might only be seen in an older animal. Dr. Germolec responded that the NTP uses two strategies to investigate developmental effects. Animals are exposed

during gestation through weaning to 42 days of age when Tier 1 endpoints are measured. If an effect is observed, an attempt is made to determine at which time point in the exposure regimen development of the immune system is impaired. To date, exposed animals have not been tested in adulthood, so the persistence of the adverse effect is unknown.

Dr. Roberts complimented the NTP on the new areas of research being planned under this contract. He asked about the tissues being examined for their immunotoxicogenetic effects and whether whole organs or specific cell types would be studied. Dr. Germolec responded that presently the spleen and thymus would be studied without trying to isolate specific cell types. The gene expression of specific T-cell and B-cell surface markers and specific cytokines secreted by these cells are being measured as a means for evaluating the responsiveness of these cell populations. The advantage of using the spleen is that functional and genetic studies can be performed on the same tissue.

Dr. William Allaben commented on the enhancement of the immune system by *Echinacea* following challenge with antigens and asked about other immune enhancing compounds. Dr. Germolec responded that saquinavir and thalidomide also stimulate the immune system. Dr. Gasiewicz asked about the doses used in the studies and the relative sensitivity of the assays since the NTP is using doses below the maximum tolerated dose (MTD). Dr. Germolec said the program had been criticized for using doses below the MTD, but if doses at or near the MTD are used, stress effects can mask more specific chemical effects on the immune system. The doses being used are higher than the doses to which people are exposed.

Dr. Daston moved that the concept proposal be approved. Dr. Kim Boekelheide seconded the motion, and the Board unanimously (18 yes/0 no) approved the concept.

B. Analytical Chemistry for the Environmental Toxicology Program

Dr. Cynthia Smith outlined the background to this concept. She said analytical chemistry is important in biological studies, because it is essential that the concentration of a test agent to which the animals are exposed as well as the internal dose of the test compound be known accurately. This analytical chemistry contract supports the identification and quantification of numerous classes of substances including chlorinated compounds, food additives, flame-retardants, metals and pharmaceuticals. Under the present contract, the contractor is responsible for procuring the test agent, performing its chemical characterization (purity) and developing dose formulations. Other tasks include the analysis of biological samples for the test article and analysis of the unlabeled substance from toxicokinetic studies. The contractor must have state-of-the-art analytical instrumentation such as high performance liquid chromatography (HPLC), gas chromatography (GC), gas chromatography /mass spectrometry (GC/MS), MS, nuclear magnetic resonance (NMR), andMS/MS. Unequivocal identification of the test articles using NMR and infrared (IR) is required. The contract requires the identification of any impurity that is present at a concentration of 1% or greater in any test article and the reporting of any impurities that occur at concentrations of 0.1 to 1%. For dose formulation, the contractor determines the stability of the test article in the vehicle. Toxicokinetic studies often include a feasibility study, a determination of the clearance of the test substance from the body, and the development of an analytical method to analyze the test article in many tissues. Non-

compartmental parameters are measured such as the half-life of the test article and its rate of clearance from the body.

New tasks to this concept are the identification and quantification of low levels of impurities and a comparison of concentration measurements using different instrumentation, e.g., GC vs. HPLC. One important aspect of the new statement of work is the ability of the contractor to rapidly analyze and interpret the results in a timely and cost effective manner. This new assignment will not require development of methods, but rather the application of well accepted biochemical or analytical techniques to the question at hand.

Board Discussion

Dr. Popp asked whether chemical stability is evaluated along with stability of the solvent. Dr. Smith responded that stability of the test article is evaluated under three types of storage conditions. Dr. John Giesy complimented Dr. Smith on the important work that the chemical contract achieves and endorsed the assignment of identifying impurities at lower concentrations in test articles. Dr. Smith responded to a question from Dr. Carpenter and said none of the chemistry is performed in-house, as all the analyses are performed through contracts. Dr. Allaben asked about the cut-off concentration of impurities for HTS and Dr. Portier answered that eventually rigorous standards would be applied to substances tested in HTS. These standards would be developed based on recommendations by experts at a working group meeting in the future. Dr. James Klaunig, who was absent but submitted written comments, reiterated the importance of this concept and agreed with the changes proposed for the new contract. Dr. Storer said the solubility of substrates in *in vitro* HTS is an important parameter. He asked whether the program has considered automated techniques to measure solubility and whether the highest concentration used in an assay would be based on solubility. Dr. Smith responded that the program is aware of the solubility issue as it pertains to HTS and will define an approach to address this issue. At present, there are no plans to use automated techniques to evaluate solubility. Dr. Storer said the pharmaceutical industry usually uses a range of 1-10 μM as the high concentration range in HTS assays because insoluble compounds interfere with these assays. With genetic toxicology assays, the substrate is usually added to a maximum concentration of 10 mM in DMSO. Dr. Giesy asked about the physical proximity of the chemical contractor with the toxicologists at NIEHS. Dr. Smith replied that it is her responsibility to translate the study design defined by NIEHS scientists to the contracting chemists, set priorities and direct their work. She added that there is daily contact by email or landline to monitor progress.

Dr. Daston moved that the concept proposal be approved. Dr. Popp seconded the motion, and the Board unanimously (18 yes/0 no) approved the concept.

C. Development of High Throughput Screening (HTS) Assays

Dr. William Caspary, NIEHS, said the concept proposes the use of automated techniques to screen a large group of compounds in assays that measure endpoints related to human disease such as cancer, and reproductive toxicity. The use of such assays will permit the NTP to test many more chemicals than can be tested using classical protocols and to evaluate complex

environmental mixtures and the components comprising these mixtures. Analysis of the data generated from HTS will contribute to the design of appropriate research studies. The number of parameters that can be tested in a short period of time will increase. Examples of the endpoints that might be measured include DNA damage, cell cycle modulation, cell viability, and translocation of intermediates from the cytoplasm to the nucleus.

Board Discussion

Dr. Portier noted that the Board received written comments submitted by Dr. Richard Becker from the American Chemical Council. Dr. Becker asked to present oral remarks at the meeting, but unfortunately had not arrived due to flight cancellations. Dr. Storer said the pharmaceutical companies take many months to develop a high throughput assay, but testing of thousands of the compounds can take a very short period of time. Dr. Caspary envisages the testing of 1,000-2,000 compounds in selected mechanistic assays that are adapted to automated techniques. Sufficient data should be generated to enable analysis for the predictiveness of single or combinations of assays for selected biological effects. These data could also potentially be used to predict the likelihood of an exposure causing a specific disease and to regulate human exposures in the absence of traditional cancer or reproductive toxicity bioassays. Analysis of these data might also allow the identification of a specific mechanism for a group of compounds or their prioritization for further testing. Dr. Portier said initially the program might start with a small set of compounds and expand to a larger set.

Dr. Boekelheide said the concept is timely, and he asked whether other models besides *C. elegans* have been considered particularly if susceptible populations of a model organism exist. Dr. Bucher said cell lines derived from knock out mice or genetically altered cells can be used in HTS assays. In response to a question from Dr. Blair, Dr. Caspary said the 600+ chemicals already studied by NTP may be tested in HTS assays as a proof of principle study. Dr. Portier said testing would not be restricted to these 600+ chemicals, but will include untested chemicals, especially those requested by NTP-partnering agencies. Information from such testing will aid in developing strategies for setting priorities for future testing.

Dr. Birt asked how HTS assays would improve the ability to assess the toxicity of complex mixtures. Dr. Caspary responded that a larger number of well defined mixtures with different ratios of components could be tested more rapidly with HTS than using conventional methods. Dr. Storer encouraged the NTP to develop assays with multiple endpoints. His company has had experience with rat hepatocytes in which three or more endpoints (e.g., DNA damage, ATP concentration, and membrane toxicity) are measured simultaneously in one assay system. Dr. Giesy asked if there are plans to measure the concentration of the test compounds in the cells during the assay to assess the pharmacokinetic uptake into the cell. Dr. Portier responded that such measurements would be prohibitively expensive; however, since the concentration applied to each well is known, this parameter would be used. Dr. Blair asked whether assays would be contracted-out or developed in-house, or whether a central contract would be exercised that would subcontract specific assays. Dr. Caspary replied that the mechanics of the contract have not been determined; some assays may be developed in-house. Dr. Portier said contracts can be handled in a number of ways including task orders or by assigning a contract manager a specific assay to develop in concert with a contractor.

Dr. Daston moved that the concept proposal be approved. Dr. Boekelheide seconded the motion, and the Board unanimously (18 yes/0 no) approved the concept.

VI. NTP Study Nominations and ICCEC Recommendations

Dr. Scott Masten, NIEHS, briefly outlined the process for review and selection of chemicals nominated for future study and noted that this process includes multiple opportunities for public comment. Nominations can be made by anyone. Following compilation of relevant information on each nomination, the ICCEC makes recommendations on the types of studies appropriate for each nomination. These recommendations are announced in a Federal Register notice and public comments are solicited.

The International Tungsten Industry Association, which represents 48 companies producing and consuming tungsten, submitted comments on tungsten trioxide in which they clarified the processes by which tungsten metal powder is made. Du Pont, 3M, and Environment Canada expressed their support for the study of the perfluorinated compounds and offered their assistance with analytical method development. The People for the Ethical Treatment of Animals (PETA) and three other animal protection organizations commented on each of the nominations. As a result of an action alert issued by the PETA, over 1300 emails and letters opposing the use of animals in research were received. These public comments were sent to the Board before the meeting.
Dr. Masten said the ICCEC reviewed 10 new nominations; 7 were recommended for study and 3 were deferred (butylparaben, undecane and decane), either because there was not sufficient information for the ICCEC to make a recommendation or the nomination was given a lower priority. He identified the nominations based on their class:

1. Dietary supplements/consumer products – bitter orange, butylparaben and di-(2-ethylhexyl)phthalate
2. Industrial chemicals – *n*-butyl glycidyl ether, decane and undecane, ionic liquids and tungsten trioxide and fibrous tungsten suboxides
3. Environmental contaminants – perfluorinated compounds and *Stachybotrys chartarum*

Dr. Masten highlighted three questions for the Board's consideration:

1. Does the Board agree with the studies recommended by the ICCEC?
2. Are there other studies that should be conducted on any of these agents?
3. Are there some studies that should have higher priority than others? Which ones and why?

Board Discussion

Prior to the meeting, certain Board members were asked to serve as lead discussants on individual nominations.

Bitter orange extract

Dr. Birt said although the public questioned the study of substances that are "generally recognized as safe," such as bitter orange, she thought such compounds should be studied if there

is an indication of hazard. Dr. Birt asked whether the population exposed could be estimated. Dr. Masten responded that it is difficult to determine human consumption of dietary supplements, but one indication is the number of products on the market. There is heightened concern because the number of products containing bitter orange has increased recently. Dr. Birt asked if an anonymous nominator is acceptable. Dr. Mary Wolfe, NIEHS, responded that the NTP withholds the names of a private citizen because of privacy issues; however, the names of nominating organizations are publicly identified. The NTP requests that nominators identify any organizational affiliations.

Dr. Birt said the planned physiology studies should have top priority, but she does not understand the rationale for the planned developmental toxicology studies. She suggested that second tier studies should be done by testing combinations of caffeine and bitter orange. Dr. Allaben replied that FDA is concerned because many women take bitter orange for weight loss. Dr. Storer said bitter orange is touted to be safer than ephedra; however, there is no data to support that contention. It is important for the NTP to undertake these studies. He concurred with Dr. Birt that studies combining caffeine with both bitter orange and ephedra would be important. He noted that there is a significant degree of variability in composition between various bitter orange extracts and asked whether the two active ingredients, namely *p*-synephrine or *p*-octopamine might be studied instead of a bitter orange formulation. Dr. Masten responded that the NTP hopes to take advantage of an arrangement the FDA has with academic institutions to obtain bitter orange extract. Since there is a concern about susceptible populations who may have different margins of safety for cardiotoxicity, Dr. Storer suggested that an animal model with a strain susceptible for cardiotoxicity would be useful for these studies. He is pleased the NTP is being proactive with this nomination.

n-Butyl glycidyl ether

Dr. Charlene McQueen said there is substantial occupational exposure to *n*-butylglycidyl ether, but she questioned whether the general public is exposed. Dr. Masten said the NTP is not aware of consumer exposure and it would not be expected given the use pattern for *n*-butyl glycidyl ether. Because of the High Production Volume Chemical (HPV) Challenge Program, Dr. McQueen cautioned against duplication of effort by the NTP with studies requested of industry by the EPA. Dr. Masten responded that the NTP has reviewed the industry studies submitted to the EPA and said the industry sponsor volunteered to conduct a developmental toxicity study. Dr. Irva Hertz-Picciotto (absent from the meeting) submitted written comments. She expressed surprise that the ICCEC did not recommend a neurobehavioral or neurodevelopmental study, which she believes is as important as a carcinogenicity study. Dr. Carpenter noted that PETA in their written submission said a number of references are omitted from the supporting document. Dr. Masten said these studies are either not related to the toxicity of *n*-butyl glycidyl ether, but refer to a structurally related compound, or are duplicative of those already cited in the supporting document.

Butylparaben

Dr. Boekelheide asked whether the deferral of this nomination is a prejudicial decision or to gather additional data. Dr. Masten responded that the ICCEC recommended that more data be collected on this nomination and presented at the next meeting. Dr. Boekelheide said this

chemical represents a group of compounds that may be of interest for study because its biological effects may be similar to the phthalates. Dr. Karagas agreed with Dr. Boekelheide's comments and said butylparaben has been reported to cause hyperpigmentation and hypersensitivity in humans especially in the presence of ultraviolet light. She said butylparaben was tested for its carcinogenicity following oral administration, but a study with topical application in the presence of sunlight should be considered because dermal exposure is the most likely route.

Decane and Undecane

Dr. Elizabeth Delzell asked for clarification on the Voluntary Children's Chemical Evaluation Program (VCCEP). She said the ICCEC did not recommend decane and undecane for study; however, these compounds are important industrial chemicals usually found in a mixture (e.g., Stoddard solvent), and exposure is widespread. Dr. Masten said the VCCEP program has been in existence for some time at EPA and recently there was a peer review meeting to evaluate decane, undecane, and dodecane. If in the future the ICCEC recommends that the NTP study these compounds, the program will coordinate with the EPA to determine what studies are needed. Dr. Masten said the Technical Reports Review Subcommittee of the Board reviewed NTP carcinogenicity studies of Stoddard solvent about two years ago. He said the ICCEC would reconsider these compounds next year. Dr. Carpenter said from a regulatory perspective these solvents have not been studied in-depth and there is a large gap in knowledge regarding their impact on the environment. Dr. Daston, who has been a member of the panel for the VCCEP, outlined the process for review of these chemicals. He said the sponsor prepares a document with relevant hazard and exposure information; it is reviewed in a public forum by a panel of experts to determine whether these chemicals pose a risk to children. The Board urged prompt reconsideration by the ICCEC of these chemicals for study.

Di-(2-ethylhexyl)phthalate (DEHP)

Dr. Walker said this is an important compound to study because there is a susceptible human group, neonates, and because it is metabolized to mono-ethylhexylphthalate (MEHP), a toxic intermediate. Since there is little reference to MEHP in the background information, she asked if MEHP levels could be used as a dosimeter for comparing levels in animal with those in humans. Dr. Walker questioned why two studies are needed to obtain blood and urine markers of DEHP and MEHP effects when it would be more useful to combine the studies. She said primate studies would be important because they would allow a comparison to be made with levels of MEHP in neonates and this information may be helpful in determining whether these levels pose a risk to infants. Dr. Boekelheide said a major objective would be to determine the percentage of DEHP that is metabolized to MEHP, the predominant metabolite, following oral and intravenous administration. In response to PETA's written comments stating that relevant references were omitted from the information provided, Dr. Masten said the FDA's supporting document was not meant to be comprehensive and he believes the most important references were included. Dr. Walker questioned whether a study in rats is necessary and Dr. Allaben responded that the FDA requested the NTP obtain the data in rats following intravenous and oral exposure for comparative purposes. Dr. Masten said the routes of exposure and protocols for these studies are still under development and the NTP will consider the Board's advice. Dr. Daston agreed with Dr. Walker that a single study is appropriate in the primates; the rodent pharmacokinetic study should be of low priority.

Ionic liquids

Dr. Giesy said ionic liquids are not used extensively at present and little is known about human exposure to these compounds. He suggested the NTP understand exposure routes before studying their metabolism. The NTP has an opportunity to be proactive and obtain toxicological information on the fluids before they are used extensively and there is merit in being proactive. He questioned why industry is not undertaking these studies, since apparently many companies want to manufacture ionic liquids. He also questioned why the ICCEC did not defer these studies until potential use and exposure pathways are better characterized. Dr. Bucher said the NTP has EPA's endorsement for the studies since they are being developed under the "green chemistry" label as safe alternatives to traditional solvents. Dr. Giesy suggested that the NTP leverage their studies with industry.

Perfluorinated compounds (PFOS)

Dr. McQueen asked for additional information about the proposed mechanistic studies and whether studies will be performed with peroxisome proliferator-alpha (PPAR-α) receptor knockout mice. Dr. Masten said mechanistic studies are needed to understand how this very broad class of compounds causes toxicity. He said PPARα is more relevant to the perfluoroalkyl carboxylic acids (PFOA) than other perfluorinated class members. It is also unclear if PPARα is involved in the adverse reproductive effects observed for perfluorinated compounds. Apparently, the pharmacokinetics of each perfluorinated compound depends on its functional groups and the length of the side chain of the molecule. There is also a gender difference in the elimination of PFOA in rats, probably due to differential expression of hormonally regulated transport proteins in the kidney. Dr. McQueen said the NTP should take advantage of the offer from 3M and DuPont to work with the program.

Dr. Klaunig sent written comments since he was unable to attend the meeting. He said the many perfluorinated compounds are peroxisome proliferators and thus the potential for carcinogenicity is likely related to PPARα agonist action. He said short-term subchronic and acute studies should precede longer-term studies to define the relative effects of C4 to C16 compounds on important mechanistic endpoints. The use of PPAR-α knockout mice should be considered, because it might clarify the role of PPARα in the induction of toxicity. The potential effects on Leydig cells and the pancreas in acute and subchronic studies should also be assessed. He said multiple doses should be included in the studies to define threshold and no observable effect levels as well as toxic doses. The inclusion of an *in utero* exposure study on the C8 isomers is important given the concern of peroxisome proliferator exposure during fetal life stage. Dr. Carpenter said it behooves the NTP to collaborate with 3M, who has a rich database on this class of compounds. Much is known on human exposure to the C8 isomers, but little is known about exposure to the C4 and other shorter chain compounds that are being suggested as substitutes for the C8 compounds. Thus, a concerted effort to study the short chain compounds should be initiated.

Stachybotrys chartarum

Dr. Harvey Checkoway said this nomination might be premature, since it is not clear that this species of fungus is the causative agent of the apparent adverse respiratory effects reported in "sick building syndrome." Dr. Masten said the NTP is responding to a public concern and this organism is implicated as a causative agent of pulmonary disorders in infants. People alleging

adverse health effects from mold exposures have sought monetary compensation but none has been forthcoming. Recently, the Institute of Medicine suggested that studies in which animals are exposed chronically to low levels of molds or mycotoxins are needed. Dr. Masten agreed that *Stachybotrys chartarum* may not be the best organism to study because its life cycle is complex, but more than a dozen characterized strains are available from the American Type Culture Collection (ATCC).

Dr. Pence said some believe that "sick building" syndrome is a myth: however, because no one knows if this is true, this study will be worthwhile. It is important to determine whether a fungal organism is the causative agent of the illness. Dr. Maria Morandi said *Stachybotrys chartarum* might not be the only organism responsible for adverse health effects from mold exposures and questioned whether this is the right organism to study. She said there are other organisms besides *Stachybotrys chartarum*, including *Aspergillus spp*. that produce mycotoxins, are immunosuppressive, and are more likely to be the causative agent. She said *Stachybotrys spp*. is difficult to culture and she would not select it for study.

Dr. Masten said the NTP has not studied a biological agent in this context before and realizes that much information is needed before any studies are initiated. Dr. Morandi said experimentally these studies would be difficult because it is likely that the spores and fragments of the mycelium contain the toxins; thus, exposure to the intact organism would not be informative. She asked how the NTP plans to stimulate the organism to generate mycotoxins since this process is not well understood in the fungus.

Tungsten trioxide

Dr. Pence said this is a somewhat confusing nomination, because it is unclear whether tungsten trioxide or a related tungsten intermediate (e.g., a whiskered product) that may be produced in an industrial setting is the potential hazard. There is little or no information on the magnitude of exposure and whether workers are actually exposed to tungsten trioxide or a whiskered compound. One study in Sweden identified whiskered compounds in the workplace. Apparently, the whiskered compound is produced in the hard metals industry when tungsten trioxide is used. Although most of the studies on tungsten trioxide are negative, these are important compounds to study because there is widespread worker exposure. She suggested that the NTP test the whiskered product and the blue oxide in an *in vitro* assay to determine if they generate oxygen radicals or cause cytotoxicity. Dr. Popp was also uncertain which compound would be studied, because it is unclear if the ICCEC recommends that the fibers first be characterized. Dr. Masten responded that the NCI nominated potentially hazardous forms of tungsten oxides for study, and studies to identify the specific materials that warrant further testing are integral to the nomination. NIOSH will aid the NTP in this regard by performing studies to determine which of the fibrous tungsten compounds are present in the workplace. Dr. Storer asked if there are any case reports of pulmonary fibrosis in tungsten workers, and Dr. Masten said none are documented. Dr. Pence said it would be difficult to determine the causative agent for any identifiable adverse health effect since other metals, such as cobalt or silicon dioxide, are usually present in the workplace of the hard metals industry.

VII. Process to Study Small Data Sets (SDS) by the Center for the Evaluation of Risks to Human Reproduction (CERHR)

Dr. Michael Shelby said the process proposed to study SDS is in addition to the expert panel reports the CERHR presently compiles and publishes. Presently, the reports are prepared by a panel of experts working for 2-3 months to develop a draft that is available for public review through a *Federal Register* notice. The process concludes with a 2.5-3 day public meeting where the expert panel's final conclusions are written. He reported that from June 1998 to September 2004 the NTP CERHR published 11 NTP-CERHR monographs based on expert panel reports and two more monographs are nearing completion. CERHR evaluated 2-3 chemicals each year. The Core Committee composed of representatives from NTP participating agencies meets quarterly to review dossiers of chemicals nominated to the CERHR for review. Four criteria are considered in selecting a chemical for evaluation: public concern, extent of human exposure, and availability of reproductive and developmental toxicity data and production volume.

Of the nearly 400 chemicals nominated over the years and reviewed by the Core Committee, 20 chemicals have been selected for expert panel evaluation, while approximately 50 were deferred because data available on exposure and/or reproductive toxicity were too limited to warrant a full evaluation. The CERHR is proposing an abbreviated process that does not involve a panel meeting to study chemicals with SDS. Dr. Shelby quoted three examples of chemicals with SDS: dimethylphosphonate, diethylphthalate and methyl-, ethyl-, propyl-, and butyl-parabens, where there are a total of 6-12 reproductive and developmental toxicity studies for dimethylphosphonate and diethylphthalate and one study for each of the parabens in animals. Despite the relative paucity of data, there is public health concern for the phthalate and parabens because exposure is extensive. The proposed differences between the review of traditional CERHR process and SDS are: (1) the review of the draft reports by experts but not in a public forum, (2) the opportunity for the public to comment at 3 stages in the process rather than 4, and (3) the publication of an NTP executive summary in place of the NTP brief that appears in the NTP-CERHR monographs. Similarities between the two processes include: (1) the identical chemical nomination and selection process, (2) the selection of expert reviewers from the CERHR Expert Registry, (3) conformation to the expert panel guidelines, and (4) the adoption of the same format for the SDS report as used routinely. The advantages of this new process for small datasets will be the reporting on chemicals of high public interest, the subsequent identification of critical data needs, and an increase in the number of chemicals evaluated by CERHR. The final product will be a report containing an NTP executive summary, an SDS report prepared by an expert panel based on the initial draft prepared by the contractor, and all public comments received on the final SDS report.

Board Discussion

The Board raised several questions and concerns with the proposed process for review of SDS chemicals: (1) the accessibility of the public comments on a specific chemical to the expert committee, (2) who would define whether a compound is reviewed via the SDS approach, (3) how many of the 50 nominations could be reviewed using this process, (4) whether CERHR would reach a conclusion on a chemical despite the limited data, (5) whether CERHR or an expert panel would compile the first draft, and (6) whether the SDS reports would be considered

"authoritative body" reports under Proposition 65 in California. Dr. Shelby responded to the Board's concerns: (1) the expert panel members would receive the public comments, (2) CERHR would rely on the interagency Core Committee for guidance on whether a compound should be reviewed via the SDS process; (3) presently there are sufficient data to review half of the 50 deferred chemicals; (4) the expert panel and CERHR would not reach a conclusion if uncertainty exists because of significant data needs for a specific chemical; (5) CERHR would consider the use of a smaller expert panel to write the document; (6) the SDS reports would be considered authoritative and may be listed under Proposition 65 in California because they are peer reviewed.

Dr. Boekelheide supported the SDS approach for review of chemicals with limited datasets because the review might highlight compounds for which acquisition of additional data would be important. Dr. Blair suggested that the details of the SDS process be described in the preface of the document to distinguish it from the monographs. Dr. Portier clarified the compilation of the monographs and the reports on chemicals with SDS. He said the first four chapters of the monographs are always written by the contractor with oversight by CERHR staff and are revised by the expert panel before the public meeting. The only difference between the monographs and the SDS reports would be chapter 5, which would be drafted by CERHR staff for the SDS chemicals. Dr. Shelby concurred with Dr. Portier's suggestion and the Board's request that if the expert panel deems a public meeting be held for a chemical with SDS, then it would be reviewed as a typical monograph. Dr. Daston summarized the discussion and said there are instances where reports using the SDS process would be really valuable if they indicate a clear hazard or do not pose a risk. The greatest concerns are whether the reviewers can reach a conclusion regarding a hazard if there is any degree of uncertainty about a relatively limited dataset and whether political use or misuse of the SDS reports could occur.

VIII. Statistical Analysis of Data from the NTP Rodent Cancer Bioassay

Dr. Portier introduced the topic by saying that statistical analysis is an important part of the two-year bioassay specifically as it relates to results in which a trend or an umbrella-shaped response is observed as a function of dose. The motivation for developing the new test is the observation that the current poly-3 trend test does not necessarily perform well if the pattern of responses deviates from linearity. To address this deficiency, Dr. Shyamal Peddada, NIEHS, presented a "new" method of analysis that is under consideration. He asked the Board whether this new method of analysis should be used concurrently with the poly-3 method for analysis of data in the NTP technical reports for a few years. This would allow the program to ascertain if the new method is superior to the poly-3 trend test and whether or not it should replace the poly-3 test.

Dr. Peddada recognized his colleagues Drs. Joseph Haseman, Gregg Dinse and Grace Kissling for their assistance in developing the analysis. He presented the reason for development of the new test statistic, results of simulation exercises, and subsequent re-analysis of NTP data using the new statistic. He said there are two aspects to the test statistic namely, how survival adjustments are made when assessing tumor proportions in the dose and the control groups and how the test statistic is constructed using these survival adjusted tumor proportions. Both tests use a poly-3 survival adjustment, but they do so in different ways. He said the NTP's poly-3 trend test is based on a linear regression of the survival adjusted tumor proportions on dose;

therefore it is expected to perform well when the trend is linear. The "new" test does not rely on linear regression of these rates on dose, but is a nonparametric procedure that uses ideas from order-restricted inference. He showed results of studies of three chemicals in the two-year bioassay that depart from linearity. Using the poly-3 trend test, there does not appear to be a significant dose-related trend in tumor proportions, although intuitively there appears to be a chemical effect and, in each case, the NTP concluded a neoplastic effect using other criteria. However, when using this new nonparametric test statistic, the p values for the above mentioned studies were statistically significant. Based on extensive simulation studies, he said the false positive rate of the "new" test never exceed that of the poly-3 trend test when both tests operate above the nominal level (e.g. 5%). The new procedure also improves the power (sensitivity) to detect true positives.

Board Discussion

In response to Dr. Portier's question, Dr. Peddada said the test statistic discussed before the Board meeting had been modified and he presented a modified version of the test. Dr. Portier said the NTP will not use the test statistic described by Dr. Peddada, but will use the approach discussed in the publication sent to the Board for their review.

Dr. Joseph Ibrahim, University of North Carolina at Chapel Hill, served as an *ad hoc* reviewer of the proposed new method. Because there was some confusion regarding the content of the publication and Dr. Peddada's presentation, Dr. Ibrahim asked for clarification of some terms. He asked whether the new statistic tests the hypothesis that the incidences are the same although the poly 3-test tests whether all the tumor proportions are the same. He asked if the new test would include the doses as in the modification of the Cochran-Armitage test and Dr. Peddada responded by saying "no." Drs. Daston and Gasiewicz approved Dr. Portier's suggestion of running the two tests concurrently for a few years. Dr. Daston said this would be an incentive for the biologists on the Board to think about different statistical approaches and their limitations. Dr. Ho asked whether other statistical approaches could be considered because it might be premature to adopt this particular method if all the other scenarios have not been exhausted. She also asked if the NTP could explain the difference between the two methods in a language that could be understood by biologists. Dr. Portier responded that it would be impossible to test all the possible methods. Dr. Allaben requested that the NTP be receptive to comments from statisticians from NTP-partner agencies and clearly define which statistical package would be used. Dr. Allaben asked for clarification on how the NTP would use the p values in the evaluation of the data in the NTP Technical Reports. Dr. Portier concluded the discussion by stating that both statistical methods would be used in the future to analyze data reported in the technical reports and after experience with both methods, the most suitable would be chosen for future studies.

IX. Research Program on *Caenorhabditis elegans*

Dr. Portier introduced the topic by saying the project is a collaboration with the Veterans Administration and the NIEHS National Center for Toxicogenomics (NCT). Dr. Jonathan Freedman, NIEHS and Duke University, discussed his preliminary work on the use of *Caenorhabditis elegans* in short-term toxicity tests. He described the life cycle of the non-

parasitic nematode, which consists of 959 somatic cells and lives for 10 days. The nematode has highly differentiated digestive, reproductive, muscular and nervous systems. The cellular and developmental biology of the organisms is well understood and the cell lineage is known for its entire development. The organism is amenable to classic and molecular genetic analysis and its genome has been completely sequenced. Transgenic nematodes containing the β-galactosidase (lacZ) gene and green fluorescent protein (GFP) markers, as well as many knockout organisms have been made. In comparison to a rodent study, which requires 1-2 years, uses over 10,000 animals and costs $2-3M, a comparable *C. elegans* assay requires 3-5 days, takes up to 200,000 animals and costs only hundreds of dollars. He said there are many advantages of using alternative species including the absence of many animal welfare concerns, rich genetic backgrounds, conservation of many mammalian metabolic pathways, rapid assays and lower cost.

He said the project has five aims to: (1) develop toxicology tests and analysis software for measuring the responses, (2) test 200 toxicants, (3) develop transgenic strains using GFP, (4) develop microarrays and (5) adapt methods using robotics. Initially he has been monitoring apical endpoints such as feeding, fecundity, growth rate etc. He uses an instrument to dispense a specific volume of agar, food and live organisms into each well of a 96-well plate. To measure the responses of the organisms, he uses a Complex Object Parametic Analyzer and Sorter (COPAS biosorter) that are analogous to a *C. elegans* fluorescent activated sorter. With this instrument he can distinguish live nematodes from dead ones, sort developmental stages, measure three channels of fluorescence for each nematode, measure growth rates and monitor reporter gene expression.

The first task is to define the parameters for an experiment such as population density of nematodes and food (bacteria) and standardization of testing parameters, etc. He presented an outline of the protocol used for a study of growth and showed data on the effect of cadmium and methyl-n'-nitro-nitrosoguanidine (MNNG) on growth, movement and reproduction. He described nematodes with the "EAT" mutation that is manifest as abnormal pharyngeal pumping action, lethargy and absence of mating behavior. He is making transgenic nematodes linking the metallothionein, glutathione-S-transferase, multidrug resistant and heat shock protein genes to GFP, and plans to make additional transgenic animals linking superoxide dismutase, MAPK kinase, and p38 MAPK kinase genes to GFP. He discussed the development of low throughput studies involving image analysis of specific neurons in a neuronal pathway. He is developing an assay to monitor tail formation, which is dependent on a specific apoptotic pathway for normal development. He will study the effect of toxicants on the development of this anatomical feature, which is related to the normal functioning of a specific pathway. He said his laboratory in collaboration with the microarray consortium funded by NIEHS and the NCT have developed *C. elegans* custom arrays that permit genomic studies. He will use an Agilent Bioanalyzer and microarray bioscanner for these experiments. Future needs include data management software for tracking results from microarray studies and a concerted effort on the criteria for selection and purchase of toxicants for future studies.

Board Discussion

The Board asked whether the genes planned for study are conserved in rodents and humans, whether the compounds selected for study are ready for HTS, and whether a prioritization scheme for chemicals that affect neurodevelopment has been developed. Dr. Freedman replied that according to sequencing by the Institute for Genomic Research (TIGR) 40-60% of genes and a higher percentage of pathways are conserved between nematodes and humans. The program is developing a prioritization scheme for choosing and acquiring neuro-developmental toxicants based on a list supplied by EPA.

Dr. Daston was concerned that only apical endpoints, which are an integration of a variety of mechanisms, are being measured. He said it is harder to extrapolate an apical endpoint in *C. elegans* to humans than the response of a highly conserved gene or cell whose fate is well known. He said assays relying on apical endpoints might produce misleading data because of a lack of concordance of nematode data with rodent and human data. This difference is because the pathway or mechanism affected in a nematode resulting in an apical endpoint may differ from that affected in a rodent or human. He suggested that Dr. Freedman concentrate on assays measuring the response of a particular gene in a known conserved pathway. Dr. Freedman responded that this is the direction the program is taking and he will concentrate on pathways affecting muscular and nerve structure. Dr. Storer concurred with Dr. Daston and said this model is ideal to study toxicants that might affect reproductive and developmental pathways, but the program must be wary of the differences in development of mammals and the nematode, particularly as it pertains to maternal toxicity. Dr. Boekelheide said using naturally susceptible populations or toxic responses to specific mutations would be a relevant approach. Dr. Freedman said he plans to evaluate changes in nerve structure using RNAi technology and will screen genes involved in nerve and muscle structure.

Dr. Portier said the first priority is to evaluate the utility of the model and to take a step-by-step approach. He said the program is at a crossroad; and it needs to decide whether to use transgenic nematodes to screen particular pathways or to knock down the 16,000 genes in the nematode one at a time using RNAi technology. Dr. Ho said RNAi technology is appropriate for this model and it would be an unbiased approach to screen for toxicity. She asked why the Agilent oligo array was chosen over Affymetrix, which allows faster single nucleotide polymorphism (SNP) analysis and is less difficult to interpret than the Agilent array. Dr. Freedman responded that when the relationship was established with the NCT, the Affymetrix array was not well established. Dr. Daston added a word of caution regarding the difficulty of interpreting the data when individual genes or combinations are knocked out. Dr. Ho was excited about the direction the project is taking and suggested that an entire pathway be examined simultaneously.

Dr. Portier thanked the Board for attending the meeting and said that the NTP would report back on the progress of this initiative in the near future. He thanked Dr. Gasiewicz for serving as Chair of the NTP Board and Dr. Boekelheide, who assumed the role of chair at 4:15pm because Dr. Gasiewicz had to leave, and all the NTP presenters. The meeting adjourned at 4:45 p.m.

applicable, the business or professional affiliation of the interested person.

This notice is being published less than 15 days prior to the meeting due to the urgent need to meeting timing limitations imposed by the funding cycle.

Dated: September 21, 2004.

Anna Snouffer,

Deputy Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–21617 Filed 9–24–04; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Mental Health; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Mental Health Special Emphasis Panel Gene-Environment Effects and Epigenesis in Depression.

Date: October 13, 2004.

Time: 9 a.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn Select Bethesda, 8120 Wisconsin Ave., Bethesda, MD 20814.

Contact Person: A. Roger Little, PhD., Scientific Review Administrator, Division of Extramural Activities, National Institute of Mental Health, NIH, Neuroscience Center, 6001 Executive Blvd., Room 6157, MSC 9608, Bethesda, MD 20892–9608, (301) 402–5844, *alittle@mail.nih.gov.*

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.242, Mental Health Research Grants; 93.281, Scientist Development Award, Scientist Development Award for Clinicians, and Research Scientist Award; 93.282, Mental Health National Research Service Awards for Research Training, National Institutes of Health, HHS).

Dated: September 21, 2004.

Anna P. Snouffer,

Acting Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–21616 Filed 9–24–04; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP); Notice of a Meeting of the NTP Board of Scientific Counselors

Pursuant to Public Law 92–463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors on October 26, 2004, in the Rodbell Auditorium, Rall Building at the National Institute of Environmental Health Sciences, 111 T.W. Alexander Drive, Research Triangle Park, NC 27709.

The NTP Board of Scientific Counselors ("the NTP Board") is composed of scientists from the public and private sector and provides primary scientific oversight to the NTP.

Agenda

The meeting being held on October 26, 2004, begins at 8:30 a.m. and is open to the public from 8:30 a.m. to adjournment with attendance limited only by the space available. Persons needing special assistance should contact the NTP Executive Secretary (contact information below) at least seven business days in advance of the meeting. A draft agenda with a tentative schedule is provided below. Primary agenda topics include: (1) NTP initiatives to enhance toxicology, (2) substances nominated to the NTP for study and recommendations of the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC), (3) new approaches for statistical analyses for chronic tests, (4) a proposed process for evaluating chemicals with limited data sets by the Center for the Evaluation of Risks to Human Reproduction, and (5) a research program on *Caenorhabditis elegans.* The NTP Board will also review three concept proposals for the conduct of research through the use of a contract mechanism. These concepts include: (1) The evaluation of chemicals for their potential to modulate immune responses, (2) chemical characterization of substances for testing in high-throughput screening and chronic assays, and (3) application of automated techniques to toxicity testing. Time is allotted during the meeting for the public to present comments to the NTP Board and NTP staff on any agenda topic.

The agenda and background materials on agenda topics, as available, will be posted on the NTP Web site (*http://ntp-server.niehs.nih.gov, see* What's New) or available upon request to the NTP Executive Secretary (contact information below). The NTP is making plans to videocast the meeting through the Internet at *http://www.niehs.nih.gov/external/video.htm.* Following the meeting, summary minutes will be prepared and available through the NTP Web site and upon request to Central Data Management, NIEHS, P.O. Box 12233, MD E1–02, Research Triangle Park, NC 27709; telephone: 919–541–3419, fax: 919–541–3687, and e-mail: *CDM@niehs.nih.gov.*

ICCEC Recommendations for Substances Nominated for Future NTP Studies

Information about substances nominated to the NTP for toxicology and carcinogenicity studies and the ICCEC's recommendations were published in the **Federal Register** on August 20, 2004 (Vol. 69, No. 161, pages 51691–51693). This notice is available on the Web (*http://ntp-server.niehs.nih.gov/htdocs/liason/04JuneICCECFR.html*) along with the list of nominations (*http://ntp-server.niehs.nih.gov/NomPage/2004Noms.html*) and supporting documents for each nomination (*http://ntp-server.niehs.nih.gov/NomPage/BkgrSum04June.html*) or is available by contacting the NTP Executive Secretary (contact information below). This meeting provides an additional opportunity for the public to provide comment on these nominations and study recommendations to the NTP Board and NTP staff. Comments submitted to the NTP in response to the August 20, 2004, **Federal Register** notice are under consideration and do not need to be resubmitted or readdressed.

Public Comment Encouraged

Public input at this meeting is invited and time is set aside for the presentation of public comments on any agenda topic. At least 7 minutes will be allotted to each speaker and, if time permits, may be extended to 10 minutes. Each organization is allowed one time slot per agenda topic. Persons registering to make oral comments are asked to provide their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any). To

facilitate planning for the meeting, persons interested in providing formal oral comments are asked to notify Dr. Barbara Shane, NTP Executive Secretary, NIEHS, P.O. Box 12233, MD A3–01, Research Triangle Park, NC 27709; telephone: 919–541–0530; and e-mail: *shane@niehs.nih.gov* by October 18, 2004. Persons may also submit written comments *in lieu* of making oral comments. Written comments should be sent to the NTP Executive Secretary and must be received by October 18, 2004, to enable review by the NTP Board and NTP staff prior to the meeting.

Persons submitting written comments should include their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any) with the document. Individuals will also be able to register to give oral public comments on-site at the meeting. However, if registering on-site and reading from written text, please bring 30 copies of the statement for distribution to the NTP Board and NTP staff and to supplement the record.

Registration

The NTP Board meeting is open to the public. Due to changes in security policies at the NIEHS, individuals who plan to attend are asked to pre-register with the NTP Executive Secretary (contact information above). The names of those registered will be given to the NIEHS Security Office in order to gain access to the campus. Persons attending who have not pre-registered may be asked to provide pertinent information about the meeting such as the title or host of the meeting before gaining access to the campus. All visitors (whether or not you are pre-registered) will need to be prepared to show 2 forms of identification (ID), for example, a driver's license and one other form of ID, such as company ID, government ID, or university ID.

NTP Board of Scientific Counselors

The NTP Board 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 Board 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. The NTP strives for equitable geographic distribution and minority and female representation on the NTP Board. Its members are invited to serve overlapping terms of up to four years and meetings are held once or twice annually for the NTP Board and its two standing subcommittees (the Report on Carcinogens Subcommittee and the Technical Reports Review Subcommittee).

Dated: September 15, 2004.

Samuel Wilson,

Deputy Director, National Toxicology Program.

Preliminary Agenda

National Toxicology Program (NTP) Board of Scientific Counselors

October 26, 2004

National Institute of Environmental Health Sciences, Rodbell Auditorium, Rall Building, 111 T.W. Alexander Drive, Research Triangle Park, NC.

8:30 a.m. Welcome and Opening Comments.
NTP Update.
NTP Initiatives to Enhance Toxicology.
Concept Review.
- Evaluation of Chemicals for Their Potential to Modulate Immune Responses.
- Chemical Characterization of Substances for Testing in NTP Studies.
- Application of Automated Techniques to Toxicity Testing.

12 p.m. Lunch.

12:45 p.m. NTP Testing Program.
- Study Nominations.
- New Approaches to Statistical Analyses for 2-year Toxicology and Carcinogenicity Studies.
- Center for the Evaluation of Risks to Human Reproduction—Proposed Process for Evaluating Chemicals with Limited Data Sets.
- Research Program on *Caenorhabditis elegans*.

4:45 p.m. Adjourn.

[FR Doc. 04–21618 Filed 9–24–04; 8:45 am]
BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Center for Substance Abuse Prevention; Notice

Pursuant to Pub. L. 92–463, notice is given of the meeting of the Substance Abuse and Mental Health Services Administration (SAMHSA) Drug Testing Advisory Board (DTAB) that was held on September 14 and 15, 2004, at the Residence Inn by Marriott, 7335 Wisconsin Avenue, Bethesda, Maryland 20814.

A summary of the meeting is as follows. The Board met in an open session on September 14 from 8:30 a.m. to 11:15 a.m. The open session included a Department of Health and Human Services drug testing program update, a presentation on the comments submitted on the proposed revisions to the "Mandatory Guidelines for Federal Workplace Drug Testing" published in the **Federal Register** on April 13, 2004 (69 FR 19673–19732), and a Department of Transportation drug testing program update.

The Board met in closed sessions on September 14 from 11:15 a.m. to 4:30 p.m. and on September 15 from 8:30 a.m. to noon to review and discuss the public comments submitted regarding the Revised Mandatory Guidelines for Federal Workplace Drug Testing Programs (69 FR 19644, April 13, 2004) and the Notice of Proposed Revisions to the Mandatory Guidelines for Federal Workplace Drug Testing Program (69 FR 19673, April 13, 2004). This meeting was conducted in closed sessions since discussing preliminary information on the Guidelines in open session would significantly frustrate the Department's ability to develop the Final Notice of Revisions to the Mandatory Guidelines for Federal Workplace Drug Testing Programs, which must include the policies and procedures that will assure accurate and reliable specimen validity testing as well as drug testing using alternative specimens and when using on-site drug tests.

A roster of the board members may be obtained from: Mrs. Giselle Hersh, Division of Workplace Programs, 1 Choke Cherry Road, Room 2–1035, Rockville, MD 20857, 240–276–2600 (voice). To ensure that all interested parties receive information presented at the DTAB meeting, the transcript of the open session will be available on the following Web site *http://workplace.samhsa.gov* as soon as possible after the meeting.

Dated: September 20, 2004.

Toian Vaughn, Committee Management Officer, Substance Abuse and Mental Health Services Administration.

[FR Doc. 04–21568 Filed 9–24–04; 8:45 am]
BILLING CODE 4162–20–P

Attachment 2

Tentative Agenda
NTP Board of Scientific Counselors Meeting

Rodbell Auditorium, Rall Building
National Institute of Environmental Health Sciences
Research Triangle Park, NC
October 26, 2004

8:30 AM	Introductions and Welcome	Chair, Dr. Tom Gasiewicz, University of Rochester
8:40	Recognition of Retiring Members	Dr. Christopher Portier, NIEHS
8:45	NTP/NIEHS Update	Dr. Christopher Portier, NIEHS
9:00	**NTP Initiatives to Enhance Toxicology** • Public Comments o Board Discussion	Dr. Christopher Portier, NIEHS
10:00	**BREAK**	
10:30	**Concept review** Evaluation of the Potential for Chemicals, Biologics and Therapeutics to Modulate Immune Responses • Public Comments o Board Discussion	Dr. Dori Germolec, NIEHS
11:00	**Concept review** Analytical Chemistry for the Environmental Toxicology Program • Public Comments o Board Discussion	Dr. Cynthia Smith, NIEHS
11:30	**Concept review** Application of Automated Techniques to Toxicity Testing • Public Comments o Board Discussion	Dr. William Caspary, NIEHS
12:00	**LUNCH**	

12:45	**NTP Study Nominations and ICCEC Recommendations** • Public Comments ○ Board Discussion	Dr. Scott Masten, NIEHS
2:30	**BREAK**	
2:50	**Research Highlights** Research Program on *Caenorhabditis elegans* ○ Board Discussion	Dr. Jonathan Freedman, Duke University/NIEHS
3:30	**NTP Testing Program** New Approaches to Statistical Analyses for 2- year Bioassays • Public Comments ○ Board Discussion	Dr. Shyamal Peddada, NIEHS
4:00	**Center for the Evaluation of Risks to Human Reproduction** Proposed Process for Evaluating Chemicals with Limited Data Sets • Public Comments ○ Board Discussion	Dr. Michael Shelby, NIEHS
4:45	**ADJOURN**	

NATIONAL TOXICOLOGY PROGRAM
Board of Scientific Counselors Meeting
October 26, 2004

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