Summary Minutes
NTP Board of Scientific Counselors
December 9-10, 2014

Table of Contents

I. Frequently Used Abbreviations and Acronyms

AI	artificial intelligence
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BDCA	bromodichloroacetic acid
BSC	Board of Scientific Counselors
DC	District of Columbia
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
ER	estrogen receptor
FDA	U.S. Food and Drug Administration
HHS	Health and Human Services
HTS	high throughput screening
ILS	Integrated Laboratory Services, Inc.
MCHM	4-methylcyclohexanemethanol
Mn	manganese
NAS	National Academy of Sciences
NICEATM	NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OLRP	Office of Liaison, Policy, and Review
ONS	Office of Nomination and Selection
ORoC	Office of the Report on Carcinogens
PD	Parkinson's disease
PFC	perfluorinated chemicals
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
RoC	Report on Carcinogens
SAR	structure-activity relationship
SSS	Social and Scientific Systems, Inc.
TCE	trichloroethylene

II. Attendees

Members in Attendance:

Robert Chapin, Pfizer
George Corcoran, Wayne State University
David Dorman, North Carolina State University
Mary Beth Genter, University of Cincinnati
Jack Harkema, Michigan State University
Dale Hattis, Clark University
Steven Markowitz, City University of New York

Lisa Peterson, University of Minnesota (chair)
Sonya Sobrian, Howard University
Iris Udasin, University of Medicine and Dentistry of New Jersey

Member not in Attendance:
Milton Brown, Georgetown University Medical Center

Other Federal Agency Staff:
Cheryl Estill, National Institute for Occupational Safety and Health (NIOSH), BSC Liaison
Paul Howard, U.S. Food and Drug Administration (FDA), BSC Liaison

National Institute of Environmental Health Sciences (NIEHS) Staff:

Scott Auerbach	Stephanie Holmgren	Stephanie Smith-Roe
Linda Birnbaum	Kembra Howdeshell	Diane Spencer
Chad Blystone	Jui-Hua Hsieh	Vicki Sutherland
Abee Boyles	Ruth Lunn	Kristina Thayer
John Bucher	Robin Mackar	Raymond Tice
Warren Casey	Scott Masten	Velvet Torain
Natasha Catlin	Elizabeth Maull	Molly Vallant
Helen Cunny	Barry McIntyre	Suramya Waidyanatha
Jennifer Fostel	Esra Mutlu	Nigel Walker
Paul Foster	Richard Paules	Lori White
Rachel Frawley	Cynthia Rider	Kristine Witt
Dori Germolec	Andrew Rooney	Mary Wolfe
Georgia Hinkley	Kristen Ryan	Yun Xie

Public:
Philip Agee, Attain
Dave Allen, Integrated Laboratory Services, Inc. (ILS)
Julie Bishop, ILS
Neepa Chokski, ILS
Ella Darden, ILS
Michael Easterling, Social and Scientific Systems, Inc. (SSS)
Sanford Garner, ILS
Katy Goyak, ExxonMobil Biomedical Sciences
Charles Hebert, Southern Research
Ernie Hood, Bridport Services
Kyathanahalli Janardhan, ILS
Michael Megginson, Northrop Grumman Health Division
Steven Morefield, ILS
Arun Pandini, Experimental Pathology Laboratories, Inc.
Pam Schwingl, ILS
Fikri Yucel, SSS

Webcast Participants:
Kenneth Bogdan, New York State Department of Health
Brad Collins, NIEHS
Katherine Groff, People for the Ethical Treatment of Animals
Alison Harrill, University of Arkansas, Medical Sciences
Cynthia Hines, NIOSH

Joseph Hughes, NIEHS
Mingyu Qiao, Auburn University
Les Recio, ILS
Pat Rizzuto, Bloomberg BNA, Inc.
Veronica Robinson, NIEHS
Jonathan Slone, NIOSH contractor
Cathy Sprankle, ILS
Chris Forgues Schlenker, Morgan, Lewis and Brokius

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met December 9 - 10, 2014 in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. The first day of the meeting (December 9) had sessions closed to the public in accordance with provisions set forth in section 552(c)(6), Title 5 U.S.C., as amended, to review Dr. Paul Foster and the NTP Toxicology Branch. Dr. Lisa Peterson served as chair and opened the general meeting on December 10 at 9:00 AM. She welcomed everyone and asked BSC members and other attendees to introduce themselves. Dr. Lori White, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Report of the NIEHS/NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, updated the BSC on developments at NTP and NIEHS since the last BSC meeting in June 2014. She reported that the FY 2015 House budget indicated a $2 million increase in the NIEHS budget over the FY 2014 appropriation. She noted that, thanks to sequestration, the totals are still below FY 2012 levels.

In her legislative report, she described some of the recent Congressional hearings and briefings involving NIEHS and NTP on topics including autism and the Freedom Industries chemical spill in West Virginia. She also discussed several relevant pieces of legislation impacting environmental health under consideration in Congress, all of which are unlikely to pass in the near future. These include the *Secret Science Reform Act*, *Ban Poisonous Additives Act*, the *Research and Development Efficiency Act*, *Accelerating Biomedical Research Act*, and *Autism Collaboration, Accountability, Research, Education, and Support Act*. In science news, she highlighted two new publications by NTP scientists and collaborators, one on genomic models of short-term exposures, the other reporting results associated with the diversity-outbred mouse.

Reporting on recent meetings and events of interest, Dr. Birnbaum highlighted the *Symposium on Assessing Exposures and Health Effects Related to Indoor Biomass Fuel Burning*, which was held at NIEHS in August 2014. She also described several other significant meetings and events held since the last BSC meeting.

She noted that NIEHS would be hiring a Science Information Officer, a new position dedicated to supporting the scientific computing needs of all NIEHS staff.

She described new sections recently added to the *NTP Nonneoplastic Lesion Atlas*, and recognized several NIEHS and NTP individuals and teams who received NIH Director's Awards.

V. Contract Concepts: Introduction

NIEHS Contracting Officer Velvet Torain briefed the BSC on contract concepts and the BSC's charge with regard to the concepts being presented.

VI. Contract Concepts: Scientific Information Management and Literature-Based Evaluations for NTP

A. Presentation

Dr. Mary Wolfe, Office of Liaison, Policy, and Review (OLPR), briefed the BSC on a contract concept titled *Scientific Information Management and Literature-Based Evaluations for NTP*.

Scientific information management involves collection, organization, and control of the structure, processing, and delivery of scientific information. Literature-based evaluation includes analysis and interpretation of published literature, with elements of systematic review and evidence integration. Dr. Wolfe provided background information about both aspects of the contract, which would cover services for the Office of Health Assessment and Translation (OHAT), the Office of the Report on Carcinogens (ORoC), the Office of Nomination and Selection (ONS), and OLPR.

Previous and current contract support necessitated separate contracts to obtain scientific, technical, and administrative support for literature-based activities. The proposed support centralizes contract activity to address the changing landscape of methodologies and tools in environmental health sciences. The specific requirements include environmental health literature searching and management; literature screening; scientific data extraction, management, and visualization; study quality assessment, data interpretation, and scientific evidence integration; document preparation and publication; logistical management for meetings and events; and provision of scientific and technical consultants. The centralized contract would provide a variety of benefits including greater responsiveness to public health needs.

Dr. Wolfe said the NTP seeks comment and approval from the BSC for the contract concept considering: (1) the overall value and scientific relevance as well as fulfilling the program's goal of protecting public health and (2) whether a contract is an appropriate mechanism for support of these types of activities.

B. BSC Discussion

Dr. Steven Markowitz asked whether NTP currently uses contracts for some of the specified functions. Dr. Wolfe said ORoC currently has a contract for support, and the contract is nearing

its end. ONS has had contract support in the past, but does not have one in place currently. OHAT has some contract support on an *ad hoc* basis, and OLPR does not have contract support at present. She said it makes sense to bring the four groups together under a shared contract. Dr. Markowitz asked how the quality of the work of the contractors has been evaluated and how the issue of conflicts of interest among contractors had been dealt with in the past. Dr. Wolfe said quality evaluations had been done by each of the project officers, who work with the contracting officer technical representatives assessing deliverables, statements of work, operating procedures, and other parameters to ensure that the completed work has been appropriate to the contract's requirements. Conflict-of-interest provisions have been built into the current contracts, with screening on individual and organizational levels. She added that the appropriate firewalls are in place in the case of contractors working for other entities.

Dr. Jack Harkema asked whether there might more interchange with other agencies such as the Environmental Protection Agency (EPA) that do similar evaluations. Dr. Wolfe said currently NTP uses technical advisors from other agencies to assist with evaluations. Also, databases are shared with other agencies, and are eventually made available on the Internet; there is an effort to share more, especially when topics of mutual interest are involved. Dr. Harkema asked if there are guidelines so that all agencies are following the same rigorous review procedures. Dr. John Bucher noted that the application of systematic review to environmental health sciences is still fairly new, with NTP leading the effort. Work is underway to make the procedures as similar across agencies as possible. Dr. Wolfe said, in developing the process, there has been much interaction with agency partners to allow sharing of resources and practices.

Dr. David Dorman said the proposal mixes information sciences with meeting logistics, and that he was unsure about the logic of doing so at a time of elevating the role of information sciences and systematic review, potentially signaling that they are perceived almost as administrative functions. Dr. Wolfe said meeting logistics would be a very minor part of the contract; there would be a real advantage having the same group providing the administrative support for bringing in the technical experts. The main focus of the contract is the scientific information management and development of the evaluations, although from an operational standpoint, it makes sense to add the minor piece to the larger contract.

Dr. Iris Udasin asked whether the systematic reviews would be dynamic, taking into account new information after the evaluations are completed. Dr. Wolfe said NTP could certainly revisit reports if new information becomes available suggesting other areas of health concern, or potentially re-review of a substance to change, for example, an RoC listing. However, new information would not be added arbitrarily, since it had not been used to support the initial decision. Dr. Udasin asked if someone would be monitoring the literature, for example, in the case of a major publication or event, since it would be part of their expertise to do so. Dr. Wolfe said that would happen.

Dr. George Corcoran, first BSC discussant, said the logic of a "blanket purchase order" type of contract has much attraction for an organization of this complexity. He said it seems an extremely efficient process but expressed concern that with increased flexibility there could be

less granularity in the actual terms of the contract. Dr. Wolfe said, in terms of contract management, with several groups working under one contract, it would be very important to have a project manager with much experience in managing multiple deadlines and excellent communications capabilities. Dr. Corcoran was concerned that deliverable outcomes would be moving targets, making it difficult to assess contractor performance. Dr. Bucher said procedures for development of the various documents are very well delineated, and NTP staff would have enough experience to know when things are not going well. He did not have concerns about achieving the products expected from the contract. Dr. Corcoran asked about the length of the contract. Ms. Torain said the proposed contract could run up to 10 years. Dr. Bucher noted that generally such contracts are structured so there are options for continued activity upon subsequent contract years, allowing for termination in the event of poor performance. Dr. Corcoran noted that NTP does not report to Congress the number of projects completed annually and considered that an important metric. He asked if there were any elements of the contract that would support a more rapid time to completion of work, such as incentives for earlier delivery of deliverables. Ms. Torain said there are contract mechanisms that allow for those types of incentives, depending on the type of work being done. The other incentive to the contractor is the past performance evaluation, which goes into a database available to other government agencies. Dr. Wolfe noted that events would be staggered under the contract, with different types of deliverables at different times. Dr. Corcoran asked whether a plan was in place to utilize NTP resources freed up by having been outsourced under the contract. Dr. Bucher said the hope is that the additional contract support will allow such activities to be completed more quickly.

Dr. Udasin, second BSC discussant, said her main concern was with the flexibility and dynamics of the contract. She felt those issues had been addressed in the discussion.

Dr. Corcoran moved to approve the proposed contract mechanism and Dr. Udasin seconded the motion. The BSC voted unanimously (9 yes, 0 no, 0 abstentions) to approve using this contract mechanism for support of these activities.

VII. Contract Concepts: Support for Toxicological Data for the NTP

A. Presentation

Dr. Jennifer Fostel, Program Operations Branch, briefed the BSC on the contract concept titled *Support for Toxicological Data for the NTP*. The objectives of the contract are to ensure that NTP toxicological endpoint data, study meta-data, and summary/conclusion data are housed efficiently and completely in the NTP data system. Thus, NTP data from toxicological studies should be available in an accurate, effective, and biologically meaningful context. This will support decision-making by NTP scientists, other government agencies, and the public at large about the hazards associated with exposure to environmental toxicants.

Dr. Fostel described in detail the data workflow associated with the concept, including use of licensed Provantis® software, a laboratory information management system, which will help integrate data production and usage. A goal of the contract is to have standardized lexicons,

measurements, work schedule activities, and statistical methods. Current challenges include increasing diversity of toxicological data, management and integration of numerous data streams, increasing complexity of NTP study designs, and the need for scientists with expertise in toxicology and experience in toxicological testing. The new contract should provide for housing of NTP data efficiently and completely in the NTP data system; support the use of NTP's version of Provantis® for data capture and data reporting; support training and publication; maintain, enhance, and extend current functions of the NTP data system; and make NTP data available in an integrated, biologically-meaningful context to enhance decision-making

Dr. Fostel said the NTP seeks comment and approval from the BSC for the contract concept considering: (1) the overall value and scientific relevance as well as fulfilling the program's goal of protecting public health and (2) whether a contract is an appropriate mechanism for support of these types of activities.

B. BSC Discussion

Dr. Harkema asked how digitized histopathology images would be handled under the new system. Dr. Fostel said the described data system would be appropriate for managing histopathology images. She said the advisory board for the data system had just met and discussed histopathology image management. There is a plan to work with the Cellular and Molecular Pathology Branch to incorporate the digitized images as part of the proposed system. The contract will be written to allow development of an individual project for electronic image analysis using high-content screening.

Dr. Dale Hattis noted that NTP is increasingly getting results from outbred animal strains, with the possibility of meaningful interindividual variability information. He asked whether NTP would be storing information on an individual animal basis. Dr. Fostel said NTP would go to the lowest possible unit, including individual animal data if it is available.

Dr. Mary Beth Genter, first BSC discussant, said she appreciated Dr. Fostel's clear summary of the concept. She asked if there is currently a gatekeeper making sure that management of the data from the various sources is happening properly, or if that is part of the new contract. Dr. Fostel said she is the contracting officer's technical representative for the current contract, and it would be good for some of the expertise she provides to be covered in the new contract. Dr. Genter noted that one of the goals is to have all data on the NTP Website, and asked what the backup system for that would be. Dr. Fostel said the Provantis® database is currently in the process of being backed up and moved to NTP, allowing querying of the database for completed studies, formatting, and streamlining the data for NTP. Dr. Genter asked about the process for entering reproductive toxicity and other types of data into the system. Dr. Fostel said there is no systematic approach for entering reproductive toxicity data, so the data were previously entered manually. Provantis® supports the entry of reproductive toxicity and toxicokinetic data, which is a reason it was chosen as the NTP data system.

Dr. Peterson, second BSC discussant, said she could see real value in having everything centralized and was very supportive of the concept. She asked if there are always multiple

scientists reviewing the entered data. Dr. Fostel said the contract includes multiple steps for quality assurance.

Dr. Robert Chapin noted that NTP is not the only organization dealing with issues of data management. He described the challenge at Pfizer, where there has been much attention to the advent of artificial intelligence (AI) and the next generation of searching tools. He said there might be opportunities to leverage interest in AI for NTP with activities underway at other NIH institutes. Dr. Fostel said work is underway to create an NTP ontology to allow semantic reasoning over the data. Currently, the effort is to get all of the data into an integrated format, so the interest is in human intelligence and supporting that first. But AI would be within the scope of this contract as technologies develop, she added. Dr. Bucher asked Dr. Chapin if he thinks that AI might allow much less effort to be expended working to standardize data formatting, with AI searching much more diverse types of information without the need for standardization. Dr. Chapin said that ultimately that may be true, but it is unclear when it might occur.

Dr. Hattis noted that the trend appears to be going beyond analyses of data sets to analyses of databases. Dr. Fostel agreed that summary data across platforms is a goal.

Dr. Genter moved to approve the proposed contract mechanism and Dr. Chapin seconded the motion. The BSC voted unanimously (9 yes, 0 no, 0 abstentions) to approve using this contract mechanism for support of these activities.

VIII. Assessing the Biological Relevance of In Vitro Data: A Case Study Using Estrogen Pathway Signaling

A. Presentation

Dr. Warren Casey, NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods (NICEATM) Director, presented a case study illustrating how the high throughput screening (HTS) data currently being generated in government-sponsored research programs such as Tox21 and ToxCast can be handled. He noted that it is a critical time to establish how HTS data can be used for regulatory purposes, screening, and prioritization. He described validation as a process by which the reliability and relevance of a test method are established for a specific purpose.

Dr. Casey said the estrogen receptor (ER) agonist bioactivity project was conducted by NICEATM in collaboration with EPA's Office of Science Coordination and Policy, which is responsible for the Endocrine Disruptor Screening Program, and the National Center for Computational Toxicology, which oversees EPA's ToxCast HTS Program. It was designed to evaluate the performance of a mathematical model of HTS data from 16 *in vitro* assays that measure ER-mediated bioactivity. It focused on establishing the reliability and biological relevance of the approach as measured against outcomes in the rodent uterotrophic assay, an animal model validated by the EPA and the Organisation for Economic Co-operation and Development (OECD) for assessing ER-mediated bioactivity. The evaluation necessitated the development of a database of high-quality uterotrophic test results against which the model

output could be compared. A comprehensive literature search was performed, which ultimately yielded 442 uterotrophic bioassays in 98 chemicals that were considered "guideline-like."

Ultimately, the ER agonist area under the curve (AUC) model, which was developed using HTS data, demonstrated excellent performance against *in vivo* (uterotrophic) reference chemicals (95% accuracy, 97% sensitivity, 92% specificity). This indicates that the ToxCast HTS data may provide a rapid and effective resource for identifying substances with potential ER activity.

B. BSC Discussion

Dr. Hattis noted that AUC was used in a non-standard way and asked Dr. Casey to provide more details on how it was used in this context. Dr. Casey said the AUC was an interval of a composite curve generated using all of the ToxCast data. He said it would help to think of it as the area of the averaged response curves across all 16 assays. The two axes, he noted, are response relative to estradiol and dose.

Dr. Dorman asked if there was any attempt to assess EC_{50} values, as opposed to AUC. Dr. Casey said determination of EC_{50} values were calculated for each chemical in each of the 16 methods, but that information was not used in calculating the AUC values.

Dr. Hattis said he would prefer a log/log comparison of predicted versus observed potency. He said the comparison used addresses lowest effect level, which is subject to statistical noise. Dr. Casey asked what Dr. Hattis would propose as a better approach. Dr. Hattis replied that the non-linear aspect of the study was troubling; he would prefer a measure of potency such as the dose that causes half of the maximum effect level. He also would look for a quantification providing an indication of potency beyond a plus/minus designation, because that is what matters for risk. Dr. Casey noted that the AUC is actually a log ratio.

IX. Office of Health Assessment and Translation (OHAT)

A. Update on OHAT

Dr. Kristina Thayer, OHAT, provided the BSC with an update. She described the types of functions performed by OHAT, including literature-based evaluations, methods development, and research. She reviewed the OHAT evaluation process, which ultimately results in the publication of a final OHAT monograph. She noted that in the next presentation Dr. Rooney would outline a draft concept, which is an early step in the evaluation process.

Dr. Thayer said an OHAT publication is expected in January 2015 titled *Handbook for Conducting a Literature-Based Health Assessment Using the NTP OHAT Approach for Systematic Review and Evidence Integration.* An expert panel meeting will be held on May 11-12, 2015, to identify research needs for assessing safe use of high intakes of folic acid. Other activities include developing monographs for previously presented concepts on pregnancy outcomes associated with traffic-related air pollution and adverse health effects associated with occupational exposure to cancer chemotherapy agents.

Dr. Thayer reviewed a list of topics for presentation to the BSC at its June 2015 meeting.

B. Concept: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

Dr. Andrew Rooney, OHAT, presented the NTP evaluation draft concept titled *Immunotoxicity Associated with Exposure to PFOA or PFOS*. He said both PFOA and PFOS are compounds used extensively in the last 50 years in commercial and industrial applications, such as food packaging and water-resistant coatings. They are extremely persistent and widely distributed in the environment, although they are no longer manufactured in the United States. He presented information from previous human studies indicating PFOA- and PFOS-associated functional immune changes, citing recent reports of PFOA-contaminated public drinking water and general population exposures to PFOA and PFOS, as well as data from animal studies and mechanistic studies.

Dr. Rooney described the context in which the evaluation is taking place. He said the perfluorinated chemicals (PFCs) as a class are under toxicological testing by NTP, but immunotoxicity testing of PFOA and PFOS is not taking place because there are a number of published studies. There is interest in PFCs from federal partners such as the Agency for Toxic Substances and Disease Registry (ATSDR) and EPA. He noted that OHAT has experience in the area already; over the past two years case studies involving these chemicals were developed to test the OHAT framework for systematic review and evidence integration. NTP has received multiple requests to develop hazard identification conclusions for PFOA- and PFOS-associated immunotoxicity.

He related the three key issues and scientific questions involved in the concept, as well as the proposed approaches for addressing each one, with the overall objective being to develop hazard identification conclusions as to whether PFOA or PFOS exposures are associated with immunotoxicity or immune-related health effects. The evaluation will be accomplished through use of the OHAT framework for systematic review and evidence integration.

The literature-based evaluation is anticipated to reach hazard identification conclusions for PFOA- and PFOS-associated immunotoxicity and will leverage the previous case study work. Potential next steps will involve possible use of the PFOA and PFOS data to explore immune- and inflammation-related endpoints in Tox21 data, and consideration of methods for using the PFOA and PFOS data along with mechanistic or *in vitro* data on other PFCs to evaluate the potential immunotoxicity of data-poor chemicals.

C. BSC Discussion

Dr. Dorman noted that the plan is to develop separate hazard identification conclusions for PFOA and PFOS, although the selection criteria include instances of exposures to both compounds. He questioned how that would be handled. Dr. Rooney said there are studies with exposures to both, but many include analyses to address either the differential effects or the potential for one compound driving the effect. In other cases there would not be that type of analysis, so there would be no ability to discriminate whether one or the other compound drove the effects observed. He said, in some cases, the compounds act in opposite directions, particularly with inflammatory endpoints, making it easier to tease the data apart.

Dr. Dorman said the ToxCast data had not been specifically identified as another stream for mechanistic data, and wondered whether those data would also be included. Dr. Rooney said the ToxCast data are being actively pursued; however, at this point they are not retrieved within the literature search. He said those data mostly include inflammatory effects, and thus are not directly relevant to the immune effects data being sought. Dr. Dorman said intent for use of *in vitro* data was still confusing, and asked if it were a third hazard identification data stream that would be integrated while primarily relying on human and animal data. Dr. Rooney said *in vitro* data would be used, and biological plausibility would determine whether to potentially either upgrade or downgrade data streams.

Dr. Harkema asked whether the key questions (evaluating confidence in the human and animal studies, and assessing the biological plausibility of the mechanistic evidence) could be expressed as hypotheses to ensure that they would be appropriately assessed in the evaluation. Dr. Rooney further explained the three key scientific issues and the three key questions incorporated in the concept and said it was important not to prejudge the conclusions.

Dr. Dorman, first BSC discussant, felt that the proposed project is a very logical extension to the work that OHAT has already done with these chemicals, and fits very well within the NTP's stated goals and the objectives of OHAT to do systematic reviews. He questioned whether the work that had already been done as a scoping exercise could lead to more focused questions about immunotoxicity, and wondered why the overarching issue of immunotoxicity had been chosen. He suggested more discussion about analytical approaches to be employed, especially where this review could be used as a model. He felt the overall public health significance was moderate, but when put in the context of the need for OHAT to take projects to completion, he would rate it as fairly high in significance.

Dr. Harkema, second BSC discussant, said he originally viewed the project from a public health standpoint, with a moderate significance rating. The presentation gave him an increased level of enthusiasm and he encouraged getting EPA's input on the project.

Dr. Markowitz, third BSC discussant, said he matched the enthusiasm levels of Drs. Dorman and Harkema. He noted that osteoarthritis, which was discussed in the project document, is not generally considered an immunologic disease. He was skeptical that there were enough human studies to arrive at a hazard conclusion. He asked whether any data from other countries regarding production of the materials were available, and if so suggested they be included.

Dr. Harkema asked whether individual studies in the OHAT approach were looked at in terms of what was not done, or what the authors would identify as research needs.

Dr. Rooney agreed with Dr. Dorman that there could have been more refinement in the approach to narrow the topic on a particular immune outcome such as the antibody response. However, the NTP wanted to address the full range of potential immune effects and was confident that the number of studies available across all immune endpoints was reasonable, given knowledge of the existing database. He noted the consistency of the antibody effect, which was exciting to see. He said the intention is to not restrict the evaluation to just one health effect, but to evaluate any immune effect. He was skeptical about being able to

accurately predict most *in vivo* immune-related health effects from *in vitro* assays alone, particularly because there are very little immune-related mechanistic data on PFOA or PFOS. Dr. Rooney said further work identifying data sets with immune effects *in vivo* as well as mechanistic and *in vitro* studies may allow some of those predictions to take place. He had more confidence in the ability to examine the inflammatory endpoints because there are a number of inflammatory endpoints in the ToxCast datasets, and these data could be examined as a potential next step after the evaluation. Regarding Dr. Harkema's comment on research needs, he said they would follow where the data allowed them to make conclusions. Regarding Dr. Markowitz's comment on osteoarthritis, he said OHAT had struggled as to whether or not to include it. He said inflammation is a widespread mechanism across endpoints, and in this case it was difficult to see where inflammation stops and immunotoxicity begins. OHAT chose to keep inflammation as an endpoint because many of the immune assays are also providing inflammatory outcomes. This was a case of following where the data were leading. Regarding the sufficiency of human data, Dr. Rooney said there are three studies, which were adequate in the initial risk-of-bias evaluation that could constitute a solid database. Dr. Thayer added that human data are not required for hazard identification.

Dr. Peterson summarized the BSC's comments and said the enthusiasm for going forward with the project was strong.

X. Report of the NTP Associate Director

A. Presentation

Dr. Bucher, NTP Associate Director, updated the BSC on NTP activities since the last BSC meeting, concentrating on staff changes and the Division of the NTP (DNTP) review.

New hires included Dr. Esra Mutlu, a chemist in the Program Operations Branch; Andrew Shapiro, a data scientist in the Program Operations Branch; and Dr. Nisha Sipes, a computational toxicologist who joined the Biomolecular Screening Branch.

The DNTP review was conducted between February and July 2014. The panel's report was approved July 14 and sent to the NIH Deputy Director for Intramural Research on July 28. Drs. Birnbaum and Chapin co-chaired the committee, with Dr. Bucher serving as Executive Secretary. Dr. Bucher described several key points that constituted the essence of the report: (1) the recognition of NTP's unique mission, structure, and mode of operation; (2) the directions taken and accomplishments in-line with 2004 NTP Roadmap and NTP's recognized leadership in evolution of toxicology; (3) the recommendation of greater efforts to integrate data-intensive mechanistic and adverse outcome pathway information with findings from traditional models; (4) the recommendation of enhanced effort in epigenetics, exploration of the utility of stem cells, organotypic models, organs-on-a-chip, and *in silico* modeling approaches; and (5) the rrecommendation of continued efforts to exert a global influence on advancing the understanding of the human health significance of toxicological studies of all types

Dr. Bucher summarized the barriers that the panel had identified, which include (1) insufficient funding, (2) insufficient training of staff to carry out increasingly complicated science, (3)

inflexible hiring mechanisms, (4) a principal investigator-driven culture that fails to recognize and reward team science, and (5) the need to accommodate "big data." He listed some of the areas for future activity that the panel had suggested including systems biology, tissue-on-a-chip, preclinical safety assessments on orphan drugs for environmental diseases, mechanisms of cancer causation, 21st century exposure science, mixtures research, physical agent studies, public health emergencies, and climate change and disease.

B. BSC Discussion

Dr. Hattis suggested that it also would be important to develop biomarkers to assess long-term, cumulative, chronic losses associated with disease states, such as loss of neurons in Parkinson's disease, as well as measures of current progress in the cumulative process. Dr. Bucher said those areas are recognized as being deficiencies, and that they are being viewed in terms of similarity profiling with acute effects of agents that are known to cause those types of outcomes.

XI. NTP Testing Program

A. Update on Nominations

Dr. Scott Masten, ONS, briefed the BSC on the status of several recent nominations, along with an update on some other issues the office is working on.

He provided background information about the NTP studies, the sources of nominations for research and testing, and the criteria for selection, along with the process employed by the NTP to respond to nominations. Recent nominations include the flame retardants Firemaster 550 and decabromodiphenylethane; hydrochlorothiazide, a widely prescribed diuretic to treat hypertension; and the January 2014 West Virginia chemical spill. Dr. Masten recounted status information for each nomination. He also described new work being considered for arsenic, polychlorinated biphenyls, and microcystins.

Regarding the availability of microcystins for research, Dr. Dorman suggested that NTP contact people with expertise in bioreactors to see whether it might be possible to engineer cyanobacteria strains that produce large amounts of microcystins. Dr. Masten said it was a good suggestion, although the fact that some cyanobacterial toxins are actually considered to be threat agents is a potential hurdle.

B. West Virginia Chemical Spill

Dr. Scott Auerbach, Bimolecular Screening Branch, briefed the BSC on the background, current status, and future timeline for NTP activities related to the chemical spill that occurred in West Virginia in January 2014, when 10,000 gallons of a liquid used to wash coal and remove impurities were spilled from a leaking tank into the West Virginia Elk River.

In January 2014, the NTP performed a preliminary SAR (structure-activity relationship) analysis of the chemicals identified in the spill. In July 2014, the spilled chemicals were nominated by Center for Disease Control and Prevention/ATSDR. A study plan was formulated, addressing

three issues: (1) providing additional data to support the drinking water advisory level for 4-methylcyclohexanemethanol (MCHM), one of the main chemicals involved; (2) identifying potential hazards following acute exposure (long-term and short-term effects); and (3) generating information in a one-year time frame.

After covering the background information, Dr. Auerbach provided details and results to date from the different studies/approaches NTP is using to address the issues of concern related to chemicals spilled into the Elk River.

Dr. Auerbach described SAR analysis, which uses a chemical structure to forecast its toxicological properties. The results of the MCHM SAR studies showed that four positive model calls were deemed of moderate reliability and that information was taken under consideration when formulating the longer-term project plan.

Next, results from the Tox21 HTS of six chemicals (4 spilled, 2 Tox21 structural analogs) were described. None of the chemicals was active in any of the assays conducted; however, analytical chemistry evaluation of the library is ongoing.

Dr. Auerbach said nematode toxicity studies, which evaluate toxicity at different life stages, are nearing completion; however, results are not yet available. Zebrafish developmental toxicity studies are set to begin soon. They will more broadly and efficiently characterize the potential developmental effects of MCHM and propylene glycol phenyl ether classes of compounds.

Both *in vitro* and *in vivo* genotoxicity studies are included in the set of studies to determine if the chemicals from the spill can damage DNA. Dr. Auerbach said three of the four chemicals being evaluated in the micronucleus assay have been run and the data are under review. Bacterial mutagenesis studies should start in January 2015.

Five-day toxicogenomics studies are being performed to characterize the quantitative and qualitative biological effects of the Elk River chemicals. Three of the chemicals have gone through the 5-day rat toxicogenomic studies, with results pending.

A guideline dermal hypersensitivity and irritation study is about to start on MCHM and the technical mixture to determine if these agents are immunotoxic and to obtain detailed dose-response information on dermal irritancy effects.

Dr. Auerbach described guideline rat prenatal developmental toxicity studies that will be used to evaluate MCHM. The prenatal, range-finding, developmental toxicity study is complete and the main study has begun. It is anticipated that all of the study results will be reported by June 2015.

NTP has been disseminating information on the West Virginia chemical spill efforts through Website (*ntp.niehs.nih.gov/results/areas/wvspill*) updates, newsletter, and a fact sheet, along with study updates. The goal is to provide rapid communication of study findings.

C. BSC Discussion

Dr. Chapin asked if there were any plans to follow the prenatal study with a Modified One-Generation Reproduction Study. Dr. Auerbach replied that it was a possibility, but there were no plans to do so at present.

Dr. Dorman asked if the group had considered including any type of biomonitoring data. Dr. Auerbach said there are plans to do internal dosimetry in the prenatal developmental toxicity studies. He said that as far as he knows, there are no internal dosimetry data available for humans in West Virginia. Dr. Dorman asked about the rationale for using a corn oil vehicle versus a drinking water study. Dr. Auerbach responded that it was an issue of dose formulation. Dr. Bucher added that corn oil was also chosen because MCHM is a particularly "smelly" compound, which would make it difficult to get high doses into rodents in their drinking water.

Dr. Hattis said fetal weight reduction is an early indicator of adverse effects of exposure. He recommended a comprehensive study using that parameter. Dr. Auerbach said fetal toxicity is typically assessed. Dr. Hattis agreed, and noted that fetal weight reduction is a linear response that might be useful in risk assessment.

Dr. Chapin praised the effort, particularly the nimbleness NTP is displaying in its approach. Dr. Bucher said NTP has pledged to communicate results as they are generated, and communicate them in a way that reflects the confidence NTP has in the outcomes for predicting human health effects. He said this is a challenge to NTP, which is not used to reporting results that are not as absolutely final.

XII. Update on NIOSH Projects

A. Presentation

Captain Cheryl Estill, NIOSH (BSC liaison), updated the BSC on current collaborative research projects being conducted by NIOSH and NTP. She described the agencies' common goals, and the goals and impacts of the collaboration. The impacts of the collaboration include findings that inform testing priorities, guidance in selection of relevant laboratory test exposures and doses, and development of methods for generation of laboratory test exposures. She reported on the status of five current collaborative projects: manganese (Mn) fractions in welding fume, carbon nanotubes and carbon nanofibers, bisphenol A, coal tar pitch volatiles containing polycyclic aromatic hydrocarbons in coal tar sealant applications, and flame retardants.

B. BSC Discussion

Dr. Markowitz noted that most of the studies seemed to be driven by materials nominated to NTP, and asked if that was exclusively the case. Captain Estill replied that the program itself does have other elements, although the joint projects include only nominated materials.

Dr. Hattis inquired about the status of work on the association between welding and Parkinson's disease (PD) due to the Mn used. Captain Estill replied that the association between Mn and PD is a reason the study is being conducted, but she did not have current information about this

health relationship because the study is an exposure study. Dr. Birnbaum noted that there are now epidemiologic studies showing an association of Mn with PD.

Captain Estill confirmed for Dr. Udasin that the NTP collaboration is primarily with the NIOSH Industry-Wide Studies Branch, which includes industrial hygienists and epidemiologists. She said she is the section chief for the industrial hygiene section, and all of the collaborative studies are within that section. Dr. Udasin asked about an epidemiology component in the welding fume/PD study. Captain Estill replied that there is no epidemiologic component at present; one purpose of the study is to determine if there is a population that might be suitable to follow with an epidemiologic study.

Dr. Birnbaum noted that the flame retardant hexabromocyclododecane is to be removed from the market in Europe next year.

XIII. NTP Technical Reports Peer Review Panel Meeting, May 22, 2014

A. Presentation

Dr. Chad Blystone, Toxicology Branch, reported to the BSC on the NTP Technical Reports Peer-Review Panel meeting held on May 22, 2014. He provided background information about the technical reports and NTP's levels of evidence of carcinogenic activity.

The draft technical reports peer reviewed at the meeting included bromodichloroacetic acid (BDCA, TR-583), indole-3-carbinol (TR-584), green tea extract (TR-585), and Cimstar 3800 (TR-586). Dr. Blystone described the panel's membership and their charge, which was to review and evaluate the scientific and technical elements of the study and its presentation and to determine whether the study's experimental design, conduct, and results supported the NTP's conclusions regarding the carcinogenic activity and toxicity of the substance tested.

Bromodichloroacetic acid is a drinking water disinfection by-product. The panel unanimously (6 yes, 0 no, 0 abstentions) recommended accepting the draft conclusions regarding clear evidence of carcinogenicity, while recommending that the conclusions of "some evidence" be changed to "equivocal evidence."

Indole-3-carbinol is a dietary supplement. The panel voted (4 yes, 2 no, 0 abstentions) to accept the draft conclusions as written.

Green tea extract is a botanical dietary supplement. The panel recommended accepting the draft conclusions with one edit (5 yes, 1 no, 0 abstentions): recommending that neoplasms of the female mouse tongue were not supportive of "equivocal evidence," and were considered "no evidence."

Cimstar 3800 is a metal working fluid used as a lubricant and coolant. The panel unanimously (6 yes, 0 no, 0 abstentions) recommended accepting the draft conclusions as written with one change: they felt that the granular cell tumors of the brain should be considered as "no evidence" instead of "equivocal evidence" in male rats.

Dr. Blystone reviewed the other topics covered at the meeting, and outlined the next steps in the process, with the four NTP Technical Reports anticipated to be published in 2015.

B. BSC Discussion

Dr. Sobrian, BSC discussant, attended the peer-review panel meeting as BSC liaison. She noted the excellent scientific presentations and the animated, interactive, and open discussions among the panel members.

Regarding Cimstar 3800, Dr. Genter noted that it is hard to induce prostate tumors in rodents, but it was a finding in the male rats. She asked Dr. Blystone why that was an equivocal finding. He said it was a low incidence, but a rare finding, and thus equivocal evidence was the conclusion. Dr. Genter asked if there was dose response. Dr. Blystone said there was not a strong dose response. Dr. Nigel Walker added that the incidence was extremely low, but due to the rarity, it was considered unusual.

Dr. Chapin asked about follow-up plans to the BDCA study, given the large opportunities for public exposures. Dr. Blystone said he was not aware of any specific follow-up plans. Dr. Birnbaum noted that over 20 years ago bromodichloromethane was found to be carcinogenic in male rats. She mentioned some of the epidemiology literature showing associations between chlorinated drinking water disinfection by-products and bladder tumors.

XIV. Office of the Report on Carcinogens

A. RoC Update

Dr. Ruth Lunn, ORoC, briefed the BSC on recent RoC activities. She first provided background information about the RoC, which is a congressionally mandated document, prepared by the NTP for the Secretary of Health and Human Services to identify substances that pose a cancer risk for people in the United States.

She described the National Academy of Sciences (NAS) reviews of the 12th RoC listings for styrene and formaldehyde. The NAS conducted independent assessment of the literature for each chemical, both of which were released in summer 2014. The NAS reports endorsed the RoC listings of styrene as *reasonably anticipated to be a human carcinogen* and of formaldehyde as *known to be a human carcinogen*.

Dr. Lunn provided details about the 13th RoC, which was released in October 2014 and includes 243 listings. It included 4 new listings: 1-bromopropane, cumene, pentachlorophenol and by-products of its synthesis, and *ortho*-toluidine. Dr. Lunn described current evaluations in progress: cobalt and certain cobalt compounds, goldenseal root powder, shift work at night, and five selected viruses.

Dr. Birnbaum noted that the NAS reports both endorsed the RoC conclusions and praised the RoC evaluations.

Dr. Sobrian asked how the five viruses were chosen for evaluation. Dr. Lunn said there are some viruses already in the RoC, and that the five currently being evaluated were nominated from outside NTP.

Dr. Corcoran asked for more information on the cobalt compounds the RoC is most interested in. Dr. Lunn noted that the ORoC had previously evaluated some cobalt-related compounds. The NTP study on cobalt metal spurred more interest in cobalt, along with the recognition that several of the cobalt compounds work in similar fashions. Dr. Corcoran asked if ORoC would include cobalt alloys and medical devices in the evaluation. Dr. Lunn said they are not being considered.

Regarding 1-bromopropane, Dr. Markowitz asked whether NIOSH had issued a hazard alert to occupational workers given the compound's listing as "reasonably anticipated to be a human carcinogen." Captain Estill replied that a hazard alert was produced last summer, not in relation to the RoC, but following a New York Times article. Also, NIOSH issued information specific to the dry cleaning industry, as the substance was being used more in that occupational setting.

B. Draft RoC Monograph on Trichloroethylene

Dr. Lunn reported to the BSC on the peer-review meeting for the Draft RoC Monograph on Trichloroethylene (TCE), which was held August 12, 2014. She provided background information about the substance and the rationale for the evaluation. Trichloroethylene is currently listed in the RoC as *reasonably anticipated to be a human carcinogen*, and the updated evaluation was undertaken due to the availability of additional human cancer studies published since the last RoC review. She described the draft RoC monograph, which focused on three cancer sites: kidney, liver, and non-Hodgkin lymphoma. She delineated the membership of the peer-review panel, the panel's charge, and requested actions. The panel agreed with the draft NTP conclusions, including the listing recommendation of *known to be a human carcinogen*. The monograph has been revised based on the panel's comments. The next steps are to finalize the monograph and post it on the NTP Website.

Dr. Hattis, BSC discussant, attended the peer-review panel meeting as BSC liaison. He noted that the panel generally agreed with the NTP's evaluation of the literature. He said they did have a number of suggestions, some of which were accepted and some of which were not. He emphasized the finding about human kidney cancer, which was bolstered by evidence of a polymorphism in TCE metabolism by the glutathione pathway. He thought the NTP process went well, in that useful suggestions were gathered. He said the public comments were heard, noted, and given the weight they deserved.

XV. Assessing NTP's Effectiveness: A Case Study on Hexavalent Chromium

A. Presentation

Drs. Mary Wolfe and Yun Xie, OLPR, presented a case study titled *Assessing NTP's Effectiveness: A Case Study on Hexavalent Chromium*.

Dr. Wolfe provided historical background on the NTP's establishment in 1978, mission, and past accomplishments. She described how the NTP's output is recognized as authoritative by several regulatory agencies. She said that by undertaking the case study project, NTP hoped to develop a useful approach for identifying methods that would yield comprehensive and credible assessments of NTP's effectiveness, for demonstrating the feasibility of assessing NTP's impacts in multiple sectors and for identifying strategies to improve existing methods for assessing research impacts. The intent was to test the approach with a pilot project, the hexavalent chromium study, with the objective of demonstrating the effectiveness of NTP's science at advancing toxicology and being translated to public health decision-making.

Dr. Xie described the impact of NTP research as dynamic, affecting different groups of people with changing impact over time. The challenges to measuring impact are attribution (a clear connection between NTP work and impact), lag time (time from research to publication, to citation, to policy impact, and to public health impact), and external factors over which NTP has no direct control (such as regulations and public health).

She outlined strategies from the literature to yield impact assessments that are comprehensive, credible, responsive, and rigorous. She described a logic model for NTP studies, flowing from inputs (money, time, and staff) to outputs (activities and products) to outcomes (proximal, intermediate, and distal). She described several metrics using the logic model.

Dr. Xie noted that hexavalent chromium (chromium (VI)) was chosen for the study because it was a high profile nomination and NTP's work was completed several years ago, with presumably sufficient time having elapsed to identify its use by stakeholders and evaluate its impacts.

She presented data illustrating a variety of metrics, including webpage views, document requests, bibliometrics (citations of NTP's work in the scientific literature), and citations in grants and reports (state, federal, and non-government). Searches were conducted for NTP product references in a variety of databases. Data presented included proximal, intermediate, and distal outcomes. As one illustration of a distal outcome, she described NTP's research as key to California's drinking water standard for chromium (VI), and outlined the path involved.

Dr. Xie said that the case study demonstrated that NTP's science on chromium (VI) had an impact in many areas, including public health. The study identified a broad and objective approach for assessing NTP's effectiveness and discovered data and methodological gaps that need to be addressed for more thorough and efficient assessments in the future. She concluded by presenting several ideas for improvements in future evaluations.

B. BSC Discussion

Dr. Dorman suggested that the study might be underestimating some of the impacts, because the metric is citation of NTP reports. He noted that some companies use studies from NTP to add a substance to a blacklist, mandating that their supplying manufacturers not use it. He felt there was a huge impact of NTP studies on industry. Also, the logic model may miss impact on material safety data sheets, which may contain carcinogenicity data derived from NTP studies. Dr. Xie said attribution is the main problem in those areas, as NTP studies are often not directly cited, and a clear attribution is needed to document impact.

Dr. Markowitz felt that the standard was too high and too narrow and that NTP should be able to take credit for impacts beyond direct citations.

Dr. Udasin asked Dr. Xie about the identification of NTP studies in lawsuits. She said she sometimes provides expert testimony, often cites NTP studies, and wondered how those citations could be identified. She also mentioned state fact sheets, including New Jersey's on chromium. Dr. Xie said NTP searched for lawsuits using LexisNexis and added that New Jersey's fact sheet had been accessed. She said there is a danger of overstating attribution by citing both a report and a fact sheet related to that report. Dr. Xie said the objective was to be clear and avoid overselling attributions and impact.

Dr. Hattis asked if LinkedIn had been used as a source, given its citation activity. Dr. Xie said a variety of sources were used to find citations in journal articles, particularly Web of Science and Scopus.

Dr. Chapin suggested using ResearchGate as a source of citations. Dr. Xie said alternative metrics are being considered to track mentions of NTP work, particularly in social media, which would help expand beyond metrics of citations alone.

Dr. Markowitz noted that since the goal is the reduction or elimination of human exposure, he said exposure should be measured as well, and asked if that was an objective of the program. Dr. Xie said it could be a very long time until it would be possible to detect changes in exposure. A problem with that type of measure would be attribution due to lag time and the inclusion of many other factors.

Dr. Howard suggested that NTP could simply ask the various regulatory agencies about what they know about product changes due to NTP studies. It would not be a quantifiable metric, but could be used as a "soft list." Dr. Xie said surveys could definitely be used in an evaluation project. They were not used in the chromium (VI) case study, and would be desirable in the future as one way to access impact beyond citations.

Dr. Sobrian asked why the District of Columbia (DC) had not been included in the study. Dr. Xie said a LexisNexis search had no hits for DC. She said they realize that the databases currently being used may not be complete. Dr. Sobrian noted that DC should be included due to the many Congressional committees and agencies there. Dr. Xie said that many of the media articles cited were from trade media based in DC.

Dr. Birnbaum noted that just after she became NTP Director in 2009, she conducted a town forum in New Jersey, where there was considerable concern about chromium (VI). She wondered if the case study search had come up with the news coverage of that town forum. Dr. Xie said it had.

Dr. Dorman asked if the search engine was set up to detect other ways that cancer gets classified, such as World Health Organization designations. He said such categorization schemes get used fairly heavily in industry. Dr. Xie said the searches started very generally, with a wide sweep of the terms "NTP" and "National Toxicology Program," and "chromium," which yielded many thousands of hits. A person reviewed each hit to see if it actually related to NTP work. Dr. Wolfe added that sometimes the attributions were very general. She said legal or regulatory documents often do not have reference lists.

Dr. Hattis suggested it might have been useful to look for references to a distinctive biological effect of chromium (VI), such as perforation of the nasal septum. He said it would be interesting to see whether articles referring to such effects would cite NTP work. He added that there are also distinctive uses of hexavalent chromium such as chromium plating, which may also yield references to NTP work. Dr. Xie said their research strategy had found such instances.

XIV. Adjournment

Closing the meeting, Dr. Birnbaum thanked the BSC members for their ongoing engagement and hard work. Dr. Bucher thanked the NTP staff members for their work in making the BSC meeting possible. Dr. White added her thanks and noted that the next BSC meeting would be held June 16 - 17, 2015.

Dr. Peterson adjourned the BSC meeting at 4:30 PM.