National Toxicology Program

Board of Scientific Counselors

June 17-18, 2019

National Institute of Environmental Health Sciences
Research Triangle Park, NC

Summary Minutes

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1. Abbreviations and Acronyms

ASPIRE	A Specialized Platform for Innovative Research Exploration
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
CDMs	Cancer driver mutations
CounterACT	Countermeasures Against Chemical Threats
CV	Cardiovascular
DOE	Department of Energy
DNT	Developmental neurotoxicity
DNT-DIVER	Developmental NeuroToxicity Data Integration and Visualization Enabling Resource
DNTP	Division of the National Toxicology Program
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HEIs	Health Effects Innovations
IAA	Interagency Agreement
iPSC-CMs	Induced pluripotent stem cells - cardiomyocytes
MOA	Mode of action
NCATS	National Center for Advancing Translational Sciences (NIH)
NCCT	National Center for Computational Toxicology (EPA)
NCTR	National Center for Toxicological Research (FDA)
NCEA	National Center for Environmental Assessment (EPA)
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health (CDC)
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation (NTP)
OP	Organophosphate
ORNL	Oak Ridge National Laboratory (DOE)
R&D	Research & development

2. Attendees[1]

Board of Scientific Counselors

Chair: Kenneth McMartin, Louisiana State University Health Sciences Center
Cynthia Afshari, Janssen Pharmaceutical Companies of Johnson & Johnson
Norman Barlow, Seattle Genetics
David Berube, North Carolina State University
Paul Brandt-Rauf, Drexel University
Weihsueh Chiu, Texas A&M University (*by telephone*)
Myrtle Davis, Bristol-Myers Squibb
David Eaton, University of Washington
Susan Felter, Procter & Gamble
David Michaels, George Washington University
Kenneth Ramos, The Texas A&M University System
Anne Ryan, Pfizer, Inc.
Jennifer Sass, Natural Resources Defense Council
James Stevens, Paradox Found Consulting Services, LLC
Susan Tilton, Oregon State University

Government Agency Personnel

Gonçalo Gamboa da Costa, U.S. Food and Drug Administration (FDA)/National Center for Toxicological Research (NCTR), BSC liaison and Invited Speaker
William Slikker, FDA/NCTR
Elizabeth Whelan, National Institute for Occupational Safety and Health (NIOSH), BSC liaison

Invited Speakers

Christopher Austin, National Center for Advancing Translational Sciences (NCATS)
William Mattes, FDA/NCTR
Kyle Messier, Oregon State University
Barbara Parsons, FDA/NCTR
John Piacentino, NIOSH

[1]The meeting was webcast. Individuals who viewed the webcast are not listed except as noted.

National Institute of Environmental Health Sciences/Division of the National Toxicology Program (NIEHS/DNTP) Staff

Pamela Bayles
Mamta Behl
Natalie Bell
Brian Berridge
Linda Birnbaum
Warren Casey
Mark Cesta
Sheba Churchill
Brad Collins
Helen Cunny
Jesse Cushman
Sally Darney
Michael DeVito
Darlene Dixon
June Dunnick
Askia Dunnon
Susan Elmore
Sue Fenton
Robbin Guy
Laura Hall
Alison Harrill
Jean Harry
Sandy Henriquez
Ron Herbert
Michelle Hooth
Troy Hubbard
Gloria Jahnke
Angela King-Herbert
Nicole Kleinstreuer
Ramesh Kovi
Shagun Krishna
Chris Long
David Malarkey
Ahmed Mashal
Scott Masten
Barry McIntyre
Chris McPherson
Suril Mehta
Alex Merrick
Esra Mutlu
Sri Nadadur
Arun Pandiri
Richard Paules
Arif Rahman
Cynthia Rider
Georgia Roberts
Andrew Rooney
Janine Santos
Sheena Scruggs
Keith Shockley
Robert Sills
Nisha Sipes
Jennifer Smith
Stephanie Smith-Roe
Jason Stanko
Gregory Travlos
Suramya Waidyanatha
Nigel Walker
Vickie Walker
Amy Wang
Atlee Watson
Donna Webb-Wright
Kristine Witt
Mary Wolfe
Leroy Worth
Rick Woychik

Contract Support Staff

Jeanne Luh, ICF
Steve McCaw, Image Associates
Blake Riley, ICF
Kelly Shipkowski, ICF

Public Attendees

Reshan Fernando, RTI International
Jenni Gorospe, Battelle
Ernie Hood, Bridport Services
Barney Sparrow, Battelle
Carol Swartz, ILS
Raymond Tice, RTice Consulting

Day 1: June 17, 2019

3. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened on June 17, 2019, in Rodbell Auditorium, Rall Building, National Institute for Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. Dr. Kenneth McMartin served as chair. Representing NTP were Drs. Linda Birnbaum and Brian Berridge. Dr. Mary Wolfe served as the Designated Federal Official.

Dr. McMartin called the meeting to order at 8:30 a.m., welcomed everyone to the meeting, and asked all attendees to introduce themselves. He noted that Dr. Chiu would be attending by telephone and board members Drs. Daniel Kass, Donald Stump, and Katrina Waters would not be in attendance. Dr. Berridge welcomed all participants to the meeting. Dr. Wolfe read the conflict of interest policy statement and briefed the attendees on meeting logistics.

4. Report from NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, briefed the BSC on developments at NTP and NIEHS since the February 2019 board meeting. She began with a report regarding the federal budget and appropriations. She said that the National Institutes of Health (NIH) has had a $9 billion increase in its budget since 2016 and that a budget for the next fiscal year is not yet in place; however, she anticipates a continued increase in the overall budget. The U.S. House of Representatives mark for FY2020 shows a $2 billion increase for NIH and a $38 million increase for NIEHS, which looks relatively promising.

Dr. Birnbaum reported on Congressional testimony she delivered before the Senate Environment and Public Works Committee, focusing on per- and polyfluoroalkyl substances. She also summarized three other recent Congressional hearings related to environmental health.

Turning to scientific advances and recent publications, Dr. Birnbaum described papers falling under the One NIEHS rubric and emerging from the Division of the National Toxicology Program (DNTP). She mentioned the new process for faster publication in place at *Environmental Health Perspectives*, as well as the search for a new editor-in-chief for the journal.

She provided details on several recent workshops, and highlighted recent awards and recognition of DNTP personnel. She recognized several recent staff departures and new arrivals, and previewed the NTP 40th anniversary recognition, scheduled for later in the day.

Dr. Birnbaum concluded her remarks by presenting certificates of appreciation to retiring BSC members Cynthia Afshari, Norman Barlow, Kenneth McMartin, Kenneth Ramos, and James Stevens. She also noted the retirement of BSC members Katrina Waters and Daniel Kass. All had reached the conclusion of their appointments to the board.

5. Strategic Realignment

5.1 Update and Recap of February 2019 BSC Meeting

To set the stage for the ensuing presentations on NTP's Strategic Realignment, Dr. Berridge provided his reflections on the February 2019 BSC meeting, at which several of the topics on the current agenda were originally introduced under the title, "The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment." He related several of the points that had been made by BSC members at the meeting and described the DNTP Translational Toxicology Pipeline, which was designed for "Innovating the Paradigm." He reviewed the plans for Health Effects Innovations (HEIs) in three areas:

- Carcinogenicity Testing for the 21st Century
- Developmental Neurotoxicity Modeling
- Cardiovascular Hazard Assessment in Environmental Toxicology

He discussed remarks that had been delivered by representatives of several NTP partner agencies, and concluded by introducing the next four presentations, which would constitute updates to the board on the agency portfolios in support of NTP.

Clarifying Questions

Dr. Afshari asked Dr. Berridge to elaborate on his discussion about the need for increased speed in NTP decision-making. He said there were two elements involved: 1) being timelier in delivering usable data, and 2) being able to make decisions on more fundamental information.

Dr. Tilton asked Dr. Berridge about the need to build more confidence in the early part of the pipeline – *in vitro* and *in silico* methods for predictive capabilities. She asked what NTP is doing specifically to address that need. He replied that it is an integration of several elements, and said the pipeline would be deliberately worked to integrate the information emerging from the problems being taken on by NTP. By bringing in more human relevance and context, biological platforms can be built that have the same level of confidence as animal studies. He said that the HEIs will: 1) intentionally populate the pipeline, and 2) look critically at the platforms used to generate data.

Dr. Berube suggested setting a specific goal to accelerate the process. Dr. Berridge thought that was a brilliant idea, in that it would give NTP something to aim for and build a sense of urgency. He emphasized the need to do this in a realistic way, however, in order to avoid creating a sense of anxiety or ambivalence.

Dr. Felter asked whether reframing the initial questions could help enable more timely delivery of data. Dr. Berridge said that NTP had already started doing so prior to his arrival, including focusing on using points of departure and high-throughput screening to identify bioactivity, which can enable earlier decision-making.

Dr. Eaton felt that despite recent changes in toxicology, the basic risk paradigm, a function of hazard and exposure, has not changed. He said that NTP has been largely focused on hazard identification, and asked where they were headed in terms of exposure. Dr. Berridge said that NTP positions itself as a hazard identification organization; however, there is concern for ensuring NTP data is human relevant. He emphasized an effort to better contextualize hazard,

giving the example of using geospatial information, while staying away from the risk assessment purview of other federal agencies.

5.2 Agency Portfolios in Support of NTP

5.2.1 NIOSH Portfolio in Support of the National Toxicology Program

Dr. John Piacentino, Associate Director for Science at the National Institute of Occupational Safety and Health (NIOSH), briefed the board on his agency's portfolio in support of NTP. He presented background information about NIOSH and its partnership with NTP, and described current projects within the partnership, which included selected human exposure assessment studies, targeted risk assessment of xenobiotics, and subchronic immunology and toxicology studies. He also described NIOSH intramural and extramural research outside the partnership, including etiologic research in areas such as pulmonary, cardiovascular, cancer, reproductive health, and immune system effects. He cited several examples demonstrating the success of the partnership.

5.2.2 FDA Update on NTP Portfolio

Dr. Gonçalo Gamboa da Costa, U.S. Food and Drug Administration (FDA)/National Center for Toxicological Research (NCTR), liaison officer to NTP, briefed the board on FDA's portfolio in support of NTP. He described the FDA-sponsored portfolio and the NIEHS-FDA interagency agreement (IAA)-sponsored portfolio. They encompass five broad areas of research:

- Biochemical and molecular basis of toxicology
- Computational toxicology
- Nanotoxicology
- Neurotoxicology
- Bioassay and biomarker development and evaluation

Dr. Gamboa da Costa discussed each of the 5 areas in turn, including the number of protocols involved, their percentage of the investment effort, and an example protocol. He provided information about the NIEHS-FDA IAA, including examples of past research with clear translational impact. The current (FY19) IAA portfolio includes food additives and contaminants, dietary supplements, drugs, and the Enhancing Toxicology Program.

Clarifying Questions

Dr. Eaton stated his approval of the strong interaction between FDA and NTP, emphasizing that the collaboration covers a number of chemicals that don't fall within another agency's direct purview.

5.2.3 NIEHS/DNTP Portfolio in Support of NTP

Dr. Scott Masten, director of the NTP Office of Nomination and Selection, briefed the board on the NIEHS/DNTP portfolio in support of NTP. He provided background information about NTP, including where DNTP lies within the organizational structure. He described the institute's capabilities and mechanisms, including NIEHS contracts, in-house research, and research stemming from IAAs with FDA/NCTR, Centers for Disease Control and Prevention (CDC)/NIOSH, NIH/National Center for Advancing Translational Sciences (NCATS), U.S.

Environmental Protection Agency (EPA)/National Center for Computational Toxicology (NCCT), EPA/National Center for Environmental Assessment (NCEA), and Department of Energy (DOE)/Oak Ridge National Laboratory (ORNL). He went over the primary NTP products and their public health impact, and detailed how the DNTP portfolio is organized largely around capabilities and disciplines. He provided multiple examples of capabilities and a rundown of current DNTP research portfolio broken down by project categories. Research and testing activities include:

- Toxicology studies
- Tox21 and biomolecular screening
- New, revised, or alternative test methods
- Investigative studies

Analysis activities include evaluation of non-cancer health effects and evaluation of human cancer hazards.

Dr. Masten discussed the strategic shift underway at DNTP and its potential impact on the portfolio – retaining some of the more traditional areas while shifting to newer elements such as the HEIs. He described the institute's strategic aims related to the future portfolio.

Clarifying Questions

Dr. Afshari asked whether NTP was wrestling with any big decisions regarding discontinuing activities to create the space needed to move forward. Dr. Masten said NTP was actively working on this, and emphasized that the goal was less about removing activities and more about making sure there's room to do everything NTP wants and/or needs to do. To get better answers about human safety and context, the portfolio needs to be trimmed and pruned to stay sustainable. Dr. Berridge added that NTP cannot walk away from commitments; however, they can influence how those commitments are delivered. Dr. Birnbaum agreed that there are plenty of opportunities for change.

Dr. Ryan inquired about opportunities to say no to new activities that don't match the focus areas. Dr. Birnbaum emphasized NTP's nomination and selection process, and Dr. Berridge added that NTP has a history of not saying no enough. Dr. Masten clarified that saying yes is fundamental to NTP's culture and personality, as the landscape of what NTP can do is vast. A lot of the decisions to say yes or no are also simply based on capacity.

5.2.4 NCATS-NTP Collaboration

Dr. Christopher Austin, director of the NIH NCATS, briefed the board on the NCATS portfolio in support of NTP. He described the history and status of the Tox21 Program, which is primarily based at NCATS. He provided details about the new Tox21 strategic and operation plan, which aims to increase predictivity and reduce uncertainty. He alluded to the NCATS BioPlanet, which is an integrated platform for exploring the universe of cellular signaling pathways for toxicology, systems biology, and chemical genomics.

Dr. Austin related the mission of NCATS, as well as several programs to accelerate and enhance translation, including the NCATS Division of Preclinical Innovation, the NCATS Stem Cell Translation Laboratory, and the Tissue Chip Program 2.0. Translation will also be aided by

ASPIRE: A Specialized Platform for Innovative Research Exploration and the NCATS Biomedical Data Translator Program.

5.3 BSC Discussion

The four lead BSC discussants shared their remarks on the strategic realignment, followed by a general discussion.

Dr. Ramos was the first lead discussant. He said he enjoyed the presentations, particularly in the context of the strategic realignment. He asked Dr. Berridge to describe the process that was used to get NTP to where it is currently, as well as the level of stakeholder engagement. Dr. Berridge replied that there had been a re-examination of the NTP portfolio in the context of the 2004 articulation of an aspiration to a new model of toxicology in the 21st century. The conversation evolved from there, but NTP is still fundamentally doing toxicology the way it has always been done. There was reflection on NTP's processes and its ability to deliver products, shift gears, and refine focus, including discussion with interagency partners. Thanks to interactions with several stakeholder groups, the concept evolved. The HEIs were a byproduct of Dr. Berridge's background in the pharmaceutical industry, and they gained traction as the conversation evolved.

Dr. Ramos shared five key observations/recommendations:

1) The greatest gap exists between identifying areas for improvement and the need to devote adequate time for actionability of identified issues. NTP should identify the actions that will be taken and not simply identify where changes are needed.
2) To achieve 80% right is okay; NTP should be open to taking some risks instead of trying to develop the perfect plan.
3) NTP should invest time in selling its realignment to internal stakeholders. Actionability comes from internal staff engagement, and the organization's goals need to be embraced for strategic realignment to work.
4) Much of the concept development has focused on structure, leaving functionality less developed. He said that the Translational Toxicology Pipeline speaks more to knowledge integration, which is far away from the human health assessments NTP needs to serve.
5) There is a need for an honest assessment of true capacity. It will be difficult to create deliverables and introduce actionability until NTP's capacity is fully understood.

Dr. Berridge thanked Dr. Ramos for his recommendations, and said they illustrated the importance of engagement with outside perspectives. Dr. Wolfe noted that there had been considerable internal communication on the process.

Dr. Afshari was the second lead discussant. She said that collaboration among the different agencies is critical to demonstrate good stewardship of public funding and establish confidence in the science with stakeholders. She challenged the group to consider a common visualization platform for NTP's mission that can drive a decision-making framework. She acknowledged that environmental health science has historically struggled with looking at biomarkers of effect, and emphasized leveraging technologies that allow non-invasive monitoring (i.e., occupational exposure testing at NIOSH and clinical testing at NCATS). She recommended spending some time assessing how molecular biology and physiology will advance with burgeoning technology,

and whether NTP's partnerships afford opportunities to dig into translational aspects. She noted that communication with the public was an NTP strength that cannot be taken for granted, and commended efforts on data transparency. Dr. Birnbaum mentioned the new Office of Data Science as part of ongoing data transparency efforts, as well as a number of NIEHS communications activities.

Dr. Michaels was the third lead discussant. He said that the challenge lies in converting collected information into actions that will reduce exposures and prevent illness. Even though NTP's data are pre-regulatory, the information still needs to be communicated. He suggested that NTP and its partners should plug into the Globally Harmonized System of Classification and Labelling of Chemicals, the international standard managed by the United Nations.

Dr. Sass was the fourth lead discussant. She had been impressed by the presentations and reminded the group that there is not much public understanding about the exposure component of *in vitro* to *in vivo* extrapolation. There is a need to facilitate public knowledge about exposure assumptions – what they are based on, what the limitations are, where it is appropriate to use the information, and which populations the information can be applied to. She praised NTP for the communication efforts around computational toxicology projects like Tox21 and mentioned bioavailability as an area needing better public understanding. Dr. Sass raised concern with assumptions such as that even if a chemical is toxic, if it's not bioavailable, then it's considered safe – such presumptions, if wrong, can lead to health harms. Steps need to be taken to help the public understand concepts like physicochemical properties and adverse outcome pathways. She felt that NTP does a great job of putting out information in process while explaining the limitations of draft products, such as with the rapid response model used in the Elk River response. She recommended expanding programs like the Office of Health Assessment and Translation (OHAT), particularly when considering groups of chemicals.

Dr. Masten said that the 80/20 suggestion is consistent with what NTP is trying to do, and noted the flexibility in the program.

Dr. Brandt-Rauf asked about the NTP talent development pipeline. Dr. Masten replied that there are some areas that are thin and some that need more talent. Dr. Berridge said that personnel are needed with a fundamental background in relevant areas of science, as well as the flexibility to accommodate rapidly changing technologies. There is a need for scientists who are not comfortable inside a particular box and can work across disciplines.

Dr. Davis challenged the fully collaborative model, and asked whether it would create enough space for maximum productivity and advancement. An overly collaborative space can put a chokehold on creativity, and she wondered whether there would be space for originality, especially for trainees. Dr. Berridge agreed, and noted that a balance is needed between impact and innovation; depth can be lost by being overly collaborative and committed to team science. Part of the strategic realignment is finding opportunities for innovation and creativity that do not diverge so far from the focus that they undermine the program. Dr. Birnbaum agreed that no one can be collaborative all the time.

Dr. Austin said there is a tendency for collaboration to be an end in itself, as sometimes you need a team of people with different backgrounds to accomplish a goal. He said that principal investigators have told him that team projects were some of the most creative they had ever done, but also noted that effective project management is absolutely necessary.

Dr. Davis drew a distinction between large collaborative efforts and smaller, focused innovation groups.

Dr. Stevens said that he has had unique opportunities to attend NTP events, which has allowed him to informally survey personnel to ask how they are responding to the new NTP agenda. He has gotten a sense that there is a tremendous amount of excitement and engagement, and that the internal communication is generating great interest. He asked Dr. Masten about the ability for quick response by a contract research organization. Dr. Masten replied that only recently have questions arisen regarding how contracts and capabilities might be handled under the new strategies, with a recognition that there are other mechanisms available. Dr. Birnbaum noted that there are two types of contracts, time-and-materials and performance-based, the latter of which is more interactive. She said that an NIEHS performance management office had been established to help work with those types of contracts. Dr. Austin noted another category called "other transactions" that is neither grant nor contract and may be useful. Dr. Birnbaum noted that certain contracts are more research & development (R&D) contracts, with much more give-and-take than a traditional arrangement. Dr. Berridge acknowledged that the area is challenging and will require creative use of NTP's considerable resources.

Dr. McMartin briefly summarized the discussion, noting that the board had been complimentary about the presentations, was excited about the strategic realignment, and had offered specific suggestions on implementation.

6. Translation as a Scientific Framework: Human Relevance (Part 2)

6.1 Introduction

Dr. Berridge provided a brief introduction to the session and described what he called "translation the NTP way." NTP translates using traditional approaches based on animal models, and the government context moves from the science to regulation and policy; those two approaches constitute past bias. In the realm of future bias there is precision toxicology, which is moving from the idea of anybody to somebody. Predictive toxicology also moves from cells to tissue to organs to the organism. New approaches incorporate innovation, which leads into practice, and the future is one where NTP will be able to increasingly contextualize its data for more individual risk assessment, apply more mechanistic/mode of action assessments in simpler but human-derived platforms, and apply technical advances at pace.

6.2 Cancer Driver Mutations in Experimental Rodents and Prediction of Human Cancer

Dr. Barbara Parsons from the Division of Genetic and Molecular Toxicology at FDA/NCTR briefed the board on her research involving cancer driver mutations (CDMs).

There is a long-standing unmet need for alternative approaches to the two-year rodent cancer bioassay. The objective of Dr. Parsons' research is to develop panels of cancer-driver mutational targets to serve as reporters of carcinogenic effects. The application incorporates analyses of CDMs into 28-day to 6-month repeat-dose rodent studies, and the long-term goal is to predict rodent lifetime carcinogenicity from shorter-term exposures.

Dr. Parsons defined CDMs, which tend to cause clonal expansions, and elaborated on the strength and sensitivity of CDMs as biomarkers of effect. She provided several examples to illustrate the potential utility of CDMs.

Looking forward, datasets are needed that define relationships between measurements from panels of hotspot CDMs and tumor responses for rodents and humans. Dr. Parsons' group recently developed a human amplicon panel with analysis by error-corrected next-generation sequencing. The method reports expected tissue-specificities for CDMs in breast and lung cancers, as well as in normal breast and lung.

Panels of hotspot CDMs appear to be promising biomarkers of carcinogenic effects and may be translatable between rodents and humans.

6.2.1 BSC Discussion

Dr. Birnbaum asked Dr. Parsons about her source of normal human breast and lung tissues, and whether they were taken from biopsy material; Dr. Parsons said that they were autopsy specimens from tissue banks. Dr. Felter asked about the information on age in humans, and whether there was analogous information in rodents. Dr. Parsons was not aware of such information, but acknowledged that it may be data NTP could contribute.

Dr. Ryan was the first BSC discussant. She said that CDMs are an interesting concept that industry has thought about, and felt that they present a potential opportunity for collaboration across agencies or with industry. There are vast archives of historical data, with advances in science leading to enriched abilities to analyze them, and she thought this was an intriguing idea that could lead to more predictive work.

Dr. Barlow was the second BSC discussant. He said that although he is a believer in the 3Rs (reduce, refine, and replace) and looks forward to *in silico* methods to predict disease in people, there is still a reliance on rodent models. He approved of Dr. Parsons' work comparing and contrasting human and rodent data, and asked her about information on time course, suggesting that the NTP Archives may be able to contribute. He noted that she referenced pharmacology in her presentation, and it struck him that CDMs are types of mutations that may not necessarily have a toxic effect, but still lead to tumor progression. He asked what the rationale was for looking at specific tissue types, other than simply knowing where a chemical is active. Dr. Parsons replied that she could not see analyzing every tissue in a rodent, and these methods would allow for prioritization. She said one would likely see the mutations, but not clonal expansion, and the difference could be discerned if there was a carcinogenic effect. Dr. Barlow asked how the testing might be applied in humans, and Dr. Parsons replied that even though there is an element of chance involved, differences in levels of CDMs would at least be partially stochastic. She said she was very enthusiastic about looking at treatment groups, and that her research group was looking at developing panels for blood that could be incorporated in the genetic safety assessment of Phase 1 clinical trials.

Dr. Davis asked Dr. Parsons if she had considered looking at mutations that influence the immune response. Dr. Parsons said she was not familiar with that specifically, but, since all CDMs are not created equal, a systematic analysis was used in considering which mutations to put in the panels. She noted that there are shorter-term goals for CDM usage to improve risk assessment, such as contributing to quantitative dose response analysis on genetic toxicity data. CDM data could also be used to address some direct questions about rodent-to-human extrapolation in terms of uncertainty factors.

Dr. Birnbaum asked how much congruence there is in CDMs in humans versus rodents. She asked if it would be possible to obtain data on CDMs in human tumors from the National Cancer

Institute, and then use animal tumor data from the NTP Archives to look at congruence. Dr. Parsons said that was exactly what she envisioned, but clarified that inter-animal and inter-human variability need to be considered.

Dr. Ramos suggested that more attention be paid to temporality, especially outside of clonal expansion. Dr. Parsons noted that CDMs can be selected for or against, and noted that the temporality question would largely be taken care of if it could be shown that earlier measurements of CDMs correlated with tumor responses.

Dr. McMartin asked Dr. Parsons to elaborate on how CDMs could be applied to human treatment studies. She said that because there is so much more variability in humans, particularly in terms of spontaneous levels and exposures, a stochastic element would be present.

In summary, Dr. McMartin said that the board was obviously very interested in the idea of CDMs, and looks forward to NTP analysis of its usefulness in future studies. He adjourned the meeting at 3:00 p.m. and announced that the final talk scheduled for the day, by Dr. Kyle Messier, would be moved to the following morning.

Day 2: June 18, 2019

Dr. McMartin reconvened the meeting at 8:15 a.m. and asked BSC members and other attendees to introduce themselves. Dr. Wolfe read the conflict of interest policy statement.

6.3 Geospatial Human Health Exposure Science Connections to Toxicology

Dr. Kyle Messier from Oregon State University briefed the board on his work connecting geospatial models to population-based human health risk assessments. Spatial modeling can effectively bridge gaps between disease outcomes obtained through epidemiological studies and disease mechanisms obtained through toxicological studies, to better inform risk assessments. He highlighted two examples to cover issues of uncertainty quantification in exposure assessments: 1) applications of geospatial methods in pharmacokinetic modeling, and 2) translation of internal dosimetry models and toxicological endpoints.

In the first example, Dr. Messier described an epidemiological analysis of groundwater radon and stomach cancer, with geospatial methods used in the exposure assessment. In the second example, he discussed an epidemiological analysis of traffic-related air pollutants and cardiovascular disease in Oakland, California.

Such air quality and human health outcome studies can connect human external exposure to internal exposure measured in NTP mechanistic studies. Dosimetry models can be used to make comparable units, which helps interpretation and dissemination to the public. Together, the integration of geospatial statistical modeling into toxicological studies could serve a novel utility towards improving the characterization of relationships between chemical exposures, disease outcomes, and translation for public dissemination.

6.3.1 BSC Discussion

Dr. Berube asked Dr. Messier to elaborate on his discussion of the relative effectiveness of mapping in risk communication, which had been received positively, specifically regarding how it had been assessed. Dr. Messier said that his group had worked closely with a local community grassroots organization in a very iterative process. Dr. Berube suggested that there should be an

experimental design to enable valid assessment, and Dr. Messier mentioned that they had used focus groups to test how the maps were perceived.

Dr. Eaton asked whether the statistics could be used in uncertainty analyses and provide a way for epidemiologists to address confounding and covariance in population/demographic data. Dr. Messier replied that that was certainly a potential use, and that there could be numerous applications as long as some basic assumptions are met.

Dr. Brandt-Rauf was the first BSC discussant. He asked Dr. Messier to discuss how well the modeling correlates to data coming from personal monitoring tools. Dr. Messier said his group had recently received data from an application monitoring external exposure with wristbands and had not yet analyzed the differences between temporal or spatial models and the monitoring; it is not yet clear which method would represent the best standard. Dr. Brandt-Rauf expressed concern about the validity of the model in correlation with human exposures. Regarding the radon study, he said he was confused about the direct connection between radon exposure and lung cancer. Dr. Messier further described the ingestion of radon through off-gassing from drinking water, and said indoor air exposure had been controlled for in the study. Dr. Brandt-Rauf said he was unclear how the methods would aid toxicology. Dr. Messier noted that the ideas were quite new and that he had presented examples of potential applications.

Dr. Tilton was the second BSC discussant. She felt that the primary potential benefit of the geospatial modeling approaches was risk-based prioritization of chemicals. The approaches could be useful for identifying data gaps, quantifying uncertainty, and improving communication. She asked Dr. Messier to elaborate on how the approaches could be used in scenarios with mixtures and multiple stressors. He described several of the methods being tested for dealing with mixtures, and noted that in 2014, NIEHS had hosted a workshop on statistical approaches specific for dealing with mixtures. The spatial method acknowledges that a model will not include all of the information needed, and adjusts for residual confounding. Dr. Tilton asked if the geospatial methods might be useful in physiologically based pharmacokinetic modeling. Dr. Messier said it could certainly help identify uncertainty and improve predictions, and went on to describe two potential applications.

Dr. Chiu said there were three basic areas where the methods could be relevant to NTP. First, the spatial statistics methods could be applied to imaging data. Second, they could be useful for translation, particularly for decision-making at the community level. However, he was somewhat skeptical about how useful they would be for toxicokinetics due to human variability. Third, he cited susceptibility to environmental justice factors. Dr. Messier said that the datasets may not currently be available nationwide, but could be soon with the amount of personal information being collected. He said that in the Oakland study he had worked with Kaiser, gaining access to personal, high-resolution health information.

Dr. Gamboa da Costa noted that in some instances, organs are inaccurately regarded as compartments. He felt there was considerable potential in Dr. Messier's methods.

Dr. McMartin summarized the board's impressions. He said the presentation was a very exciting look at new methods that are still works in progress. He noted that the board made some excellent comments and suggestions for Dr. Messier to consider when he revises and improves the statistics. The methods appear to have potential use in toxicology.

7. New NTP Programs: Health Effects Innovations

7.1 Introduction

Dr. Berridge introduced the session devoted to the Health Effects Innovations (HEIs). He defined the aims of the program:

- Define and build a strategic assessment pipeline for key health effects
- Understand the mechanism of action, mode of action (MOA), and health effect continuum for these areas
- Increase confidence in the predictivity of MOA assessments
- Align capability development to problems they are trying to solve
- Maximize the collective strength of the NTP organization
- Build novel partnerships in and outside NIH

He described the HEIs as an opportunity for flipping the paradigm – adjusting the program's focus from being agent-based to being disease-based and dealing with problems that actually exist in the population as opposed to hypothetical ones. The change would affect the NTP Translational Toxicology Pipeline framework, and Dr. Berridge outlined a variety of expected outcomes arising from the paradigm shift.

7.2 Cardiovascular Hazard Assessment in Environmental Toxicology

Dr. Berridge introduced the cardiovascular (CV) HEI. He acknowledged the Program Management Team and described the aim and value of the program. He integrated the wide variety of CV health effects opportunities with the NTP Translational Toxicology Pipeline graphic.

As an example of leveraging partnerships, Dr. Berridge described the recently signed Memorandum of Understanding among NTP, the FDA Center for Drug Evaluation and Research, and the nonprofit Health and Environmental Sciences Institute; a research collaboration to foster assessment of CV safety in nonclinical drug development. The aim will be to generate relevant data that will enable decision-making.

Dr. Berridge related a series of thoughts he referred to as "reasons to believe" that the CV HEI effort would be successful. He noted that a lot is known about the CV system, including what controls it and how it responds to injury. He said that technology is advancing rapidly and described several recent innovations, such as a new visualization tool called CardioToxPi.

He concluded by listing the tasks facing the DNTP CV HEI:

- Define discrete problem statements
- Scope the biology/pathobiology of interest
- Analyze capability and knowledge gaps
- Identify contemporary environmental toxicology problems of which to align capability development
- Develop a CV HEI Program/Project Strategic Plan

- Build a project and data management framework

Clarifying Questions

Dr. Afshari asked Dr. Berridge about phenotypic anchoring, specifically whether certain CV disease phenotypes would take priority. He said it would be useful to have a conversation with colleagues at the National Heart, Lung, and Blood Institute about breaking down the full spectrum of CV disease. It is much harder to replicate a component of a disease and then screen for agents that may contribute to that disease, relative to using an agent-based approach. The disease-based approach also bridges toxicology to novel drug development. He felt that there are fundamental pathways that can be extracted from the myriad of clinical manifestations of CV disease.

7.3 Evaluating Cardiotoxicity Potential: Translational Approaches and Models

Dr. William Mattes, director of the Division of Systems Biology at NCTR, briefed the board on work being done to evaluate cardiotoxicity potential, which is a concern for both drug development and environmental chemicals. His presentation was in support of the CV HEI.

He outlined many cardiotoxic agents, including not only drugs, but also metals such as lead and cobalt. He described the many adverse CV events elicited by tyrosine kinase inhibitors and discussed the drug development safety pharmacology studies for CV liabilities.

Cardiotoxicity research at NCTR has explored computational, *in vitro, in vivo,* and clinical models; he gave the example of patient-specific induced pluripotent stem cells-cardiomyocytes (iPSC-CMs). Agents with known clinical adverse effects, such as proarrhythmia drugs, anthracyclines, and tyrosine kinase inhibitors, have been used to characterize those models. NCTR has examined cellular, electrophysiological, and transcriptional endpoints *in vitro*; circulating and tissue biomarker, electrophysiological, and histopathological endpoints *in vivo*; and circulating biomarker and cardiofunctional endpoints clinically. The goal is to integrate those endpoints to best implement the models for screening and characterizing compounds for potential cardiotoxic risk.

Clarifying Questions

Dr. Eaton asked Dr. Mattes about the difference between drugs, in the pharmaceutical sense, and non-drug chemicals, in terms of dose response and relationship to a target. Pharmaceuticals are developed to target a specific receptor, and he asked about the shape of a dose-response curve for cardiotoxicity and its relationship to the target for which the drug was developed. Dr. Mattes said that the cardiotoxicity assessment is conducted *in vitro*, with target engagement measured at the same time. Dr. Eaton asked how much of the cardiotoxicity induced by tyrosine kinase inhibitors is related to the intended therapeutic target, versus off-target effects, and what the dose response looks like in each case. Dr. Mattes said that most of the cardiotoxicity is non- specific, and that he did not think anyone had ever looked at the cardiotoxicity dose response in terms of target engagement.

7.4 Developmental Neurotoxicity

Dr. Robert Sills delivered the first section of the presentation on the developmental neurotoxicity (DNT) HEI. He delineated the DNT-HEI Program Management Team, and the aims of the program:

- Have global public health impact by identifying environmental chemicals with the greatest potential to affect susceptible populations (developing embryo/fetus, infants, children)
- Provide a forum for collaborations among NIEHS scientists, NIH, EPA, and NCTR; engagement with external stakeholders, including clinicians and children's health advocacy groups
- Train the next generation of scientists on all aspects of neurodevelopmental disorders related to environmental exposures and on the very latest technology

Dr. Sills defined the public health problem – an increasing prevalence of learning and behavioral disabilities and neurodevelopmental disorders in children. The economic costs are estimated to be approximately $461 billion by 2025.

The DNT-HEI program is designed to provide information on the potential for DNT risks for the thousands of chemicals that have not been evaluated for DNT. Dr. Sills noted that one of the goals of the program is to aid understanding of mechanisms linked to major neurodevelopmental processes, and said that NTP is developing a battery of *in vitro* assays anchored to key neurodevelopmental processes for evaluating DNT effects. He connected the work to the NTP Translational Toxicology Pipeline, fostering a new framework for applying NTP capabilities in deliberate, integrated, and complementary ways.

Team member Dr. Mamta Behl took the podium to present on NTP's integrative testing strategy for DNT, comprised of *in vivo* testing, DNT screening, exposure assessment, and clinical translation. For DNT screening, NTP has created a free, publicly available, interactive web-based tool: Developmental NeuroToxicity Data Integration and Visualization Enabling Resource, or DNT-DIVER. Dr. Behl described DNT screening work being done in complementary animal models such as zebrafish and planaria, and discussed the creation of a DNT screening battery. As work progresses, the group plans to build on its database and expand to incorporate more chemicals, improve assay coverage, and evaluate the status of current assays. Also, parallel work will proceed on lower-throughput, relevant assays employing genetically diverse mouse and human lines. Goals for ongoing *in vivo* testing include more comprehensiveness and objectivity, reduced time and animal use, and improved translation.

Ultimately, the goals are to improve methods to identify compounds in the environment with unknown neurotoxic potential, provide data for timely public protection, and better understand how *in vitro* studies can inform evaluation in animals and humans.

Clarifying Questions

Dr. Birnbaum asked whether the *in vivo* DNT testing had only been done in rats; Dr. Behl confirmed that was correct. Dr. Birnbaum suggested widening the *in vivo* testing program to include mice in the future to account for genetic diversity.

7.5 Re-envisioning Carcinogenicity Assessment at NTP

Dr. Warren Casey briefed the board on the HEI regarding carcinogenicity testing. He introduced the Program Management Team and presented background information on cancer and its relation to environmental exposures.

To re-envision NTP carcinogenicity testing, it is necessary to move beyond the traditional two-year rodent bioassay, in order to provide information that is more translatable, predictive, and

timely. That will require development of deep knowledge of specific cancer pathways, focusing on those cancers deemed most likely to be associated with environmental exposures. Dr. Casey cited the example of the estrogen receptor pathway to breast cancer, including description of the "tipping point" on the pathway when there is a high likelihood of progression to cancer.

He discussed the importance of accessing disease registries and large cohorts such as the NIH All of Us Program and the Million Veterans Program. Ultimately, by considering individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine.

Dr. Casey delineated the next steps necessary to build the HEI:

- Work with internal and external stakeholders to establish a problem statement and define scope
- Survey available resources
- Identify initial areas of focus
- Develop a strategic plan to set goals and establish timelines
- Develop a communication plan

Clarifying Questions

Dr. Stevens said his understanding is that NTP's focus is hazard identification; he felt that Dr. Casey's presentation implied more of a role for risk assessment, and asked if that was where NTP was moving. Dr. Casey replied that he felt that NTP was "doing a disservice if we do not start incorporating exposure", and that NTP should be able to provide health officials and regulators the information they need to do their jobs more easily. He felt that exposure and exposed populations should be the criteria for prioritization. Dr. Berridge said he understands the debate about NTP not bridging into risk assessment; however, from his perspective, what NTP is doing is contextualizing hazard, which is slightly different. He said that NTP will embrace the notion of putting context around hazard characterization to better enable policymakers, regulators, and the public to make decisions on the information NTP provides. Dr. Stevens noted that he agreed with that approach, but it does represent a scope expansion for the program that the board should consider. Dr. Birnbaum said she approves of the goal of contextualization, which is overdue, but clarified that NTP would not be expanding into the formal risk assessment process.

Dr. Birnbaum also noted that at a recent NIEHS Council meeting, a discussion had arisen about the need to begin looking at environmental exposures that may affect the progression of disease, not just the initiation. Exposure may not be the causative agent of a cancer, but may aggravate and accelerate progression. She said she would expect to see some grant proposals in that area as the ideas take hold.

7.6 BSC Discussion

Dr. McMartin initiated the discussion period covering all the HEIs.

Dr. Berube was the first of four BSC lead discussants. He said he had spent his career in health and crisis communication, and felt that the biggest problem with the HEI approach is the amount of "noise" associated with information on health and medicine. There is an overabundance of

information available, and both the public and professional worlds are experiencing "risk fatigue." He discussed heuristics, specific to medicine and health, in that once a person moves into the role of patient, they change, and the audience dynamics become different. He felt that public communication protocols were missing from the proposal, as the public is not interested in hearing about science. Two additional factors to consider are probability neglect, with the public not fully understanding probability, and the Goldilocks effect, with the public and stakeholders seeking the right amount of information. He said that most of the public is now getting their health information on the internet, relative to other sources, and that a dense textual web page will not work; the new world of science communication is all data driven.

Dr. Eaton was the second BSC lead discussant; his comments addressed the HEIs one at a time. Addressing the CV/cardiotoxicity area, he said he is a bit of a skeptic of the overall importance of the area to NTP, as the heart is not commonly a primary target of environmental exposures. Cardiotoxicity is very important in the world of drugs, but they are taken at relatively high doses by people daily, sometimes for many years. Finding chemicals for which CV effects and cardiotoxicity are possible through screening is important, but when those chemicals are environmental exposures, he wondered how often they would be the drivers of toxicity and not an effect of high doses. The flip side of his skepticism, he said, was the example of the relationship between PM2.5 and cardiovascular disease. Thus, there is much advantage in the HEI screening approaches, and there may be unexpected findings as a result. He emphasized the importance of assay validation for both cardiotoxicity and DNT. Neurodevelopment is one of the most important areas for NIEHS and NTP to build upon, but there is concern that only four compounds have been run through an *in vivo* DNT study. He cited phenotypic anchoring as an important consideration. Regarding the carcinogenicity HEI, he said the change is a very important paradigm shift and long overdue. He said he was excited about the changes, particularly the move toward contextualization.

Dr. Felter was the third BSC lead discussant. She observed that this is an exciting time to be at NTP, both as a scientist and as a member of the public. Regarding cardiotoxicity, she said that looking for early biomarkers is a great approach, to the extent that blood levels can also be measured in order to look at the role of toxicokinetic differences in patient response. In terms of the DNT proposal, she thought that it was one of the most important areas for research, and recommended looking at non-chemical stressors and how they relate to the development of neurological disorders. She felt that the NTP vision for carcinogenicity was fantastic, and was happy to see the focus on protecting the American people and communication. She cited the phenomenon of chemo-phobia in the public as a needed area for improved communication, as translation must address ways to communicate to the public. She approved of the discussion of putting context around hazard, while not encroaching on risk assessment, and noted that while "flipping the paradigm," the traditional, agent-specific work would continue.

Dr. Stevens was the fourth BSC lead discussant, and took a high-level view without addressing any of the specific HEIs. He felt that NTP is an organization in transformation, with the HEIs as the first phase of that transformation. The dialectic of the transformation is the "as is" and the "will be" – NTP is no longer the as is, but is not yet the will be. NTP is an organization that contracted for specific studies, but is now changing into a learning organization, taking on an exponential increase in complexity in the disease processes being studied. He noted that there is a significant operational challenge in looking at the contract model, and that the scientific challenge of taking on much larger areas of pathophysiological complexity is equally daunting.

Those challenges cannot be executed with internal expertise alone, and need to be more externally focused. Work products will need to be sound and unassailable, and may need to change. He approved of the idea of work groups, with internal panels helping external scientists capture the complexity of the scientific areas. He said he was fully on board with the HEIs.

Dr. Eaton added to his remarks related to the CV HEI. He said it was quite important to appreciate that environmental exposures may not cause disease, but may aggravate it, especially in susceptible populations. He found the *in vivo* neurodevelopment work to be exciting, and recommended using functional MRI imaging.

Dr. Slikker addressed the DNT HEI in three areas. First, he wondered how it would be translated to the human condition, as blood-borne biomarkers are one way. It is an area where much can be learned from animal models and translated to humans, particularly examining whether biomarkers could be useful for prediction and translation between species. Second, he referred to *in vivo* imaging, which is expanding, and mentioned cognitive function tests and behavioral outcomes, which can be difficult to monitor. Lastly, he described some of the translatable technologies in the DNT area.

Dr. Behl thanked everyone for their comments. She agreed with Dr. Eaton's point about assay validation and mentioned that phenotypic anchoring will be critical to the DNT efforts. She said that the four *in vivo* DNT studies discussed had been conducted in conjunction with evaluating other non-DNT endpoints in littermates (e.g., subchronic, reproductive & developmental). She appreciated Dr. Felter's comment on non-chemical stressors and agreed that assessing them would be very important.

Dr. Brandt-Rauf wondered if new developments in miniaturizing functional MRI technology could be applied to the rat, and asked if synaptic pruning was being captured in the DNT model. Dr. Behl said that it would be considered as the program goes forward.

Regarding the DNT HEI, Dr. Sass said she was very supportive. She recommended retaining redundancy and not throwing out the DNT test too quickly, and appreciated the focus on neurobehavioral observations. It will be very important to examine groups of chemicals, and a good test case might be the organophosphate (OP) pesticides, which are known to be neurotoxic. Dr. Birnbaum mentioned that Dr. Behl is currently examining the OP flame retardants. Regarding the cancer heat maps Dr. Casey had shown, she felt that they provided valuable information and should not be dismissed because people move around; Dr. Casey said the data were being used to provide context. Dr. Sass said that public health policies that protect the population should be adopted, in order to address the question of health at the population level. She felt that the NTP two-year bioassay is still the gold standard and should not be abandoned, as regulations that protect public health and workers are based on it. Dr. Casey said the misperception is that the two-year bioassay is all NTP does.

Dr. Davis asked how exposure-gene interactions and genetic susceptibility would be incorporated into the CV HEI, and also encouraged Dr. Mattes to undertake a gap analysis in his area. Regarding the iPSC-CMs, she urged retention of the variability between sources of cardiomyocytes. Dr. Mattes said his group is using transcriptomics to assess the cell lines, and, regarding assay validation, he said the labs are putting together a cross-comparison.

Dr. Gamboa da Costa noted a need to include metabolic competency in the current activities, and suggested it be incorporated in the new programs.

Dr. McMartin related some points left by Dr. Ramos, who had departed the meeting. He said that Dr. Ramos approved of the HEI plans, and pointed to the importance of surveying the existing literature for each. He recommended integrating non-invasive diagnostic tools into the clinical population-based studies, and focusing on key regulatory pathways that emerge from co-expression efforts.

Dr. Birnbaum felt that the air pollution story was a great example of epidemiologists and toxicologists learning from each other. She agreed that genetic variability is important, and that different rats and mice can respond differently.

Dr. Chiu said he saw three interrelated issues regarding the three HEIs. First, he felt that screening prioritization in the CV area was important. Second, for all three HEIs, the idea of accelerating or aggravating disease susceptibility was critical, and would potentially influence screening prioritization. Third, he alluded to the issue of hazard versus broader contextualization, citing the example of cancer bioassays being used in a risk context.

Dr. McMartin summarized the session. He said that the board was enthusiastic about the HEI initiatives, and felt that the enthusiasm was highest for the DNT and cancer HEIs. He noted the specific comments made regarding assay validation and metabolic competence, as well as exposure and communication. Evaluating exacerbation of disease by environmental chemicals was an important concept. Although the HEIs are new and important initiatives, it should not be forgotten that NTP does other things quite well, adding to the paradigm as opposed to flipping it.

8. Contract Concept: Genetic Toxicology Testing in Support of NTP

Ms. Jennifer Smith from the NIEHS Office of Acquisitions briefly reviewed the Institute's process for contract concepts. Prior to voting on a concept, the board should engage in a high-level discussion of the project to identify the basic purpose, the scope, and the overall objectives of the work. Ms. Smith delineated several elements that should be considered by the board, and the board was reminded not to discuss specifics.

Ms. Kristine Witt briefed the board on the contract concept. She provided background about the history of genetic toxicity testing at NTP, which has continued since 1979. It is one of the six basic testing areas required by the Organisation for Economic Co-operation and Development in screening chemicals for toxicity. The NTP Genetic Toxicology Database is the largest publicly available single repository of genetic toxicology data in the world and is considered authoritative by groups worldwide. As of May 2019, NTP has completed approximately 5,900 assays. The rationale for the genetic toxicity testing contract includes:

- Assist NIEHS, FDA, EPA, and other government scientists in evaluating chemical toxicity and investigating mechanism of action
- Evaluate all chemicals for genotoxicity under this contract that enter NTP testing
- Consider genotoxicity data in designing NTP testing strategies
- Use genotoxicity data on chemicals in evaluations conducted by the NTP Office of the Report on Carcinogens and in NTP Technical Reports
- Influence international policies in genotoxicity testing and regulation

Ms. Witt described the current genetic toxicology testing capabilities at NTP and detailed several of the newer technologies. The testing approaches proposed in the concept include a mix of the

traditional, well-characterized assays and newer molecular approaches. They would provide enhanced understanding of mechanism of action and quantification of the low end of the dose-response curve and assist in determining benchmark doses/points of departure to support refined risk assessment. The newer molecular approaches, some of which are in early stages of development, would be used as adjuncts to traditional assays to provide clarifying data, while the genetic toxicology community works to achieve international harmonization of protocols.

The proposed statement of work will include all current capabilities plus the requirement for additional capabilities for generating detailed molecular data to better define MOA and low-dose effects, as well as a means for detecting early mutational changes *in vivo* that are consistent with known toxicological endpoints.

Clarifying Questions

Dr. Brandt-Rauf asked about the rationale for retaining the slide-based Comet assay along with the platform-based assay. Ms. Witt said that the platform-based assay is good for testing groups of compounds or for tissue studies, but that the Comet chip platform has not yet been well-validated for *in vivo* testing. Thus, there is still a need for the slide-based assay.

Dr. Davis asked to clarify that this is an R&D contract; Ms. Witt confirmed that it is.

Dr. Afshari asked about data continuity, and whether that would be a requirement under this concept. Ms. Witt noted that all NTP data from the past 40 years are contained in NTP's Chemical Effects in Biological Systems database, and the new contractor would be expected to continue to provide data to the database.

8.1 BSC Discussion

Dr. Davis was the lead BSC discussant. She approved of Ms. Witt's coverage of the intent of the contract, justification for use of the contracting mechanism, and value of the resultant data. Her concern was with the flexibility of the contract itself, particularly in light of emerging new assays that would need to be tested, and asked how that type of testing would be done. Ms. Witt said that to test an assay, samples could be collected and sent to another lab with instructions, and the resultant information used to judge the appropriateness of the new assay. Under the R&D contract, it is possible (and has been done previously) to train a lab in the testing and validation of a particular assay. Dr. Davis asked whether there is adequate support from the contracting office for these types of contracts. Ms. Smith replied that there is a good working relationship with the contracting officer. Ms. Witt agreed with that assessment.

Dr. Stevens said that given this is an expansion in the scope of what NTP currently does in genotoxicity, he wondered if there would be a need to re-prioritize in terms of mutagenesis capabilities relative to next generation sequencing approaches. Ms. Witt replied that it was difficult to answer that question at present, as so much is unknown in terms of new technologies. She did not see the genetic toxicology contract "exploding," even with the advent of new assays rendering existing ones obsolete. She also did not see the contract taking away from any other NTP resources, but rather providing additional information, for example to some of the HEIs.

Dr. Davis noted that since it is an R&D contract, there are capabilities within the contract labs to answer questions beyond just an assay-based readout for a single compound, and that expertise would still be available to NTP as a complementary resource.

Dr. Afshari challenged the concept, and said that to be truly nimble with the new technologies, there must be considerable flexibility. She suggested a split mechanism, with one part of the contract concentrating on delivery of the traditional assays with an eye toward cost, throughput, and value, and a second part offering focus on new technologies. Ms. Witt said that was an interesting idea and noted that the new statement of work addresses nimbleness and flexibility. Dr. Afshari said that the contract seemed to ask contractors to disrupt themselves. Dr. Davis suggested that it might be useful to include academic labs in the R&D contract.

Dr. Stevens endorsed Dr. Afshari's idea, and asked whether the board would be voting on allowing her proposed concept to be included. Dr. Davis said her understanding was that the vote would be about whether the R&D contracting mechanism would be appropriate; Dr. McMartin agreed. Dr. Eaton noted that it was not committing NTP to a single contract, but that after voting in favor, more than one contract could be created – one focused on routine work and another on innovation.

Dr. McMartin called for a vote to approve the contract concept. Dr. Brandt-Rauf motioned that a contract mechanism is the appropriate mechanism to support the proposed activities, Dr. Eaton seconded the motion, and the board voted unanimously in favor.

9. Converging on Cancer Workshop

Dr. Cynthia Rider briefed the board on the Converging on Cancer Workshop, held April 29-30, 2019, in Washington, D.C.

The workshop was co-chaired by Dr. Rider and Dr. Nicole Kleinstreuer, and brought together scientists working in cancer biology, assay development, mixtures toxicology, *in silico* modeling, and cancer risk assessment. Its objectives were to identify technologies and models that can be used in a systems-toxicology approach for cancer risk assessment. Specific applications to understanding the joint effects of multiple chemical exposures were a focal point of the workshop. Prior to the workshop, a series of webinars provided background information to orient participants and facilitate breakout session discussions during the workshop. The workshop included plenaries (webcast), breakout discussions, a poster session, and a real-time polling event. One hundred thirty people registered to attend the workshop in person, with over 500 more registered for the webcast. A workshop report is in progress.

Clarifying Questions

Dr. Eaton asked why the possibility of less-than-additive interactions among mixture constituents was not included in the hypotheses generated during the workshop. Dr. Rider said that that type of mechanism was not ruled out as a possibility.

9.1 BSC Discussion

Dr. Chiu was the lead BSC discussant and had three main comments. First, he commented on the role of mechanisms and adverse outcome pathways. There is a distinction between the hallmarks of cancer and key characteristics of carcinogens, and he felt that moving to a disease-centered versus agent-centered approach could be misleading. He cited the example of the role of chronic inflammation in cancer. His second comment was related to mixtures and focused on the definitions of carcinogen and non-carcinogen – if everything is considered a carcinogen, what is the point of hazard identification? He said that communication is important for putting results in an appropriate context, and supported the idea of starting with co-carcinogen research, because it

would be easier to communicate. His third point related to issues from the breakouts and discussions. For example, it was stated that the two-year bioassay is still the bedrock for cancer-based decision-making, and there was concern that it is premature to consider abandoning it, as no replacement is ready.

Dr. Stevens said he was not a big fan of pathway-based models and delineated several reasons why. He encouraged NTP to look at network-based methodologies instead.

Dr. Eaton said that since multiple chemicals and chemical interactions are being examined, it would be important not to lose sight of the fact that the vast majority of drug-drug interactions and other chemical interactions occur at the very first step, biotransformation, and focusing everything downstream of that would miss important interactions.

Dr. McMartin summarized the board's sentiments. He said that it was felt that the workshop was an important tool that NTP has used to guide its future work in carcinogens, and that the board had made constructive suggestions to focus that work even further.

10. Report on Peer Review of Draft NTP Monograph on Sarin

Dr. Andrew Rooney reported to the board on the peer-review meeting held February 4, 2019, on the draft NTP Monograph on the Systematic Review of Long-Term Neurological Effects Following Acute Exposure to Sarin. He provided background information about sarin and the known health effects of acute exposure. The Countermeasures Against Chemical Threats (CounterACT) program requested that NTP conduct a systemic review to inform the need to develop therapeutics to treat long-term neurological effects of sarin.

Dr. Rooney described NTP's OHAT approach to systematic review and evidence integration used to evaluate the evidence and reach hazard conclusions presented in the monograph. He then specifically summarized the sarin systematic review.

The peer-review meeting was chaired by Dr. Pam Factor-Litvak from Columbia University Medical Center. It was held via WebEx.

NTP concluded that sarin is:

- *Known to be a neurological hazard to humans* in the initial time period of >24 hours – 2 days after exposure based on suppression of cholinesterase, which results in nervous system disruption due to acetylcholine buildup.
- *Suspected to be a neurological hazard to humans* in the intermediate time period of 8 days – 1 year after exposure based on multiple effects, including suppression of cholinesterase, visual and ocular effects, and morphological and histological changes in nervous system tissues.
- *Suspected to be a neurological hazard to humans* in the extended time period of >1 year after exposure based on multiple effects, including effects on learning and memory and morphological and histological changes in nervous system tissues.

The panel agreed with the draft conclusions for all three time periods and provided valuable comments that were considered during finalization of the monograph. For example, NTP expanded the discussion of key data gaps based on the panel's feedback. NTP is in the process of formatting the document for publishing.

10.1 BSC Discussion

Having served as the BSC liaison to the peer review meeting, Dr. McMartin was the lead board discussant. He said it was a very interesting meeting and that he had learned a great deal. He felt that, for a WebEx-based meeting, there was a large amount of discussion. He acknowledged some of the points of disagreement that arose, one of which was some concern about the animal models that had been used for evaluating learning and memory. He congratulated NTP on a great review.

Dr. Stevens said that he loved NTP's evidence evaluation mechanism, not just as a compound-specific mechanism of systematic review, but the process of scoping and evidence mapping to couple to the HEIs.

11. Adjournment

Dr. McMartin adjourned the meeting at 2:45 pm, June 18, 2019.

12. Approval of the Summary Minutes by the NTP BSC Chair

These summary minutes have been read and approved by the chair of the June 17-18, 2019 NTP Board of Scientific Counselors.

[redacted]

Dr. Kenneth McMartin

NTP BSC Chair

Date: 8-15-19