

Summary Minutes December 12, 2018
NTP Board of Scientific Counselors

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I. Abbreviations and Acronyms

BPA	bisphenol A
BSC	Board of Scientific Counselors
CLARITY-BPA	Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity
CRUK	Cancer Research UK
DNT DIVER	Developmental NeuroToxicity Data Integration and Visualization Enabling Resource
DNTP	Division of the National Toxicology Program
ER	estrogen receptor
FDA	U.S. Food and Drug Administration
FOIA	Freedom of Information Act
IRIS	Integrated Risk Information System
MOA	mode of action
NCTR	National Center for Toxicological Research
NGS	next-generation sequencing
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
PD	Parkinson's disease
PFAS	per- and polyfluorinated alkyl substances

II. Attendees

BSC Members and Ad hocs in Attendance:

In Person:

James Stevens, Paradox Found Consulting Services, LLC (interim chair)

Via WebEx:

Norman Barlow, Seattle Genetics

Paul Brandt-Rauf, Drexel University

Weihshueh Chiu, Texas A&M University (*ad hoc*)

Myrtle Davis, Bristol-Myers Squibb

David Eaton, University of Washington (*ad hoc*)

Susan Felter, Procter & Gamble (*ad hoc*)

Daniel Kass, Vital Strategies

Kenneth McMartin, Louisiana State University Health Sciences Center

David Michaels, George Washington University (*ad hoc*)

Anne Ryan, Pfizer (*ad hoc*)

Jennifer Sass, Natural Resources Defense Council

Donald Stump, WIL Research

Susan Tilton, Oregon State University (*ad hoc*)

Katrina Waters, Pacific Northwest National Laboratory

Other Federal Agency Staff:

Goncalo Gamboa, FDA, BSC liaison

John Piacentino, NIOSH

William Slikker, Jr., FDA

Elizabeth Whelan, NIOSH, BSC liaison

National Institute of Environmental Health Sciences (NIEHS) Staff:

Mamta Behl

John Bucher

Vickie Walker

Brian Berridge

Robbin Guy

Mary Wolfe

Linda Birnbaum

Arun Pandiri

Rick Woychik

Windy Boyd

Andrew Rooney

Contract Staff:

Steve McCaw, Image Associates

Kelly Shipkowski, ICF

Anna Stamatogiannakis, ICF

Public:

Ernie Hood, Bridport Services

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened December 12, 2018, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC.

Dr. James Stevens served as interim chair. The other BSC and ad hoc members, along with additional federal agency staff, attended via WebEx. The meeting was originally scheduled for December 11-12; however, due to inclement weather, it was changed to one day and held via remote participation by the BSC.

Dr. Stevens welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. Dr. Birnbaum and Dr. Berridge also welcomed everyone to the meeting, and noted that once again inclement weather had prevented an in-person gathering. Dr. Mary Wolfe, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Report from the NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, briefed the board on NTP developments since the June 2018 BSC meeting.

She described the new NIEHS 2018-2023 Strategic Plan, calling it “an evolution, not a revolution” as it built upon the foundation established in the prior five-year plan.

She updated the board on budgetary and Congressional appropriations matters. Following budget increases in FY2016, 2017, and 2018, the NIEHS budget is slated to increase by \$23.5 million for FY2019. She noted that over 40% of the National Institutes of Health’s (NIH’s) budget is now earmarked. She said that this is the first time in 22 years that NIEHS has had a dedicated budget by the start of the new fiscal year, which began October 1. However, seven of the twelve appropriations bills have not yet been passed by Congress, and there is the possibility of a federal government shutdown affecting those seven agencies. In the event of a shutdown, very few NIEHS employees would be affected. All in all, she said, it is a time of great uncertainty.

Dr. Birnbaum discussed her recent Congressional testimony on “The Federal Role in the Toxic PFAS Chemical Crisis” at the Senate Homeland Security and Governmental Affairs oversight hearing held September 26. Congressional interest in PFAS, or per- and polyfluorinated alkyl substances, is expected to continue in 2019.

She outlined authorization legislation affecting NIEHS that has become law: the National Defense Authorization Act for FY2019 and the Federal Aviation Administration Reauthorization Act of 2018.

Turning to scientific advances, Dr. Birnbaum briefly summarized recent publications, beginning with a One NIEHS paper recently published in *Environmental Health Perspectives*: “*Expanding the Concept of Translational Research: Making a Place for Environmental Health Sciences*”, authored by several Division of Extramural Research and Training, Division of Intramural Research, and Division of the National Toxicology Program (DNTP) employees. She also highlighted two recent publications by DNTP scientists.

She discussed recent developments at the National Academies of Science, Engineering, and Medicine, and featured the long history of engagement and support by NIEHS, particularly the Institute of Medicine Roundtable on Environmental Health Science, Research, and Medicine, which was established in 1998, and the Standing Committee on Emerging Science for Environmental Health Decisions. The latest effort is the Environmental Health Matters Initiative, which NIEHS began scoping in 2015. A concept paper on the initiative was published in December 2017, and in February 2018 an advisory committee was named.

She related a timeline of recent and upcoming events of interest, and featured awards won recently by the *Environmental Factor* newsletter and NIH 2018 Directors Awards for involvement in the *Optimize NIH* program.

Dr. William Slikker, from the U.S. Food and Drug Administration (FDA) asked Dr. Birnbaum to elaborate on the recent increase in Freedom of Information Act (FOIA) requests, and asked whether NIEHS could charge for fulfilling these requests. She replied that in theory NIEHS could charge, but in practice that has not been done. She said that over the past few years, there have been particular law firms that have filed many of the FOIA requests.

V. NTP Updates

Nearing his first anniversary as NTP Associate Director, Dr. Brian Berridge summarized recent NTP developments.

He discussed staff changes, including the retirement of Molly Vallant from the Program Operations Branch after 40 years of government service, as well as newly hired personnel. He updated the board on recent advisory meetings and an upcoming peer review meeting, and reviewed recent NTP publications.

Dr. Mamta Behl, DNTP Toxicology Branch, took to the microphone to describe the new Developmental NeuroToxicity Data Integration and Visualization Enabling Resource, or DNT DIVER. It is a new, public web-application tool that enables users to analyze, compare, and visualize data from divergent assays, and is accessible at the NTP

website. Dr. Behl provided examples of the different types of integrative analyses available through DNT DIVER.

Dr. Berridge returned to the podium to describe recent presentations on DNTP strategic realignment.

Dr. Stevens asked Dr. Behl about the data sources for DNT DIVER. She replied that the assays were derived from contract research organizations, academia, and other government agencies. Dr. Stevens asked how additions to the data set available through the website would be curated. Dr. Behl said internal discussions were considering that issue.

VI. Update on DNTP's Strategic Realignment

Dr. Berridge provided an update regarding the DNTP strategic realignment process. He recounted the previous conversations on the topic, which began at the June 2018 BSC meeting and continued at the October 2018 remote meeting.

He refreshed the board's memory about the background and goals of the strategic realignment, and described the core principles underlying translational toxicology at NTP. He summarized the feedback that had been received at and since the October meeting, including answers to the specific questions that were asked at that session. That feedback was integrated into refined NTP vision and mission statements:

- Vision:
 - To improve public health through the development of data and knowledge that are translatable, predictive, and timely.
- Mission:
 - Collaborate with public stakeholders and global partners to identify and address public health issues.
 - Generate and communicate trusted scientific information to support decision making on environmental hazards of public interest.
 - Lead the transformation of toxicology through the development and application of innovative tools and strategies.

He asked the board to help consider "how we get from where we are to where we want to be faster than we're currently getting there." He noted that there has been significant progress, but NTP is still struggling to become more predictive. He went over the various tools in the toolbox that make NTP unique in the toxicology field. He discussed the development of *in silico* modeling, mechanism of action and mode of action modeling, and health outcomes modeling as they contribute to reporting health effects. "We are making meaningful progress in not only the tools that we use, but how we use those tools," he said.

Dr. Berridge described the Translational Toxicology Pipeline, with added terms designed to help innovate the paradigm, starting with the importance of iterative learning. He also discussed the importance of evolving NTP's portfolio to allow improvement in sustainability and impact, particularly through a new focus on strategic areas of Health Effects Innovation. The Health Effects Innovation program will initially focus on:

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

Each area represents an area of contemporary public health interest, a gap in current NTP capabilities, and an opportunity for NTP to leverage its key value to NIH and the field of toxicology. The aims of the Health Effects Innovation are:

- Define and build a strategic assessment pipeline for key environmental 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 NTP's capability development to problems they're trying to solve
- Maximize the collective strength of the NTP organization
- Build novel partnerships within and outside of NIH

Dr. Berridge illustrated the concept through an example of the cardiovascular health effects strategy.

In summary, he told the board that their feedback had been important and is being integrated into the strategic realignment. He noted that a more deliberate application of the pipeline of capabilities would enable NTP to improve its rate of progress in reaching its "predictive" aspiration. He felt that focusing on discrete areas of health effect innovation would increase NTP's visibility and impact in biomedical science, as well as increasing the value of NTP's efforts to lead a strategic transformation of toxicology.

Dr. Waters encouraged Dr. Berridge to be cognizant of the quality of some of the existing data, ensuring that high-quality data are being utilized. Dr. Waters added that data required for models is often different from other existing data.

Dr. Birnbaum commented that Dr. Berridge "is doing a phenomenal job" as NTP Associate Director. She noted that cardiovascular disease is a major cause of death and disability worldwide, and is a good example of a non-communicable chronic disease. Thus, it is very appropriate for NTP to pursue innovations in the area.

Dr. Stevens complimented Dr. Berridge on the way he had implemented the vision for the NTP strategic realignment around the cardiovascular initiative. He asked Dr. Berridge whether he thought the infrastructure is available to conduct chronic animal studies with cardiovascular assessments. Dr. Berridge replied that the capability exists but needs to be more fully leveraged, and that there are likely to be novel capabilities that should be considered. He added that it would not be enough to simply model the chronic condition, but would also be important to understand what contributes to its development. He said it would be important to leverage what is already known about chronic, progressive disease.

Dr. Davis commented that it would be important to consider genetic predisposition to cardiovascular disease; Dr. Berridge agreed.

Dr. Eaton asked Dr. Berridge to comment on the issue of dose response as it relates to human relevance. Dr. Berridge agreed that dose response is a critical component of human relevance.

Dr. Gamboa noted that one of the challenges currently facing toxicology is how to interpret non-monotonic dose responses, and felt that NTP is well-positioned to address that challenge. Dr. Berridge agreed that NTP should be exploring that area.

VII. DNTP Strategic Realignment: Translation as a Scientific Framework

A. Introduction to the Session

Dr. Berridge introduced the session devoted to the DNTP Strategic Realignment: Translation as a Scientific Framework, to provide a context for the rest of the meeting's presentations.

He discussed the impact, aims, and tools associated with translational toxicology at NTP, with the aspiration of supporting the evolution of toxicology from a predominantly observational science to a predominantly predictive science, with a primary focus on the human condition. He described the role of translation in traditional approaches, government context, precision toxicology, predictive toxicology, and as it applies to new approaches in the field. He noted that historically, there has been a bias toward animal-based studies, but as newer approaches become more prevalent, innovation will turn into practice.

He concluded his introduction by going over the agenda for the rest of the meeting, which was focused on the role of translation.

B. Translating Science to Support Decisions

1) Overview of Assessing Health Effects Evidence

Dr. Andrew Rooney, Acting Director of the DNTP Office of Health Assessment and Translation (OHAT), led the translation session by providing an overview of assessing health effects evidence.

He described how literature analysis activities are the front line for translating published scientific literature into useable information to support public health decisions, with new approaches being developed to better inform evidence-based research decisions. He pointed out that more than two million research publications are issued per year, making the process of identifying relevant information from the volume of available data a growing challenge.

Dr. Rooney presented more details about the systematic review process, which was originally developed to help answer clinical questions. NTP has led the development and conduct of systematic review approaches to address environmental health questions, which require integration of evidence streams from disparate sources, including human data, experimental animal data, and mechanistic data. He described the tools used in systematic review and evidence integration, and provided several examples of instances where systematic review of health effects evidence has been used to translate evidence into conclusions that support policy; these examples included occupational exposure to cancer chemotherapy agents, sarin, traffic-related air pollution, and fluoride.

Dr. Rooney also noted that systematic reviews are not always the most effective answer. They are effective at reaching conclusions and addressing narrowly focused questions, but face several challenges: they are resource-intensive, the process takes time, and they are less effective at addressing broad questions that may include multiple exposures or multiple health outcomes. There has been considerable debate and methods development in the field in recent years, including development of literature scoping, evidence mapping, and literature analysis.

Dr. Birnbaum asked Dr. Rooney how the alternatives he described would address the limitations of systematic review. He replied that in the case of multiple exposures, for example, evidence mapping would be a good first step to lay out the research so that an informed decision could be reached about how to proceed. Dr. Birnbaum added that the issue of multiple effects would be of greater concern than a focus on a single effect. In terms of multiple exposures, focusing on one exposure at a time would not be productive, she observed. Dr. Rooney said that the questions raised by Dr. Birnbaum were issues that OHAT is actively working to address.

Dr. Sass asked how closely OHAT is coordinating with the U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) program. Dr. Rooney said that OHAT coordinates "very heavily" with the IRIS program, including working to harmonize methods.

Dr. Brandt-Rauf asked about consideration of data quality, which could skew the results of systematic review. Dr. Rooney agreed that study quality is a critical element of reaching conclusions based on systematic review.

2) Literature Scoping and Evidence Mapping Approaches

Ms. Vickie Walker from OHAT briefed the board on literature scoping and evidence mapping approaches. Systematic evidence mapping is a systematic categorization of published literature using rigorous, objective, transparent methods. It maps key concepts related to a defined topic such as exposures, health outcomes, or the evidence stream. It usually does not include study quality assessment.

Software tools are used to search, screen, code, and ultimately map the study information into a fit-for-purpose evidence map. The depth of information compiled to support decision making depends on the question. Ms. Walker illustrated the point with three OHAT examples. Less information is required for problem formulation, a moderate amount for health effect or exposure scoping, and more information is needed for a state-of-the-science assessment. In the most intensive "deep dive" mapping, the map and high-level information are captured along with full data extraction and study quality assessment.

Evidence maps support a wide range of goals, with the level of detail and key concepts tailored to fit the question. They facilitate evidence synthesis for decision-making, and provide interactive exploration of the data.

Dr. Stump asked how it would be decided when study quality assessment would be conducted within evidence mapping. Ms. Walker answered that that is the beauty of the fit-for-purpose approach – as the process progresses, study quality assessments can be one of the key concepts for decision-making that the map would inform.

Dr. Gamboa expressed some concerns about the process. First, he said that once these sorts of methods are generated, one may be getting farther and farther away from the original sources of information, with elements of study design that may be lost. He asked whether or not there is a concern that the more process there is, the less meaningful it may be. Ms. Walker said that was one of the points she was making about broad vs. specific categorization of the information and the stepwise approach used in the process. Dr. Rooney added that although the information is not presented as a thorough understanding of any specific study, it is intended to be a quick, interactive

collection of meta-data. He noted that the first step is categorization, which allows a deeper dive for more information that is essential for making decisions.

Dr. Stevens asked whether the lexicons used in the maps are taken from another source or generated internally. Ms. Walker replied that currently they are generated internally; however, work is progressing to integrate them with other sources such as National Library of Medicine search terms.

3) Integrating Literature Analysis into the Research Pipeline

OHAT health scientist Dr. Windy Boyd informed the board about another tool that has been developed to enhance systematic review: literature analysis.

She said that literature analysis would fit in throughout the translational toxicology pipeline, spanning the iterative process. She presented a project focused on environmental chemical exposures and Parkinson's disease (PD) to illustrate the approach.

She provided background information about PD and the environmental exposures implicated in its etiology. She noted that there is a need for better understanding of which environmental factors may be contributing and how they act. The PD project comprised experts in neurotoxicology, *in vitro* screening, toxicoinformatics, and literature analysis, with the intention of identifying potential chemical contributors. An integrated approach was utilized to leverage multiple information sources in order to best inform future research. Literature analysis was employed to identify the evidence base, using semi-automated and manual approaches to screen studies for environmental chemical exposures. She described the tools used to determine the PD evidence map and identify chemical-gene and chemical-assay combinations. Ultimately, interactive evidence maps of published literature were used to inform targeted testing of environmental chemicals.

Dr. Felter asked whether the evidence maps only included primary literature, and excluded meta-analyses and reviews. Dr. Boyd said that the meta-analyses and reviews are kept "in a separate pile," and, while they are not included in the maps themselves, they are referred to.

Dr. Ryan asked whether some of the analysis tools could also be applied to internal study reports versus just published papers. Dr. Boyd said that they could be; for example, in the study she described, more than 90,000 references were captured from PubMed, but if a full systematic review was planned, references beyond PubMed's database would also be captured. Dr. Rooney added that most of what is found is data extracted from the literature, but the tools could also be used with, for example, NTP studies and databases.

Dr. Sass asked Dr. Boyd if the paraquat/PD study included the 2017 publication that used the OHAT approach. Dr. Boyd identified a Brazilian protocol as the study Dr. Sass was referring to, which is an independent systematic review of paraquat and PD. The review itself has not yet been published, she noted, and therefore, not included.

4) BSC Discussion

With no further questions for clarifications, Dr. Stevens turned the board to a more general discussion.

Dr. Slikker said he wished to compare and contrast the new approaches presented to the more traditional methods of risk assessment used over the years. He asked if the process that had been outlined used pre-established criteria based on study quality in advance of a paper's inclusion in the final analysis. Dr. Rooney replied that at the level of evidence mapping, a study quality criterion is not implemented; studies are simply collected without regard to whether they would be sufficient to inform decisions. He said that a hope in the future is to establish a cut-off point for the minimum quality of a study for its inclusion.

Dr. Tilton asked how the issue of publication bias is being addressed in the process. Dr. Rooney said that it is a challenge within systematic review as to whether there is enough evidence to produce a funnel plot for a more quantitative estimate of any publication bias. However, given the heterogeneity among outcomes, endpoints, and methods, a funnel plot is less effective in environmental health questions. He said publication bias is in fact an ongoing issue, and there is hope that it may be overcome during the next decade as more investigators publish negative data.

Dr. Gamboa noted that the NTP is regarded as the gold standard in toxicological research, and expressed concern that conducting exercises such as these presented, without scrutinizing for study quality, might compromise that status. Like it or not, he said, an NTP document would be regarded as hazard identification, and there is a danger of misinforming the public and creating a misperception of hazard where it does not exist. Dr. Rooney said that when systematic review or hazard identification is approached, then study quality must and always will be part of the methodology. However, for an evidence map, there is care to communicate where the project stops in collecting and sorting the evidence. He said NTP is very clear in its messaging that study quality was not considered, and that transparent approach will be continued.

Dr. McMartin asked whether there is a movement in environmental studies for the ability to extract negative or unpublished data, as there has been in clinical trials. Dr. Rooney said there is some progress in the pre-registration of research in the systematic review community. There is a movement toward research protocols being pre-registered, so

that people can be aware of what data were intended to be collected in a given study, and whether negative data were an outcome.

Dr. Davis wanted clarification on whether the strategy for building an evidence map includes an inherent or embedded strategy for assessing quality of all of the data and papers available on a particular topic. Dr. Boyd said that for the PD project, with 2,000 studies, they were unable to employ full, individual study quality assessment; however, they could look at the group of studies as a whole and start to point out some deficiencies or gaps in the entire field. In the Parkinson's field, it was easy to identify that not enough studies of single chemical exposures other than paraquat, or studies of the most disease-relevant endpoints, had been conducted. Dr. Rooney added that evidence mapping is useful to collect the information and decide where to dig deeper, including assessing study quality. That assessment, however, is not part of the first step.

Dr. Felter asked about publications that did not show a positive association, and whether they are still captured during evidence mapping. Dr. Boyd said for paraquat, information on associations was captured for all studies regardless of the direction, although for other exposures, it wasn't necessarily captured whether there was a positive effect. Dr. Felter said it would be critically important to make sure that it is made clear that the process is used to guide research; careful explanation will be helpful, she recommended. Dr. Rooney said that OHAT is working carefully on that communication.

Dr. Rooney returned to the question of systematic reviews and multiple exposures, citing the example of the traffic-related air pollution project. For each of the exposures, there was both an individual evaluation of the data and consideration across the multiple exposures to look at traffic-related exposures associated with gestational hypertension. Dr. Birnbaum noted that traffic-related air pollution has been associated with a multiplicity of outcomes, and asked whether looking at the totality would be the next step. Dr. Rooney acknowledged that it is a challenging question, and in this case, the project's nominators were focused on exposures potentially associated with childhood health effects. A series of other outcomes have been considered, but an overall assessment of multiple exposures and multiple outcomes may not be conducted. He said it would be aspired toward, but along the way there would be the opportunity to reach some conclusions; initially, gestational hypertension. Dr. Birnbaum agreed, but said that the real issues associated with traffic-related air pollution are much broader than just gestational hypertension, including many other developmental effects. She noted that at some point, the conclusion needs to be made that "traffic-related air pollution is bad for you," and not just for pregnant women. She agreed with Dr. Boyd's earlier statement that it can always be said that more data are needed, but "there comes a time when there's enough to say that there is a problem." She cited the

example of pesticides and PD. Dr. Boyd noted that it is not so simple as to call for more studies, but more of the right kinds of studies, studies designed smartly. Dr. Birnbaum agreed, but asked whether or not NTP should be focusing more on the exposures where there is less information, although a certain amount of concern. Dr. Boyd replied that the “living maps” referred to by Ms. Walker would be a way to keep an eye on a certain area of literature to bring it to the level of an evaluation if new information became available.

C. Overview of Genomic Studies on Rodent Tumors and its Translational Relevance

Dr. Arun Pandiri, DNTP Cellular and Molecular Pathology Branch, addressed the board on the NTP genomic studies on rodent tumors, with an emphasis on translational relevance.

He provided a recap of molecular studies on rodent tumors from NTP cancer bioassays and the goals of the program, which were:

- Translational relevance of rodent tumors for human health
- Mechanisms of tumors arising spontaneously or due to chemical exposures
- Inclusion of the molecular data in NTP technical reports

As an example, he illustrated data on large intestinal tumors in F344/NCTR rats exposed to Aloe Vera Non-decolorized Whole Leaf Extract, which have morphological features similar to human colon cancer. They also share similar molecular alterations.

He described the innovative technology driving the science, including next-generation sequencing (NGS) and mutational signature analyses, both of which can be employed to understand mechanisms of disease and toxicity. He delineated several examples of environmental exposures and the corresponding cancers to their respective mutational signatures. The goals of sequencing NTP rodent tumors were to:

- Identify mutation signatures in rodent tumors from defined exposures
- Distinguish spontaneous tumors from chemically induced tumors
- Identify biomarkers for prediction of carcinogenicity from shorter-term *in vivo* studies or *in vitro* studies

Dr. Pandiri updated the board on progress on the whole exome sequencing of mouse hepatocellular carcinomas from NTP studies, including data on mutational signatures in the tumors.

He discussed a collaboration between NTP, the University of California at San Francisco, and the Wellcome trust Sanger Institute to identify mutational signatures

from approximately 150 known carcinogens, in response to the Cancer Research UK (CRUK) Grand Challenge Grant. He also highlighted NTP's collaborations with the International Agency for Research on Cancer and the Ramazzini Institute. He described elements that could lead to future studies or collaborations:

- Cancer mutational signatures from genotoxic chemicals are fairly strong and are probably conserved across species.
- Cancer mutational signatures from non-genotoxic chemicals may be variable due to multiple MOAs.
- Majority of the chemical carcinogens have a non-genotoxic MOA, often with multiple MOAs.
- Generate multi-omics data from rodent tumor tissues resulting from exposures with a well-defined *single* MOA

He said that the rodent models provide significant translational value for human disease, by comparing the tumor mutational signatures with those seen in humans. The integrated –omics approaches will add to the mechanistic understanding of carcinogenesis, and help to identify relevant biomarkers, which can be used for prediction based on short-term *in vivo* screens and *in vitro* screens.

Dr. Stevens asked Dr. Pandiri about mutational signatures in driver genes, as well as at an earlier time point before tumor development, and whether the mutational signature across the genome matched the mutational signature in the driver genes. Dr. Pandiri said a pilot study had been conducted using Sanger sequencing.

Dr. Gamboa asked Dr. Pandiri about secondary mutations not related to an initial insult. Dr. Pandiri said that the mutational signatures do not change, but there is a trend. Two to five genes are conserved across samples, which could be driver mutations. The exposures could potentially be linked to the driver mutations and the types of mutations present in the specific tumor samples.

Dr. Birnbaum asked whether, as different kinds of tumors are sequenced from the NTP Archives' tissue bank, it would help lead to cross-cutting opportunities and potentially to some mechanistic understanding that could help human data as well. Dr. Pandiri replied that it is the goal of the CRUK Grand Challenge grant. Dr. Birnbaum noted that there is a tremendous increase in early onset colorectal tumors in humans. She said it would be interesting to acquire samples from those tumors and see if they have the same profile as older people with the disease. Dr. Pandiri agreed that it is a worrisome phenomenon, and noted that Tom Webster (Boston University) is interested in establishing a database or data bank to collect those tissues. Dr. Pandiri noted that a study is being planned using a PIRC rat model, where the animals will be exposed to known colon cancer-

causing chemicals or some untested chemicals and the resulting colon tumors will be examined by NGS to identify driver genes and mutation signatures.

Dr. Birnbaum asked about the gliomas seen in the radio frequency radiation studies conducted by the NTP and the Ramazzini institute, and inquired as to which gliomas from these studies would be used in the planned NGS studies described by Dr. Pandiri. He said the tumors would primarily come from the Ramazzini institute, because the tissues were collected in ethanol, which better preserved the DNA quality.

Dr. Chiu asked whether the hepatocellular carcinoma work has any potential to address some of the long-standing controversies about the relevance of mouse liver tumors for human health. Dr. Pandiri said that the controversies support some of the future studies to look at non-genotoxic agonists and their signatures, to see how they compare to what is in the database.

VIII. CLARITY-BPA Research Program: Integration Report Preparation Update

Dr. John Bucher, DNTP Senior Scientist, updated the board on progress in the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA) Program.

He provided background information on BPA and the CLARITY-BPA program, which began with the NIEHS funding opportunity announcement in 2010. The final Core Study design was developed and agreed upon by consortium members in 2012. The program's key components were:

- The Core Study, a 2-year chronic study conducted under Good Laboratory Practice at FDA/National Center for Toxicological Research (NCTR)
- Grantee studies by 14 academic investigators
- Integration report, an interpretive integration of findings from both the Core Study and the academic investigational studies

Dr. Bucher discussed the peer review meeting that took place at NIEHS on April 26, 2018, and the NTP Research Report that was released in September 2018. He related the Core Study conclusions and named the academic grantees.

Reports of studies performed by the academic investigators are appearing in the peer-reviewed literature. The next step is to integrate those findings to provide a clearer picture of the potential associations between BPA and any health effects, and to place the findings in the context of prior publications on BPA from the academic investigators and NCTR scientists, using elements of systematic review. Thus, consensus confidence

statements will be developed for association of health effects with BPA exposures and for evidence of non-monotonic dose response.

Dr. Bucher described the planned organization of the reports and provided a timeline for the end products of the consortium, including consortium review and consensus conclusions in Spring 2019, with public peer review expected in Summer, 2019.

Dr. Gamboa alluded to his concern about the inclusion of third-party data from studies conducted outside of the consortium. He was confused about the existence of two reports, and asked Dr. Bucher to elaborate on what each report would contain. Dr. Bucher explained that the first report would include information from the Core Study and the academic studies that has been published from the consortium, using the tissues from the Core Study. It will have data integration from each of the organ systems and a synthesis of the information, plus a conclusion statement. The second report will include information from the grantees and FDA/NCTR from studies done with BPA using their own materials and methods, comparing that information with that generated in the CLARITY consortium. Dr. Gamboa asked what types of consensus conclusions were expected. Dr. Bucher replied that the questions currently are: 1) what level of confidence does the consortium have about whether there are or are not health effects related to BPA exposure in the CLARITY Core Study, and 2) if there is at least medium confidence that there is an effect, does it show a monotonic or non-monotonic dose response? He noted that the range of information received would be interesting in terms of the confidence expressed by the consortium participants.

Dr. Felter asked whether there would be information in the reports on blood levels, especially in the neonatal animals, in terms of non-linearities and kinetics. Dr. Bucher said that the information on kinetics was developed at NCTR in studies carried out prior to the CLARITY-BPA program. Dr. Felter asked if that included neonates. Dr. Bucher asked Dr. Gamboa if he recalled the age of the animals. Dr. Gamboa said they were postnatal day 4.

Dr. Sass raised concerns that had been expressed in some of the public comments, including ones from the Endocrine Society and some of the researchers. There was concern about the integration of the data and how NTP would amalgamate it. Dr. Bucher said that with respect to systematic reviews, he had hoped to emphasize that “these are not systematic reviews” but will use selected elements of systematic review to allow the rigor of consistent evaluation of the studies, but also the transparency to allow a reader to understand where a study scored well or was not considered to be high enough in quality in a certain area. Dr. Sass said the concern is that “everything would be mashed together, and it won’t really be mashable.” Dr. Bucher said that the integration report is intended to provide a snapshot, a collation of the information from each of the organ systems that have been evaluated. It will have the Core Study

information and the information from the various academic laboratories put together in one place, and there will be an integration of that information. There is no intention to do a statistical meta-analysis.

Dr. Stump said he had noted on the NTP website that some of the academic laboratories had no publications listed and wondered whether each of them would be expected to publish. Dr. Bucher affirmed that they would be expected to publish. Dr. Stump asked whether the confidence in the data would be lessened if that did not happen. Dr. Bucher replied that if the academic investigators do not publish their information, then it cannot not be analyzed and included.

Dr. Sass noted that the guideline studies are not published. Dr. Bucher said that in fact they are published as part of the Research Report, in September 2018.

Dr. Birnbaum commented that if studies were being designed or grant proposals requested today, different elements might be asked for than in 2011. Previously, the assumption was that BPA's effects were mediated solely by (estrogen receptor) ER α or ER β , and it is now known that that is not the case, with other estrogens also playing a role and exhibiting different characteristics. It is also known that BPA interacts with multiple other nuclear receptors, and that its interaction with estrogen receptors may be in a different region than the traditional ER α or ER β . She thought that this newer knowledge might impact the CLARITY analyses. She said it constituted an important lesson in keeping one's eyes wide open for unexpected developments. Dr. Bucher agreed, noting that there was considerable discussion about the use of positive controls when the studies were designed.


IX. Adjournment

Dr. Stevens observed that it had been "another exciting day of science," with NTP as an organization in transition with a focus on developing the new strategy. He said it was gratifying to see that the transition is well underway. He complimented the NTP on its ability to take on the complex issues facing toxicology, trying to have an impact on how to do risk assessment and protect human health.

Dr. Stevens adjourned the BSC meeting at 4:15 pm, December 12, 2018.

Summary Minutes December 12, 2018

NTP Board of Scientific Counselors


Dr. James Stevens

Interim Chair, NTP Board of Scientific Counselors

Date: _____

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