Summary Minutes

NTP Board of Scientific Counselors

October 9, 2018

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I. Frequently Used Abbreviations and Acronyms

AAAI	American Academy of Allergy, Asthma and Immunology
ADME/TK	absorption, distribution, metabolism, and excretion/toxicokinetics
AOP	adverse outcome pathway
BD2K	Big Data 2 Knowledge
BMD	benchmark dose
BPA	bisphenol A
BPAF	bisphenol AF
BPS	bisphenol S
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research (FDA)
CEBS	Chemical Effects in Biological Systems
CERHR	Center for the Evaluations of Risks to Human Reproduction
CLARITY-BPA	Consortium Linking Academic and Regulatory Insights on BPA Toxicity
CPSC	Consumer Product Safety Commission
CTB	Computer Technology Branch
DARPA	Defense Advanced Research Projects Agency
DERT	Division of Extramural Research and Training
DIR	Division of Intramural Research
DNT	developmental neurotoxicity
DNTP	Division of the National Toxicology Program
DPRA	direct peptide reactivity assay
ECHA	European Chemical Agency
EDSP	Endocrine Disruptor Screening Program
EFSA	European Food Safety Agency
EPA	U.S. Environmental Protection Agency
EPA IRIS	EPA Integrated Risk Information System
ER	estrogen receptor
FACT	Federal Accountability in Chemical Testing Act
FAIR	findable, accessible, interoperable, reusable
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
GO	gene ontology
h-CLAT	human cell line activation test
HESI	Health and Environmental Sciences Institute
HTT	high throughput transcriptomics
IARC	International Agency for Research on Cancer
ICs	NIH Institutes and Centers
ICATM	International Cooperation on Test Methods
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICE	Integrated Chemical Environment
IgE	immunoglobulin E

ILS	Integrated Laboratory Systems, Inc.
IPS	induced pluripotent stem cells
IVIVE	*in vitro* to *in vivo* extrapolation
LC/MS	liquid chromatography/mass spectrometry
LD50	lethal dose, 50%
LOAEL	lowest observed adverse effect level
LoC	level of concern
MPS	microphysiological systems
NASA	National Aeronautics & Space Administration
NCATS	National Center for Advancing Translational Sciences
NCTR	National Center for Toxicological Research
NGO	non-governmental organization
NICEATM	NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OCPL	Office of Communication and Public Liaison
OECD	Organisation for Economic Co-operation and Development
OESC	Office of Environmental Science Cyberinfrastructure
OHAT	Office of Health Assessment and Translation
OLRP	Office of Liaison, Policy, and Review
ORoC	Office of the Report on Carcinogens
OSC	Office of Scientific Computing
PCRM	Physicians Committee for Responsible Medicine
PFAS	per- and perfluorinated alkyl substances
PFCs	perfluorinated compounds
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PoD	point of departure
QSARs	quantitative structure-activity relationship models
RAPIDD	Rapid Acquisition of Pre/Post Incident Disaster Data protocol
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REACT	Rapid Evaluation and Assessment of Chemical Toxicity
RFAs	Requests for Applications
RFR	radiofrequency radiation
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SBIR/STTR	Small Business Innovation Research/Small Business Technology Transfer
SOT	Society of Toxicology
SSS	Social and Scientific Systems, Inc.
TSCA	Toxic Substances Control Act

II. Attendees

BSC Members and Ad hocs in Attendance:

In Person:
Kenneth McMartin, Louisiana State University Health Sciences Center (chair)

Via WebEx:
Cynthia Afshari, Amgen
Norman Barlow, Seattle Genetics
David Berube, North Carolina State University (*ad hoc*)
Paul Brandt-Rauf, Drexel University
Weihsueh Chiu, Texas A&M University (*ad hoc*)
Myrtle Davis, Bristol-Myers Squibb
David Eaton, University of Washington (*ad hoc*)
Daniel Kass, Vital Strategies
David Michaels, George Washington University (*ad hoc*)
Kenneth Ramos, Arizona Health Sciences Center
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

National Institute of Environmental Health Sciences (NIEHS) Staff:

Brian Berridge	Robbin Guy	Amy Wang
Linda Birnbaum	Gloria Jahnke	Mary Wolfe
Virginia Guidry	Ruth Lunn	

Contract Staff:
Canden Byrd, ICF
June Mader, GOFORWARD, LLC
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 October 9, 2018, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC.

Dr. Kenneth McMartin served as chair. The other BSC members and ad hocs attended via WebEx. Public attendees watched the webcast.

Dr. McMartin welcomed everyone to the meeting and asked BSC members, ad hocs, and other attendees to introduce themselves. He noted that Dr. James Stevens and Dr. Susan Felter were unable to attend. Dr. Birnbaum and Dr. Berridge also welcomed everyone to the meeting, and noted the novel nature of the gathering, with most attending remotely. Dr. Mary Wolfe, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Strategic Realignment Update

Dr. Berridge addressed the attendees, providing an update regarding strategic realignment at DNTP. He noted that the meeting was designed to continue and complete the conversation on the topic, which began at the June 2018 BSC meeting.

He refreshed the BSC's memory about the background and goals of the strategic realignment, and described the core principles underlying translational toxicology at NTP. He delineated the format for the meeting, which revolved around concepts called The Why, The What, and The How. Prior to the discussion session, he presented draft vision and mission statements, as part of The Why section, with words and phrases representing core principles highlighted:

- Vision

  To **advance public health** and the discipline of **toxicology** through the use of **innovative** tools and strategies that are translatable, predictive, and timely

- Mission

  Solve contemporary public health problems by characterizing contemporary environmental hazards in **human-relevant** systems. Inform a future state that meets rapidly changing public health needs **by bridging mechanistic insights to phenotypic outcomes**.

Dr. Berridge went over the DNTP Translational Toxicology Pipeline Plan, which is central to the strategic realignment.

V. BSC's Perspective for NTP Regarding Strategic Realignment

Dr. June Mader of GOFORWARD LLC served as the discussion session's facilitator. She reviewed the process and format for the discussion, beginning with The Why.

A. The Why

The Why section began with a poll of the BSC members, who could vote electronically in reply to a multiple-choice question:

- NTP should be distinct from a traditional academic research effort or even an industrial safety/hazard assessment function. Consider what makes NTP unique in the community of toxicology and hazard/safety assessors. Is it NTP's:
    A. Relative "freedom to operate"?
    B. Experience set?
    C. Tools?
    D. Ability to maintain focus on a challenge for prolonged periods of time?
    E. Something else?
- Polling Question: What unique value could/should NTP bring to this field of science (or science in general)? What do you think?

Board members voted as follows:

A. 3/15 (20%)
B. 2/15 (13%)
C. 0/15 (0%)
D. 8/15 (53%)
E. 2/15 (13%, 1 vote recorded verbally)
No answer 0/15 (0%)

Dr. Mader asked Dr. Sass, who voted "E, Something else", to elaborate on her vote. Dr. Sass said she felt that what is unique about NTP is the way they do science that directly impacts important policy questions and policy decisions for the federal agencies and programs they support. Dr. McMartin said that due to a technical problem he had been unable to vote, but he would also have voted "something else." He said that NTP is distinct in their ability to take on large efforts that other stakeholders and groups are not willing to take on. He provided examples of projects such as crumb rubber and cell phone radiation.

Dr. Mader asked the panelists to comment on why "D, Ability to maintain focus on a challenge for prolonged periods of time" is important to the NTP mission and vision. Dr. Ryan said that Dr. McMartin's comments resonated with her, and agreed that NTP's size and mission allow them to focus on the difficult problems. Dr. Barlow expressed the same sentiment, emphasizing that the ability to focus on a problem for an extended length of time is what makes NTP unique compared to industry. Dr. Chiu said he had chosen "A, Relative freedom to operate", as NTP is able to choose to address large problems that are also policy-relevant. He felt that "A" encompassed many of the other answer choices. Dr. Eaton reiterated the importance of NTP's ability to use state-of-the-

art science to address important public health policy questions. Dr. Brandt-Rauf, who chose “D”, noted that the biggest challenges are the ones that take a long-range perspective, such as climate change. He said the funding cycle for academia is short-term, and that NTP has the ability to ignore such constraints. Dr. Tilton commented that the board’s responses seemed to be similar, focusing on NTP’s ability to address challenging questions, despite the individual choices.

Dr. Berridge requested to probe the concepts that had been presented. He was interested in what types of problems the BSC thought would best fit the long-range operational model they had been discussing, and gave example problems including broad classes of compounds, complex biological issues, environmental agents that mechanistically contribute to cancer, and challenges that affect a broad portion of the population.

Considering how NTP might fit into the existing research landscape, which includes industry and academia, Dr. Afshari suggested a focus on more chronic health issues, particularly ones that may have environmental causes, such as cancer, reproduction and development, lung disease, and neurological disease. Dr. Waters agreed with Dr. Afshari’s comments, and said that thinking about chronic health problems from long-term exposures is the type of problem that NTP could provide impact to. She also noted that the NTP should continue to think about predictive toxicology, because it is not feasible to perform in-depth mechanistic studies of one compound at a time. Even high-throughput screening is providing more information about acute toxicity than endpoints relevant to chronic toxicity, she added. Thus, it would be important to develop approaches and assays to build more predictive models of which chemical classes or subclasses of compounds are likely to be involved in chronic health effects, she said.

Dr. Davis said that one of the things that makes NTP unique within the community is its positioning within both NIEHS and HHS, which allows direct interfacing with other institutes that are focused on disease. She noted that this positioning provides the opportunity to see gaps in disease state modeling that don’t incorporate the influence of the environment and/or chemicals on disease.

Dr. Eaton discussed the importance of mechanistic studies, particularly in validating animal models. He said that mechanistic research can provide good information but can also be misleading; therefore, it is important for NTP to incorporate both mechanistic information and more standard animal assays.

Dr. McMartin reiterated Dr. Davis’s comments about the importance of NTP interfacing with NIH disease-focused institutes. He noted that these institutes tend to look at disease from a pathological perspective, and don’t necessarily consider the contribution

of the environment to a particular disease. He particularly noted the possibility of working with NCI or NHLBI.

Dr. Mader again showed the draft mission and vision statements (see above) and asked for comments from the panel.

Dr. Stump liked the inclusion of “human-relevant” in the mission statement. Dr. Michaels felt that the word “phenotypic” was too complex for the public to understand and suggested changing the term “phenotypic outcomes“ to “health outcomes”. Dr. Berridge jocularly noted that it was his “all-time favorite word,” but that it would be acceptable to drop it.

Dr. Davis said she enjoyed the inclusion of “the discipline of toxicology” and the concept of innovation in the vision statement.

Dr. Chiu was concerned that the statements about characterizing hazard inadvertently connoted a “one hazard at a time” approach, when in fact humans are exposed to a variety of hazards. Dr. Birnbaum noted that NIEHS defines the environment quite broadly, to include many environmental stressors beyond just chemicals. She wondered if that concept should be included in the mission or vision statements, with the understanding of the complexity of the environment.

Dr. Sass asked why the term “public health” was used, as opposed to “environmental health.” Dr. Berridge replied that “public health” is fairly encompassing and a term readily understood by people, which denotes NTP’s focus on the human condition. Dr. Birnbaum noted that when the term “environmental health” is used, it’s almost always necessary to define it.

Dr. Brandt-Rauf said it would be important to think about who the primary audience would be for the statements. Dr. Berridge agreed that that is a challenge, and that the desire is for a mission and vision that have a broad resonance with the breadth of NTP stakeholders, which include the scientific community, regulators, and the general public.

B. The What

Dr. Mader moved the discussion on to The What.

- We shared with you our concept of a *Translational Toxicology Pipeline* with an intent to benefit public health. In that context, *translation* refers to deriving insights into potential human hazards from non-animal test systems. Inherent in that aim is a need for NTP to be “human relevant.”
    - What does it mean for NTP’s work to be “human relevant” and how should we incorporate this objective into the assessments that NTP carries out?

Dr. Ryan, the first lead discussant, said that when she thinks about "human relevant," she considers the multi-disciplinary integration of some of the skillsets at NTP, quantitative *in vitro* and *in vivo*, and how that can be applied to human health. She noted that it is moving from observational or phenotypic studies to more predictive approaches that minimize animal use and are more mechanistically focused to understand the end state in humans. Being able to communicate the insights gained from mechanistic studies to the diverse set of stakeholders – the public, the regulators, and the scientific community – is also important.

Dr. Michaels, the second lead discussant, said that he did not think the public understands the relevance of the new tests being developed by NTP. Even without the ethical issues related to animal studies, it is still difficult to provide all of the information needed to understand exposure/outcome relationships and mechanisms. The public and stakeholders are confused, he noted. He said a crosswalk is needed on exposure/outcome relationships, showing how the new techniques and measures relate to what has been long known through epidemiology and traditional toxicology. The same question relates to risk assessment. It is important to keep working with humans, relating some of the new biomarkers to human biomonitoring, even thinking about some intervention trials to measure the effect of interventions on biomarkers. More and more of that type of activity will show the relevance of that important work to humans.

Dr. Stump, the third lead discussant, said that when looking at human relevant research, the starting point is which compound or compounds NTP is choosing, and whether NTP is picking compounds most relevant to potential risk to the population. The other key is to go beyond hazard identification to work to gather enough information so that risk assessment can be done. This is critical in terms of looking at the likelihood of human exposure to those compounds, he observed – what is the quantity of exposure, the route of exposure, and how will the models extrapolate to bioavailability in humans and metabolic profiles?

Dr. Berridge thanked the panel for their feedback, and issued a challenge to the group. He said that even as medicine is becoming more precise and more personalized, toxicology is more population-based. There is some personalization in looking at particular life stages and individual genetic susceptibilities. He said there are many different directions that could be pursued in the context of human relevance, depending on the desired precision. He asked the panelists to comment on how far down that road NTP should reasonably go. He was interested in the group's perspective on how to find the right balance between population toxicology – big risks to a lot of people – versus a more personalized toxicology, which medicine and science are moving towards.

Dr. Davis said she had grown to appreciate the distinct difference between hazard identification and "the rest of the story": the likelihood of exposure to an adequate

amount of a toxicant to experience the hazard, the investigation of the mechanism, and whether it is appropriate for human safety.

Dr. Chiu discussed the idea of personalized toxicology, which he said is context-dependent. It would be extremely important for drug side effects, for example, but he said he was a bit wary about whether decision-makers were ready for that type of information. He observed that moving toward the ability to identify individuals who may be more at risk presents a conundrum in terms of public health policy. "I think there's a lot of policy and value judgments involved in moving toward personalized risk assessment or personalized toxicology beyond an individualized treatment or risk/benefit at an individual level as it would be with a pharmaceutical," he concluded.

Dr. Stump noted that the process should be stepwise, to first identify hazard, and then understand the potential risks. He felt that it is always better to have more data than less.

Dr. Sass agreed that mechanistic information is useful, but questioned the idea that it is needed to predict risk. She said that chemicals, exposures, populations, and genetics are all complicated, and that pathway-based approaches can be biased; hazardous information isn't always transferable across a group of chemicals.

C. The How

Dr. Mader introduced The How discussion segment.

- We shared with you an intent to build greater confidence in regulatory and policy decision-making from *in silico*, *in vitro*, and literature-based evidence.
    - What challenges will NTP face attempting to do this? What approaches might we use to build confidence in decision-making from non-traditional endpoints or evidence?

Whiteboard Question: Are there partnerships that we should be leveraging?

Dr. Chiu was the first lead discussant. He said that to him, the topic related to the previous human relevant discussion. He felt that the greater extent to which the new approaches are thought to be human relevant, the greater confidence there will be in regulatory and policy decision-making. There needs to be a good translation step, with IVIVE as an example of converting data into metrics that fit into the current regulatory and policy risk assessment processes. There are many issues in terms of validation, in assessing an actual gold standard. Confidence in the new methods for decision-making will require dialogue with regulatory and policy decision-makers, as well as with risk assessment mediators such as EPA or FDA. He said it is a combination of the scientific

confidence as well as the confidence in terms of how they can be easily folded into the existing processes.

Dr. Afshari was the second lead discussant. She said that mechanistic information will be necessary to ultimately rely on *in silico* or *in vitro* approaches. One of the strengths of NTP has been toxicologists and pathologists working side by side. It will be important not to lose sight of that combination as the scientific approaches move forward. Understanding mechanisms and whether they lead to adaptive or maladaptive effects is also important, which is where the expertise and training of particularly the pathologists will be key. NTP will need to invest in the new technologies in terms of leveraging animal and human studies. She cautioned that it is easy to get caught up in the excitement of the new approaches, but that it would be important to step back and ask, "Is this really going to make a difference in terms of how we make public health decisions? How does it inform where we need to focus or accelerate our work? How does it inform what we need to buy?"

Dr. Davis was the third lead discussant. She focused on "build confidence" in the discussion question. To build confidence, data will be needed. NTP's role will be to provide appropriate data to help the field feel that it is going in the right direction with a particular assay or approach. Thus, NTP had the right idea when ICCVAM was created. The opportunity to revitalize ICCVAM to provide more information on defining the context of use and the limitations of the approaches would build a great deal of confidence in the use of the tools. Since it is coming from NTP, confidence in the data is already somewhat inherent, she noted. The ICCVAM approach would be a good model, although it has issues in terms of turnaround time and people diving so deeply into validation that they never get out. Using the ICCVAM approach as a model would be a good place to start in building greater confidence.

Dr. Brandt-Rauf said that being honest about limitations would be critical. He cautioned against over-promising and under-delivering. It would be necessary to be confident, but also to be humble about limitations.

Dr. Tilton followed up on Dr. Davis's comment on context of use, and said that there is a need for a clear statement of purpose in how these tools will be applied. She questioned whether these new approaches would be used for prioritizing chemicals, replacing assays for apical endpoints, or providing links between *in vitro* or *in silico* data and traditional apical endpoint data.

Next, Dr. Mader introduced the Whiteboard Question (see above) and asked for councilors to fill in their responses. Among the many suggestions for partnerships that should be leveraged were:

- HHS, EPA, FDA (to a greater extent)
- Other NIH institutes
- European regulatory agencies, such as the European Chemicals Agency
- International agencies and consortia
- HESI
- CDC, NCEH/ATSDR, and NHANES
- Green chemistry experts
- NGOs/non-profits
- Media, especially digital stakeholders
- Think tanks, building on real world data and health records
- Disease-focused foundations, where the environment is a clear contributor
- Public advocacy/disease groups
- Sponsors who plan to submit data in regulatory filings

D. Rapid Response Questions

Dr. Mader introduced the final segment, which consisted of three Rapid Response Questions. Dr. Berridge explained that the context for the questions was to identify some areas where there is much conversation developing in the community. As NTP starts to think about creating programmatic areas of focus, the desire is for the BSC to offer some immediate reactions to the areas being discussed.

Rapid Response Question #1:

- Complex 3D *in vitro* systems are rapidly evolving. What is the opportunity for those systems to enhance our efforts? What are the challenges?

Dr. Tilton was the lead discussant. She said there are a number of interesting opportunities for NTP related to 3D *in vitro* systems. One of the primary goals for NTP should be to provide a link between high-throughput *in silico* or *in vitro* endpoints and traditional apical data from animal testing. She said there are a few specific opportunities for NTP in this area, related to translational goals. For example, it will be essential to use these systems to improve the predictive capability of high-throughput *in vitro* assays by confirming their mechanistic relevance. Thus, NTP can help fill the gap between data that is collected on early molecular initiating events or early cellular events. The systems could also contribute to the development of new, novel endpoints *in vitro* that are reflective of short- and longer-term phenotypic outcomes in animals *in vivo*, focusing on translating mechanisms across models. It may also involve development of animal-based 3D *in vitro* systems for comparisons. A benefit of the models is the ability to quantify pharmacokinetic parameters for tissue-specific responses *in vitro*, improving IVIVE ability. It is also possible to simply use these

complex *in vitro* systems as an alternate *in vitro* model, based on the fact that they share some structural and functional multicellular communication and signaling and metabolic activity with the tissues they are intended to mimic. Thus, they can be applied in specific studies. The challenges involve the "rapidly evolving," complex 3D *in vitro* systems. There is not agreement on any single platform or technology, thus there will be challenges with standardization, and each technology has its own technical challenges, advantages, and disadvantages. NTP should keep its fit-for-purpose focus, she recommended, while keeping in mind the benefits of some of the platforms. She added that NTP is uniquely positioned to evaluate the potential to use the systems for the translation of shorter- and longer-term outcomes in animals, and to evaluate their relevance to human health effects.

Dr. Barlow commented that this is an opportunity for NIEHS and NTP to begin to get a better understanding of some of the systems, and focus on those that have the most potential to translate to humans. The major challenge is that the field is exploding, with many different systems that function in different ways, and more coming out all the time; it will be important to understand where to make investments.

Dr. Chiu described the Tissue Chip Validation Center recently funded at Texas A&M. He said they found the technology transfer to be quite challenging. There is not a lot of interest in toxicity related to environmental compounds, and it is a struggle to add environmentally relevant compounds to their testing. In terms of translation, he said there has been good work on IVIVE, but that it is a challenge to translate the various details related to microfluidic systems to *in vivo* settings.

Dr. McMartin said that another challenge is that many of the 3D systems have advanced to include co-cultures to try and develop a more organ-like system, but they don't necessarily recapitulate multi-organ interactions.

Dr. Birnbaum said that a challenge she sees is the inherent variability between different samples, due to the variability among people.

Dr. Afshari said she saw variability as an opportunity as well as a challenge. Modeling a disease phenotype in a 3D culture may repeat the same challenges seen with animal models.

Dr. Eaton noted that he had been working in the area, and said that one of the advantages of these systems is the ability to utilize human and animal tissues in parallel. He reiterated the point that they are not high-throughput systems, but offer tremendous potential along with many challenges; NTP should continue to watch the area and get involved in it.

Dr. Davis said that in using these systems, it may be possible to define a very specific context for use simply by using them to answer particular questions. It would be “an incredible way” for NTP to take a unique opportunity for use of the systems.

Rapid Response Question #2:

- Computational approaches are also rapidly evolving. How should NTP be engaging and capitalizing on machine learning capabilities? Where are those capabilities best applied? What are the challenges?

Dr. Waters was the lead discussant. She noted that computational approaches are not restricted to machine learning, which is currently rising to the forefront in terms of algorithms and useful technologies. The community has been applying machine learning approaches for quite some time, so it is not that novel at this point. There are new and novel approaches such as deep learning that will benefit from consideration of their use, but how they are *not* useful should also be clearly described. They could be useful in identifying mechanistic assays for evaluating chemicals that may have chronic effects, in applying transcriptomics data, and in understanding population-based genetic susceptibilities. Good regression-based approaches are needed to understand dose-responsive associations. Challenges often involve having a gold standard to validate that a machine-learning approach is actually working, which will be important for getting regulatory buy-in and acceptance of any kind of predictive approach. There are still many data gaps that limit the application of machine-learning approaches. Assessment of the white space for the data gaps and working to fill them in will be important.

Dr. Sass said that much of the information from various computational approaches gets put into models, which tend to resemble meta-analyses, with many parts being assembled from many sources. There could be bias and error built into the models, particularly intentional or directional bias. She had recommendations to share about how to think about models when using them to fill in data gaps, in checklist form. She mentioned that there is a real public concern about proprietary models, and that it would be a problem to maintain public trust if the agencies continue to use them.

Dr. McMartin reiterated Dr. Brandt-Rauf’s caution that it would be important to not over-promise in this area.

Rapid Response Question #3

- There is a growing interest in revising our current approaches to carcinogenicity hazard assessments for a variety of reasons. What do you think about current approaches to carcinogenicity testing? What are the best opportunities to refine or revolutionize that approach?

Dr. Barlow was the lead discussant and said that as a pathologist, he is quite comfortable with the current approaches to carcinogenicity testing, which may continue to be the state of the science in terms of acquiring hazard assessment data that can be translated to humans. Overall, people are comfortable with the current approach, based on a vast amount of historical data in strains of rats and mice, even while recognizing that the strategy may need to change. New opportunities exist, but should be judged on their potential translation to humans. If new techniques can be shown to provide accurate hazard identification and risk assessment that is translatable to humans, they should be adopted, but that cannot be said at present. Some may offer the opportunity to conduct shorter-term acute studies revealing effects on pathways that will predict outcomes in chronic studies, obviating the need to perform the longer-term carcinogenicity studies. Assessment of the early toxicology data will be key to understanding mechanisms and pathways. NTP's experience provides vast experience and tissue samples to contribute to assessing new toxicological approaches. He said that integrating the data across multiple disciplines will be important. "The revolution will continue slowly … but we've been pushing in many different directions already, and it's a matter of time to get the right data set to feel comfortable and say that we don't need to run these studies any longer, but I think we're still a ways away."

Dr. Eaton said that two-year bioassays will continue to be important, but improvements are needed in assessing pharmacokinetics and pharmacodynamics before the studies are conducted, to help determine the appropriate dose ranges.

Dr. Afshari recommended care in terms of re-endorsing the current strategy around two-year bioassays, as it is a slow, expensive approach that is unable to meet the demand and comes with a high degree of uncertainty. Given costs, the field should strive to reach further. There is a groundswell in the field of activity to develop mechanistic weight-of-evidence approaches to determine pathways of interest. NTP should be serving as a clearing house at the center of those activities.

Dr. Chiu emphasized that there is a need for hazard assessment, and the work that has been done at NTP has been critical in terms of advancing data integration for assessing hazard and causality. There may need to be adjustments in study design to accommodate new approaches such as benchmark dosing, with fewer animals per dose group and more dose groups. He also alluded to discussions around the use of a single, inbred strain as opposed to using genetically diverse populations of mice.

VI. Reports on Peer Reviews for the Report on Carcinogens

A. Introduction

Dr. Ruth Lunn, Director, Office of the Report on Carcinogens (ORoC), provided the BSC with background information about the Report on Carcinogens (RoC), along with details about the process involved in preparation of the report. The current step is to present a summary of a peer review to the BSC and subsequently to prepare a revised draft RoC monograph, which is then finalized, published, and released, given the necessary approvals.

In this meeting, ORoC members would present peer review findings for two substances recommended for listing in the RoC: *Helicobacter pylori*, and antimony trioxide.

B. *Helicobacter pylori*

Dr. Lunn presented the background information about the *Helicobacter pylori* (*H. pylori*) draft monograph peer review. The external peer review was carried out by three reviewers, who communicated by letter. The reviewers largely agreed with the NTP preliminary level of evidence conclusions, which found sufficient evidence for gastric cancer and gastric MALT lymphoma (all three reviewers agreed), and sufficient evidence for gastric adenoma in mice and gerbils and gastric lymphoma in mice (two reviewers agreed; one agreed in principle). The reviewers concurred with the NTP preliminary listing recommendations, which concluded that *H. pylori* is *known to be a human carcinogen*.

Another part of the monograph deals with information on efforts to prevent *H. pylori*-related cancers – so-called “screen and treat” programs. That section includes expert consensus statements. The peer reviewers agreed with limiting the assessment to gastric cancers as evidence for other types of cancer is not as developed.

Dr. Kass asked for clarification about the global burden and attributable risk (estimated to be 6.2%), specifically regarding what percentage gastric cancer represented. Dr. Lunn responded that she believed it was 80% or higher.

C. Antimony Trioxide

Dr. Amy Wang from the ORoC reported on the peer review of the RoC draft monograph on antimony trioxide. She provided background information about the substance, its uses, and the peer review panel members. The panel concurred with the NTP draft recommendation regarding exposure to antimony trioxide. It agreed unanimously with the NTP draft recommendation that there is inadequate human evidence for determining carcinogenicity. Dr. Wang described the key issues that were discussed at the peer review panel meeting, which addressed the issue of male rat lung tumors. Regarding

animal studies, the panel agreed unanimously that there was sufficient animal evidence for antimony trioxide carcinogenicity. Dr. Wang described the supporting mechanistic evidence included in the draft monograph. The panel agreed unanimously with the NTP preliminary listing recommendation, which said the antimony trioxide should be listed in the RoC as *reasonably anticipated to be a human carcinogen*.

Dr. McMartin was the BSC liaison to the antimony trioxide peer review meeting, which was webcast. He said the panelists were all experts in the areas under consideration and there were excellent discussions of the different points raised. He said, “it was a very excellent meeting.”

VII. Next Steps

Dr. Berridge summarized the meeting’s proceedings and assessed the steps to be taken as a result of the deliberations. He thanked the BSC for its level of engagement in providing feedback to NTP.

He went over several of the major points that had been raised, including NTP’s ability to address difficult challenges in the long term, and desire to transition to more predictive methods and more chronic health outcomes. He noted the good input about the mission and vision statements, especially regarding how to make them more generalizable to a broader stakeholder group. He noted the discussion about human relevance, including the idea that modeling platforms should reflect human biology, and the concept that both population-based and personalized toxicology require ongoing attention. There was also discussion about building confidence in non-traditional approaches, with recognition of the benefit of demonstrating human relevance in building that confidence. Feedback on the potential uses of 3D systems noted how they might be incorporated into the traditional paradigm to fill a gap between high-throughput systems and lower-throughput, *in vivo* systems. Dr. Berridge mentioned that NTP may have a role in demonstrating how such systems could be applied. There was also discussion of new computational approaches and the state of carcinogenicity testing.

Dr. Berridge said the next steps would be to pull all of the disparate pieces of feedback together and put the BSC’s input into the context of other conversations that are being held, which will help NTP to better understand what its portfolio needs to evolve to be. “With your input, we’re getting a better sense of where our focus should be, what strengths we truly need to leverage…we’ll take that, we’ll mold it into putting more detail into the strategy, and then we will take the opportunity to share that with you in more detail at our next meeting in December,” Dr. Berridge concluded.

He thanked the BSC for its input.

VIII. Adjournment

Dr. Birnbaum said she was quite pleased with the way the format of the meeting worked, and thanked the board members for their active involvement and participation. She thanked the staff for their presentations.

Dr. Wolfe thanked everyone for their contributions.

Dr. McMartin adjourned the BSC meeting at 4:00 pm, October 9, 2018.

[redacted]

Dr. Kenneth McMartin

Chair, NTP Board of Scientific Counselors

Date: 12-2018