Summary Minutes

NTP Board of Scientific Counselors

December 7-8, 2017
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I. Frequently Used Abbreviations and Acronyms

AOP  adverse outcome pathway
API  application programming interface
BD2K  Big Data 2 Knowledge
BMD  benchmark dose
BPA  bisphenol A
BSC  Board of Scientific Counselors
CASIS Center for the Advancement of Science in Space
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
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
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
LD50  lethal dose, 50%
LoC  level of concern
MPS  microphysiological systems
II. Attendees

Members in Attendance:

Norman Barlow, Johnson & Johnson
Paul Brandt-Rauf, Drexel University (December 7 only)
Myrtle Davis, Bristol-Myers Squibb
Steven Markowitz, City University of New York
Kenneth McMartin, Louisiana State University Health Sciences Shreveport, (chair)
Kenneth Ramos, Arizona Health Sciences Center (December 7 and by phone on December 8)
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Jennifer Sass, Natural Resources Defense Council
James Stevens, Eli Lilly
Donald Stump, WIL Research
Katrina Waters, Pacific Northwest National Laboratory

Other Federal Agency Staff:
Goncalo Gamboa, FDA, BSC liaison
Danilo Tagle, NCATS

National Institute of Environmental Health Sciences (NIEHS) Staff:
Scott Auerbach  Laura Hall  Rick Paules
Mamta Behl  Alison Harrill  Julie Rice
Brandy Beverley  Janice Harvey  Cynthia Rider
Linda Birnbaum  Ron Herbert  Veronica G. Robinson
Chad Blystone  Stephanie Holmgren  Andrew Rooney
Windy Boyd  Michelle Hooth  Kristen Ryan
John Bucher  Kembra Howdeshell  Andy Shapiro
Warren Casey  Troy Hubbard  Dan Shaughnessy
Brad Collins  Gloria Jahnke  Keith Shockley
Helen Cunny  Grace Kissling  Nisha Sipes
Sally Darney  Nicole Kleinstreuer  Robert Sills
Michael DeVito  Ruth Lunn  Stephanie Smith-Roe
Anika Dzierlenga  Dave Malarkey  Molly Valant
Susan Elmore  Scott Masten  Suramya Waidyanatha
Sue Fenton  Elizabeth Maull  Nigel Walker
Gordon Flake  Barry McIntyre  Vickie Walker
Paul Foster  Alex Merrick  Amy Wang
Rachel Frawley  Mark Miller  Kristine Witt
Dori Germolec  Esra Mutlu  Mary Wolfe
Virginia Guidry  Arun Pandiri
Robbin Guy

Public:
Brian Berridge, GlaxoSmithKline
Reshan Fernando, RTI International
Ernie Hood, Bridport Services
Kyathanahalli Janardhan, ILS
Steven Levine, Monsanto
Jessica Riker, NCSU
Charles Schmitt, Kelly Government Services
Marjo Smith, SSS
December 7, 2017

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened December 7-8, 2017, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Dr. Kenneth McMartin served as chair.

He welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. Dr. Mary Wolfe, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Report of the NIEHS/NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, briefed the BSC on developments at NTP and NIEHS since the June 2017 board meeting.

She began with a report regarding the federal budget and appropriations. The House and Senate have both recommended increases in the NIEHS and NIH appropriations, while the president’s request represents a significant decrease in both appropriations. The president’s budget is not expected to advance, and the House has already passed its appropriations, representing increases in both the NIEHS and NIH funding. Superfund funding is anticipated to remain flat in the new fiscal year. Dr. Birnbaum said there is guarded optimism that the expected appropriations will pass. However, a possibility of automatic cuts triggered by the sequestration provisions of the Budget Control Act of 2011 remains. The government is currently operating under a Continuing Resolution, and it is anticipated that another one will be enacted to support operations through January.

Dr. Birnbaum described some of the key recent legislative development potentially affecting NIEHS: Airplanes Health Impact Study, Federal Accountability in Chemical Testing (FACT) Act, and perfluorinated alkylated substances (PFAS) provisions in the National Defense Authorization Act. She also discussed Congressional briefings by Friends of NIEHS; one held in October on environmental factors and autoimmune diseases, and another planned for March, 2018 on environmental factors and neurological diseases.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP staff or NIEHS grantees.

First, as an example of “One NIEHS” research, she described a paper on the effects of various bisphenol compounds on androgen receptors. She also summarized a recent publication on new rodent population models, including the Collaborative Cross and Diversity Outbred models. She discussed four recent Division of the National Toxicology Program (DNTP) publications: mountaintop removal mining, the Tox21 10K library, HepaRG cells for liver toxicity screening, and a proposed alternative chemical disinfectant.
In recent NIEHS highlights, Dr. Birnbaum mentioned organizational and personnel developments in NIEHS information technology, including establishment of the Office of Environmental Science Cyberinfrastructure (OESC), which will coordinate IT activities in the Computer Technology Branch (CTB), the Office of Scientific Computing (OSC), the Office of Data Science (ODS), and the Office of Communication and Public Liaison (OCPL). She reported on the status of Reimagine HHS initiatives and the federal government hiring freeze. She announced that Dr. Brian Berridge would officially become the Associate Director of NTP and the Scientific Director of DNTP on January 7, 2018. She described progress on the formulation of the new NIEHS Strategic Plan, with publication anticipated in the fall of 2018.

She also mentioned several recent events and upcoming meetings on the NTP calendar.

V. US Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medical Products

Dr. McMartin introduced the session, which would encompass multiple presentations, with opportunities for clarifying questions after each individual talk.

A. Introduction to Session/US Strategic Roadmap

NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods (NICEATM) Director Dr. Warren Casey provided an overview of the roadmap session, with background information about the process, the organizations involved (NICEATM, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)) and the timeline.

He said it was the third and final installment of presentations to the BSC about the strategic roadmap, and thanked the committee for its useful feedback. He noted that the expectation is that the document will be completed by late December, with publication anticipated in early January 2018.

He described the existing, linear process of new methods evaluation — working from method development to validation to regulatory acceptance and industry adoption — as lengthy, inefficient, and resource-intensive. It no longer meets the needs of federal agencies and is not compatible with modern approaches to toxicity testing. The process envisioned in the roadmap integrates the existing elements into a holistic approach, where all elements are in progress simultaneously: technology, utilization, and confidence interact, encompassing the strategic goals involved:

- Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries
- Help end users guide the development of the new tools needed to support their needs
- Foster the use of efficient, flexible, and robust practices to establish confidence in new methods
Dr. Casey emphasized that the process must be driven by the utilization element – understanding the needs of the customers and asking for their help to accomplish fulfillment of those needs, in a top-down approach, which has not been the case in the past. "If we can get the agencies involved from the top down, validation is going to go much quicker, and we’re actually going to end up with a lot more methods that are more human-relevant and reduce the use of animals," he observed. He noted that the approach is already in use within the agencies.

1) Questions for Clarification

Dr. Markowitz asked what happens when the users and scientists have different standards for validation that may be in conflict. Dr. Casey said it would be important to make sure ahead of time what the expectations are for the validation, requiring considerable communication. He noted that much of the initial work would be done in industry, in the non-regulated or pre-regulated space.

Dr. Stevens asked Dr. Casey to share his perspective on the major drivers of the alternative testing approach. He felt that there are gaps in the ability to adequately assess human health, as a data-driven decision, and that there are moral and ethical considerations. He asked Dr. Casey how to navigate between those drivers, and what could be done to help that communication. Dr. Casey replied that there are actually four major drivers: ethics, protection of human health, financial incentives, and Congressional mandates. He added that for the roadmap to move forward, it is important to understand who the customers are and their needs.

Dr. Davis noted that Dr. Casey had presented a strategy, but “a strategy is not an agenda.” She supported the concept of emphasizing strategy over any individual agendas.

Dr. Brandt-Rauf added his support for the process, but said he was concerned that there may be elements that are usable but may not achieve the goal of protecting public health. Dr. Casey said that is one reason to involve end users up front, at the beginning of the process.

Dr. Ramos asked Dr. Casey if he agreed that the strategy should inform the process, or whether the agenda should drive the strategy. Dr. Casey said that “the strategy is by far the most important thing.” The agenda, he noted, would be specific to the different sectors, and that the effort has been to look across all of them from the various stakeholders to find the common features that all agree would need to be in place for the new approach to work. Dr. Ramos asked Dr. Casey to elaborate on the point he had made regarding the need for consistency; whether it was consistency as an aspirational goal, or consistency in the actual strategy, or consistency related to the questions being asked. Dr. Casey said it is aspirational and addresses the pragmatism of how things need to happen, particularly consistency in the context of use and the need for stakeholder engagement. Training and education are also elements seen in all of the plans. Dr. Ramos asked if there are mechanisms in place to bring the stakeholders together to discuss the different programs, with that being an element of consistency. Dr. Casey replied with examples of coordination, noting that one thing that has made
ICCVAM successful in recent years is acknowledging that the agencies each have their own agendas.

Dr. Sass said she and her organization are very supportive of the initiative. She noted that although it is difficult to engage the public in the process, it is nonetheless very important to do so, and it currently is not being done very well. She said that there needs to be assurance that the approach works prior to engaging in its promotion. “To get the public support and promoting them, we need to get that last R, we need to get it right, we need to show the public that we can make decisions that will get it right,” she observed. She applauded the effort to increase attention to formulations and mixtures.

B. Agencies’ Implementation of Strategic Roadmap

NICEATM Deputy Director Dr. Nicole Kleinstreuer briefed the BSC on progress in implementation. She outlined six key endeavors to support implementation plans:

- Coordinate activities via ICCVAM workgroups
- Draft a scoping document to identify U.S. agency requirements, needs, and decision contexts
- Coordinate efforts with stakeholders
- Identify, acquire, and curate high-quality data from reference test methods
- Identify and evaluate non-animal alternative approaches
- Gain regulatory acceptance and facilitate use of non-animal approaches

She cited the need to prioritize endpoints to focus based on:

- Agency needs
- Expected impact on animal use
- Mechanistic understanding
- Ability to mitigate obstacles
- Available resources

She also cited the need to coordinate efforts with ICCVAM’s international partners. She described the active ICCVAM workgroups, including Acute Toxicity, Skin Sensitization, and Ocular and Dermal Irritation, which each have implementation plans underway. She provided details on those implementation plans, including details on the Acute Toxicity Workgroup’s implementation activities addressing the six areas outlined above. The activities include an invitation to the international modeling community to build models to predict acute toxicity using a large data set curated in-house by NICEATM, comprised of 9,000 chemicals with associated lethal dose, 50% (LD50) values. Dr. Kleinstreuer discussed several of the major events leading up to the current point, and noted the Society of Toxicology annual meeting in March 2018, which will include a session on “Implementing new approaches to evaluate the safety of chemicals and medical products in the United States.”

Challenges to implementation remain, including:

- Animal methods currently provide the reference data for evaluating alternatives
Data requirements vary across U.S. and global regulatory authorities and are often ambiguous

Overcoming regulatory and institutional inertia

1) Questions for Clarification

Dr. Stevens felt that LD50 was a very actionable target where there can be an impact, with demonstrable evidence that regulatory decision-making in the pharmaceutical industry can be moved away from acute toxicity testing. He wondered what would be next on the list. He expressed that when animal tests have been replaced by in vitro approaches, they are often better predictors when based on exposure, not administered dose. He asked how ICCVAM is thinking about addressing that question in the context of the acute toxicity target for replacement. Dr. Kleinstreuer replied that the short-term focus is on not just acute oral systemic toxicity, but on the entire 6-pack of acute toxicity tests. Longer-term, the focus certainly includes the more complex toxicology endpoints such as developmental and reproductive toxicity, she noted. She added that regarding exposure, there is work in progress at NTP on IVIVE and development of open source tools to translate in vitro bioactivity concentrations to in vivo exposures, and vice versa. “Models that incorporate both the exposure considerations and mechanistic considerations into their output will probably end up being the most successful in terms of end user implementation,” she observed.

Dr. Waters asked about the issue of LD50 variability in the various chemicals, and whether there is a single source of variability. Dr. Kleinstreuer said that the analysis effort thus far had not been to identify whether there are key individual or multiplex drivers of variability. Unfortunately, many of the primary studies are not available for the vast majority of the LD50 data obtained to date. Data-sharing initiatives and NICEATM efforts to extract protocol and other details from the data evaluation records will be important to addressing the variance question.

Dr. Waters noted that in her presentation, when she was discussing the non-animal approaches, Dr. Kleinstreuer had seemed to focus on computational methods, and asked whether in vitro screening approaches would be considered in those assays as well. Dr. Kleinstreuer replied yes, and described the importance of hybrid approaches combining chemical/structural features, physico-chemical properties, and in vitro bioactivity information on critical targets would probably be the most successful.

Dr. Barlow asked what additional data there might be along with the LD50 data. He said the value in computational approaches would ultimately be multiple endpoints in vitro that can be modeled to predict what happens in vivo, which speaks to the importance of continuing animal work, which remains the regulatory standard, while the direction is toward in vitro approaches. Dr. Kleinstreuer said that was an excellent point that highlights the fact that there are efforts going on in parallel. On the one hand, there is a drive to show that the current animal-based regulatory tests can be replaced by computation models or non-animal approaches, which need to be evaluated based on data to show how well they can predict apical endpoints. On the other hand, there is an
equally important, parallel effort to try to shift toxicology from a purely apical endpoint to a much more mechanistically driven framework that considers human biology.

Dr. Stump asked how the models would be evaluated, given the amount of variability in the older studies, with very inaccurate LD50 values. Dr. Kleinstreuer said that for the majority of chemicals, one LD50 value is being used; however, for approximately 1800, there are three or more LD50 values. It is assumed that if the chemicals that were only tested once had been tested multiple times, they would show similar variability in LD50 values, allowing bootstrapping to arrive at confidence intervals.


Dr. Brian Berridge from GlaxoSmithKline briefed the board on roadmap discussions at the September 18-19, 2017 SACATM meeting, which was held on the NIH campus in Bethesda, MD.

He noted that along with SACATM members, ICCVAM representatives, International Cooperation on Test Methods (ICATM) representatives, NIEHS staff, and ILS staff, there were 24 attendees from public health organizations, representing substantial interest and engagement with those groups.

After briefly describing the strategic roadmap and the fundamental shifts in approach it advocates, Dr. Berridge related several of the salient discussion points from the meeting. He said there was good support for the roadmap from all stakeholders, and good alignment on the need for a shift in strategy. Consistent discussion points among the attendees included:

- Early engagement with end users and stakeholders
- Importance of articulating the problems, with particular reference to patient/public health concerns
- Clearly identifying context of use
- Developing a framework for building confidence in new methods
- Clear messaging (advocacy and acceptance) from regulatory stakeholders
- Challenges
  - Benchmarking against animal vs. human outcomes
  - Importance of international partnerships and acceptance
  - Alignment on risk assessment vs. hazard identification
  - Alignment on assessment of toxicity vs. safety
  - Metrics
    - Animal numbers
    - # validated assays
    - Testing waivers

In summary, Dr. Berridge said there was broad support for the need and content of the roadmap, that it should integrate well with and support ongoing ICCVAM efforts, and represents a potentially significant turning point in the application and impact of alternative methods.
D. NCATS Tissue Chips Program Update

Dr. Danilo Tagle, Associate Director for Special Initiatives at the National Center for Advancing Translational Sciences (NCATS) updated the board on progress in the NCATS Tissue Chip Program.

He provided background information about the program, which traces its existence from NIH-FDA partnership activities in 2010 designed to advance regulatory science. A Microphysiological Systems (MPS) Workshop in 2011 with the Defense Advanced Research Projects Agency (DARPA), FDA, and NIH discussed how to launch the effort into a full human body-on-a-chip program. The program itself began in 2012, with a goal to develop an in vitro platform that uses human tissues to evaluate the efficacy, safety, and toxicity of promising therapies. The human tissue constructs represent all ten human physiological systems. Dr. Tagle described the timeline of the MPS Program from its inception in 2012 through its completion in 2017. The last three years of the program were focused on functional validation.

He detailed the MPS Consortium, led by NCATS in partnership with other NIH institutes and centers, FDA, and DARPA, along with industrial and academic participants, including biotech spin-off companies. NCATS recently awarded funds to Resource Centers at MIT and Texas A&M, which are designed to conduct independent analytical validation of tissue chip platforms, along with an award to the University of Pittsburgh to maintain an MPS database. Eleven organ-on-a-chip platforms have been or are currently being tested.

Dr. Tagle described the partnership between NCATS, the National Aeronautics & Space Administration (NASA), and the Center for the Advancement of Science in Space (CASIS) for testing on MPS technology on the International Space Station, looking at the effects of microgravity on the systems. He discussed the five projects that have been awarded under the Request for Applications (RFA).

He also described a $75 million, 5-year UG3/UH3 program, MPS for Disease Modeling and Efficacy Testing, aimed at developing highly reproducible and translatable in vitro models for preclinical efficacy studies using MPS.

He noted that there will be a Keystone Symposia conference in April 2018 at Big Sky, Montana, “Organs- and Tissues-on-Chips.”

1) Questions for Clarification

Dr. Birnbaum pointed out that NIEHS has funded the tissue chip work on the female reproductive system and the Resource Center at Texas A&M.

Dr. Ramos asked how genetic diversity is being integrated into the tissue chips. Dr. Tagle described several methods currently being used, including some ideas that are still in the planning stages, depending on progress in the Precision Medicine Initiative’s genetic sequencing. Dr. Ramos asked how restricted the tissue chip program is at this point in time in terms of the pools that can be drawn from to establish models. Dr. Tagle said there needs to be a convergence of advances in terms of induced
pluripotent stem cell (IPS) technology and reducing chip technology to practice. Dr. Ramos urged that current understanding of genomic influences on response be incorporated into the tissue chip paradigm, including pharmacogenomically and toxicogenomically active genes that have been identified. Integrating that knowledge with tissue chip technology will add value, he said. Dr. Tagle acknowledged that those efforts are already underway.

Dr. Birnbaum noted that the genetic diversity plans in the program are very relevant for pharma, but perhaps less so for general public health and population testing. She recommended further discussion about how genetic diversity in the genomic space can be modeled. She said that the NASA efforts are exciting, particularly the study of astronaut twins looking at biomarkers. Dr. Tagle said that twins are not necessary for the tissue chip work. Dr. Birnbaum said it would be useful to compare twins, with one going to space and the other staying on the ground. Dr. Tagle said there is an effort to capture the epigenetic changes.

E. NIEHS SBIR/STTR Grants Supporting NICEATM

Dr. Dan Shaughnessy reported to the board about Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) grants supporting NICEATM.

He provided background information about the two programs, including the three funding phases: feasibility, full research/competing renewal, and commercialization. The programs emphasize development of novel approaches using state-of-the-art technologies for environmental health sciences. He described the applicable current SBIR/STTR solicitations:

- RFA-ES-15-016: NIEHS SBIR Phase IIB awards for Validation and Commercialization of Approaches to Reduce Animal Use in Toxicology (U44)
- RFA-ES-17-007: Novel Assays for Screening the Effects of Chemical Toxicants on Cell Differentiation (SBIR R44)
- RFA-ES-17-008: Organotypic Culture Models Developed from Experimental Animals for Chemical Toxicity Screening (R43/R44)

1) Questions for Clarification

Dr. Birnbaum pointed out that this was an excellent example of the “One NIEHS” concept.

Dr. Walker asked how stakeholders would be involved in the review process, in that it was recognized that it is important to get the regulators involved early. Dr. Shaughnessy said that it is recommended that potential applicants talk to industry and pharma whenever possible. Applications with letters of support tend to do much better, he noted. It shows that the applicant has thought about the market and the need for the new product. He acknowledged, however, that university researchers may not necessarily have the contacts with industry or pharma to gain recommendations.
2) **BSC Discussion**

Dr. McMartin initiated a board discussion period covering the entire session.

Dr. Stump was the first BSC reviewer. He said he was pleased with the progress that had been made by NICEATM, and approved of starting with acute toxicity, as it would be somewhat easier than more complex models. He felt that one major challenge is fear of missing something by regulators, so giving them confidence in alternative methods is vital. Validation as a concept is another challenge, particularly in validating *in vitro* models from a GLP perspective. He approved of the intention to get end users involved from the start of the process, as well as having the pharmaceutical and chemical companies involved. He pointed out that the contract research organizations should also be involved, as they are often who will actually run the assays, due to outsourcing. Regarding risk vs. hazard, he noted that toxicologists are doing more risk assessment these days than they have in the past. Overall, he felt that things are moving on the right track with NICEATM’s efforts.

Dr. Davis was the second BSC reviewer. She said that the building of confidence is a critical element of the strategic plan. Focus on regulatory acceptance is fine, but there are decisions made, especially within pharma, which are not regulatory-facing, she observed. She felt that that point should not be under-emphasized. She also recommended that the strategy not be aligned with specific technologies.

Dr. Casey agreed with Dr. Davis that the non-regulated space would be a key to success.

Dr. Kleinstreuer addressed the concept of Good Laboratory Practice (GLP) in an *in vitro* scenario and how that type of mentality might be extended to the modeling world in areas such as quantitative structure-activity relationship models (QSAR) and computational modeling. She cited NICEATM's close work with the Organisation for Economic Co-operation and Development (OECD) on QSAR model validation principles, which are analogous to GLP.

In terms of economics being a driver of adoption of alternative methods, Dr. Stevens noted that as MPS technologies become more complex, costs will go down, perhaps reaching the point where the cost of doing an animal study versus the cost of doing a microphysiological study will become similar. It means that fewer compounds will be tested. He said that high-throughput assays can be really effective to stratify compounds into bins of hazard identification, i.e., what is more or less hazardous. Risk assessment, however, requires mode or mechanism of action or understanding of physiologically based adverse outcome pathways. It is “an underappreciated gap,” he observed. The assumption is being made that human tissues in culture will extrapolate more effectively to human health than *in vivo* animal data will. He felt that the problems he was describing could undermine the great progress that could be made in improving safety assessment. He encouraged NICEATM to be more explicit in effectively separating the strategies and agendas, with a firm understanding of context of use.

Dr. Casey responded that he does not buy into the concept that human cells are
human-predictive. There is very little data to support that, and he agreed that it has not been communicated effectively.

Dr. Barlow agreed that animals would be critical to the ultimate acceptance of alternative methods, with prediction to humans being the ultimate goal, eventually directly from *in silico* platforms. The animal work must still be done, because currently that is where there is the most knowledge and expertise for predicting human outcomes. As alternatives are investigated, it is important to read across all of the data, he noted. He agreed that often assays are developed and used for compound screening without the intention being regulatory acceptance.

Dr. Waters noted the issue of metabolic competence with regard to the MPS technologies, particularly in terms of dose and exposure measures to help capture variability. Dr. Tagle described a recent paper addressing metabolic competence associated with the blood-brain barrier, gut, liver, kidney, and muscle, showing metabolic competence with a number of tested compounds. He said it had been shown that that kind of data could be generated using MPS. He also replied to Dr. Stevens’s point about economics, noting that costs could be reduced by integrating biosensing capabilities into the system. He added that improved predictivity would result in cost savings, as well as the human health benefits and shortening the drug development process. Dr. Casey noted that the ToxCast program is looking into developing metabolic-competent tools, and that NTP’s Biomedical Screening Branch has worked on developing metabolically competent systems.

Dr. Brandt-Rauf wondered if the panel had any thoughts on how artificial intelligence and machine learning might help the process. Dr. Kleinstreuer replied that as the dimensionality of data increases to the point where deep learning approaches are necessitated, NICEATM is fully vested in investigating those methods, both within the group and in collaboration with other groups worldwide. “Machine learning is a tool we use every day in building our computation models for predicting endpoints, and not just using the high-throughput screening data,” she noted. Dr. Casey agreed, but observed that it is easy to overfit the models. Dr. Tagle added that one group is developing a brain-on-a-chip system, using machine learning to develop an algorithm for prediction. Dr. Davis wondered if the issue was just terminology at this point. Dr. Stevens said that way too much time is spent on classification models and machine learning, and that more efforts should be focused on modeling the underlying biological systems themselves. Dr. Kleinstreuer observed that the models are only as good as the features they use, so biologically informed feature sets should be used to yield biologically meaningful models or modeling output. She said there is a parallel effort to develop mapping of the different *in vitro* high-throughput screening assays to their gene and molecular targets as well as where those targets fall in mechanistic pathways. Dr. Stevens said that dimensionality reduction methodologies must be part of that strategy, to avoid overfitting. Dr. Casey said the question is an active issue in terms of acute toxicity classification, with practical consequences. Dr. Stevens agreed that that is an area where classification models and machine learning can be particularly useful, especially in helping determine tests that do not need to be done.
Dr. Gamboa felt that until metabolism is incorporated, it would be difficult to engage certain stakeholders, such as the FDA. The "tissues-on-chips" (not "organs-on-chips," he said), without metabolism, are missing a crucial element when conducting a risk assessment for a compound. He cautioned about over-promising — “I think we need to be honest about what we can deliver right now.”

Dr. McMartin summarized the session. He felt that the sense of the board is that it is very enthusiastic about the strategic plan, with good progress. There was enthusiasm for starting with the simpler models such as acute toxicity. The board expressed concerns about how the strategic plan was being implemented in certain ways. There were concerns about internal exposure dose, metabolism, and how they would be modeled by some of the in vitro, in silico, or computational modeling approaches. He noted that the board cautioned against over-promising about capabilities, particularly for public acceptance.

Dr. Sass added that the concept that animal models don’t work leaves the field vulnerable to challenge by litigation for all of the regulations based on animal models. Dr. Birnbaum said it is well known that animal models are useful, even if they are not always right. Dr. Casey noted that that is one of the challenges NICEATM/ICCVAM faces with communication and messaging.

VI. NTP Assessing Alternative Approaches

Dr. Bucher introduced the session, which was designed to describe NTP’s approach to assessing alternative approaches with respect to developmental neurotoxicity, dermal hypersensitivity, and perfluorinated compounds, along with new strategies for handling data.

A. Integrated Testing Strategies for Developmental Neurotoxicity (DNT)

Dr. Mamta Behl from the DNTP Toxicology Branch briefed the BSC on recent progress in assessing DNT.

She provided background information about DNT and its importance, as well as the evolution of DNT assessment at NTP. Until 2009, there was no NTP method to evaluate compounds with potential for DNT on a routine basis. There was also an increase in “class” nominations, resulting in the need for an efficient approach to identify and characterize compounds with DNT potential. A two-prong approach was developed; screening for compounds with DNT potential and improving in vivo DNT testing.

Dr. Behl described the steps taken to develop a comprehensive DNT screening strategy, which culminated in convening a workshop held in September, 2017, following the creation of a battery for comprehensive screening based on a library of more than 80 compounds from Tox21 Phase III. The library was made available to researchers interested in evaluating high-throughput and/or high-content cell-based and alternate animal model systems for DNT. The workshop brought together investigators from academia, industry, and government laboratories who evaluated the library using assays to look at DNT. It was designed to discuss how different test methods could be
integrated into a battery of cell-based and alternative animal systems to prioritize compounds for DNT testing. The battery was intended to address developmental toxicity, developmental neurotoxicity, receptor-based systems toxicity, and neurotoxicity. The workshop participants were asked to help determine which of the assays are critical for the battery, how the data can be integrated across assays, and how the information might be used in regulatory decision-making.

NTP has proposed an approach for DNT data analysis based on benchmark concentration calculations. A website for workshop participants was created for data visualization, allowing visualization of several related parameters.

The major areas of discussion at the workshop included:

- Experimental design considerations
- Biological coverage: what are we missing?
- Exposure & metabolism
- Data analysis & modeling
- Regulatory perspective

Moving forward, there will be continued global discussion on the utility of the approach and data analysis strategies, establishment of an external scientific panel to evaluate the battery, continued refinements of the battery, and implementation of the battery as a routine NTP screening approach.

1) Questions for Clarification

Dr. Brandt-Rauf said he was troubled by the idea of extrapolating from *in vitro* tests or even animal tests to humans, particularly when dealing with the nervous system or neurodevelopment. He noted that there may be functional changes that are only apparent in humans, particularly emergent properties of consciousness and behavior. He asked Dr. Behl if those emergent properties could ever be effectively addressed. She replied that the current strategy is a start, and that if it is not done, there would be chemicals out there and no one evaluating them. She agreed that the nervous system is quite complicated, but felt there is a place for the proposed type of assessment.

Dr. Stump noted the issue of exposure from maternal sources, i.e., direct vs. indirect exposure, and asked Dr. Behl if that was being examined. She replied that there had been some conversations about exposing during an early phase and looking at later effects, perhaps using alternate animals such as zebrafish. Also, there had been consideration of incorporating the blood-placental barrier and the blood-brain barrier into the models.

Dr. Sass pointed out that the DNT guideline study was not very sensitive, and that the pesticide toxicity database contains many studies that were poorly designed. She felt that DNT issues should remain at the forefront, and applauded the program outlined by Dr. Behl.
Dr. Ramos asked Dr. Behl to speak more about the positive and negative controls built into the system. She described the negative controls as compounds that were not shown to be positive for DNT. The positive controls were selected based on at least two or more publications where there was evidence of DNT in animals or non-animals. Dr. Ramos asked if that meant that only the chemical side of the experiment had been controlled for, and not the biological side. He was interested in non-neuronal cells in culture. Dr. Behl said the goal was to characterize different modes of action of DNT as well as development toxicity, with that being the focus of the positive controls. Regarding the spectrum of models depicted by Dr. Behl, Dr. Ramos asked if the intent was to utilize all models equally, or to triage chemicals with the simpler models and then advance as appropriate. Dr. Behl said the intent was to look at the models in parallel. Dr. Walker noted that all but two of the compounds were from the Tox21 10K library.

Regarding the positive controls, Dr. Barlow asked if there was any other toxicity associated with the compounds. Dr. Behl described the compounds involved, such as acetaminophen and vitamin C.

Dr. Bucher described the NTP activity to use zebrafish in toxicology testing. Zebrafish is seen as a good model of DNT.

**B. NTP Approaches to Assessment of Dermal Hypersensitivity**

Dr. Dori Germolec from the DNTP Toxicology Branch reported to the panel on NTP activities regarding assessment of dermal hypersensitivity. She noted that skin sensitization assays, primarily through the work of ICCVAM, are the leaders in *in vitro* methods.

She described skin sensitization, the existing *in vivo* tests, and current U.S. regulatory requirements and considerations. She provided more details about the local lymph node assay (LLNA), the *in vivo* test currently used by the NTP.

She discussed the Global Skin Sensitization Project, an analysis of available non-animal approaches based on OECD-submitted case studies, in collaboration with Cosmetics Europe. The project employed a 128-substance dataset of LLNA and human data, evaluating performance of *in vitro* assays for assessing dermal sensitization. The assays were the direct peptide reactivity assay (DPRA), KeratinoSens, and the human cell line activation test (h-CLAT), each of which addresses key events in the OECD AOP for skin sensitization. Dr. Germolec presented data for each of the assays in comparison to the LLNA. The studies found that:

- Most non-animal testing strategies evaluated so far perform better than the LLNA at predicting human skin sensitization hazard and potency.
- Combining multiple *in vitro* assays and *in silico* methods or physico-chemical properties increases the ability to predict sensitizers.

NTP is seeking to expand coverage of the chemical space, as most chemicals used in the validation of non-animal test methods have been cosmetics ingredients. NTP is supporting testing of other types of chemicals in three alternative test methods: DPRA,
LuSens, and h-CLAT. Nominations have been compiled from multiple ICCVAM agencies. Thus far, a total of 266 chemicals have been nominated, and NTP has procured 135 chemicals for the initial testing phase. Testing began in late 2017, and additional testing of approximately 100 chemicals will follow in mid-2018.

1) Questions for Clarification

Dr. Markowitz asked whether there are plans to test mixtures. Dr. Germolec said that many of the nominated compounds are mixtures.

Dr. Brandt-Rauf asked if the cells used in the KeratinoSens and h-CLAT assays are human cell lines, and whether they are immortalized. Dr. Germolec said that they are immortalized human cells.

Dr. Ramos asked Dr. Germolec to elaborate on how the program will differentiate between an acute response that triggers cytokine release from the keratinocyte, which could result in much false activity signal, relative to the endpoint of T-cell proliferation. Dr. Germolec said the question involves the differentiation between irritancy and sensitization. She said that irritancy is a much more local response. With an allergic sensitization, there will be an immunoglobulin E (IGE) response, which is not measured in in vitro assays. She said that different endpoints have been used to distinguish between irritants and sensitizers. Dr. Ramos asked whether the assays are actually being developed to screen for allergic dermatitis, rather than other forms of dermatitis. Dr. Germolec said they do not necessarily screen for irritancy, although there is some crosstalk, because clearly some compounds do both.

Dr. Stevens asked Dr. Germolec to elaborate on the data she had presented and how she had derived the calculations of sensitivity and specificity. She described how the machine learning approaches were used to calculate those parameters. Dr. Kleinstreuer added that it had been a very unbiased approach using 54 different models. Dr. Stevens asked if any models, absent any wet lab in vitro data, had performed as well as models that did include in vitro wet lab data. Dr. Germolec said none had.

2) Dr. Bucher recognition

Dr. Walker presided over a short segment recognizing the 10 years of service by Dr. Bucher as NTP Associate Director. He presented several images from past years, as well as a montage of images showing Dr. Bucher’s proclivity for wearing sweaters. Following the slides, Dr. Bucher was presented with a custom-made sweater with the NTP logo. All present then gathered in the NIEHS cafeteria, where Dr. Bucher was honored with a sheet cake.

C. Rapid Evaluation and Assessment of Chemical Toxicity (REACT): Per- and Polyfluoroalkyl Substances (PFAS)

Dr. Michael DeVito, acting chief of the NTP Laboratory, briefed the BSC on the development of the REACT PFAS project.
He provided background information about PFAS, which include more than 1500 chemicals, and went over the ongoing NTP PFAS studies. He noted that NTP nominations have become more complex as they have moved into classes, such as PFAS, and that with the acceleration of communications, there is impatience at the pace of traditional NTP hazard assessment studies, creating the need for rapid assessment and reporting methods.

To address the need for information on biological activity and toxicology that NTP can develop in a responsive timeframe on PFAS, the REACT program has been developed. It involves literature review and analysis, *in silico* screening (>100 PFAS), *in vitro* screening (75+ PFAS), and *in vivo* screening (<20 PFAS). PFAS assessment is based on read across, when the already available data on a data-rich substance (the source) is used for a data-poor substance (the target), with sufficient similarity.

Dr. DeVito described several projects involved in the REACT program, which is being conducted in collaboration with the USEPA. EPA's 75-chemical PFAS library will be used to generate information. *In vitro* work will be accompanied by IVIVE approaches to aid in prioritization of the chemicals for *in vivo* screening and toxicity studies. *In vivo* studies will involve a 5-day rat hepatic transcriptomic assay and 28-day toxicity studies, with other *in vivo* studies possible for a limited number of PFAS. REACT products will include:

- *In vitro* characterization and read-across grouping of PFAS chemicals
- Estimates of oral equivalent dose to attain Cmax or Css equivalent to *in vitro* Points of Departure
- *In vivo* studies on limited numbers of chemicals that provide sufficient anchors for read-across

A systematic review of perfluorooctanoic acid (PFOA) immunotoxicity has been published. A number of *in vivo* studies are currently at various stages of development. The intent is to develop an approach that will provide a rapid response to a large class of chemicals and mixtures, involving an integrated approach that incorporates data from *in silico*, *in vitro*, and *in vivo* models.

1) Questions for Clarification

Dr. Markowitz asked Dr. DeVito to define what “rapid” means in this context. Dr. DeVito replied that that was still being worked through. He said that EPA is expected to deliver on their studies by June 2018, and NTP would follow soon after that.

Dr. Ramos asked whether a timeline has been built. Dr. DeVito said that for the 75 chemicals for the hepatotoxicity assays, he would expect to meet a June 2018 timeline. He added that the *in vitro* disposition may take longer. Dr. Ramos said that may be a way to help define “rapid.” He recommended that the undefined endpoints be removed from the rapid moniker. He asked whether the collaboration with EPA is mainly on the computational side. Dr. DeVito said that EPA is actually running experiments as part of the program.
Dr. Markowitz asked if EPA or CDC are running companion studies on prevalence of exposure to the PFAS being studied. Dr. DeVito replied that they are not. Dr. Birnbaum added that there is legislation being considered for studies of PFAS exposure near US Air Force bases.

Dr. Barlow asked about collaboration with state governments. Dr. DeVito said NTP has been reaching out to the North Carolina Department of Environmental Quality, but has not been in formal contact with New Jersey’s department. Dr. Birnbaum listed many states where PFAS are of concern.

D. Office of Data Science

Interim Director Stephanie Holmgren briefed the board on the newly established Office of Data Science (ODS) at NIEHS/NTP.

She described the data science landscape in general and at the NIH. New technologies are generating significant increases in data volume. The next generation of data science relies on the ability of the data to be FAIR: findable, accessible, interoperable, and reusable. NIH has embraced data science and has launched numerous efforts, beginning with the NIH public access policy and encompassing the BD2K initiative: Big Data 2 Knowledge, which includes the NIH Data Commons and the National Cancer Institute (NCI) Genomics Data Commons.

Ms. Holmgren described the current organization of data science at NIEHS and NTP. ODS was recently established to support a holistic view of data science at NIEHS and to leverage the opportunities and address the challenges of data-driven research. The office addresses six primary strategic priorities:

- Data governance
- Research in methods development
- Application of existing methods
- Data cyberinfrastructure
- Engagement (with the community)
- Community of practice

ODS currently has an interim director and six contractors, and has proposed 5 federal staff, 6 contractors, a fellow, and 2 summer interns.

Dr. Charles Schmitt described the current ODS initiatives, which include several programs to advance FAIR practices within NIEHS. One of the major initiatives is the NIEHS Data Commons, which is a system for:

- Researchers and core labs to access, find, and share research data and metadata
- IT staff to improve data and storage management, without impacting users
- Foundation for integration or federation with external data systems
The Commons will initially include epigenomics data and is scheduled for release in early 2018. Dr. Schmitt also highlighted a few other projects, including development of an NIEHS Metadata Catalog to facilitate usage of controlled terminology across NIEHS applications, implementation of web-based application programming interface (API) on NTP databases such as CEBS and ICE, and development of an approach to automate the extraction of information from research articles using natural language processing.

E. Integrated Chemical Environment

Dr. Kleinstreuer described the establishment of the web-based data resource called the Integrated Chemical Environment (ICE). ICE addresses the Strategic Roadmap goal to foster the use of efficient, flexible, and robust practices to establish confidence in new methods. It is intended to leverage partnerships and complementary initiatives such as the NIH Data Commons.

ICE is a data integrator with a structured format designed for ease of use, allowing access to data for multiple regulatory endpoints. It exists in both computer-friendly and human-friendly formats, to allow quick comparison of data availability between chemicals.

The goals of ICE are:

- To uphold FAIR principles for ICCVAM data
- To provide intuitive access to high-quality, curated data and tools to support:
  - Chemical evaluations
  - Data integration
  - Model development
- To enable the wider community to engage in the use of alternative and computational approaches for assessing chemical safety

Dr. Kleinstreuer provided examples of data in ICE and the curation process. She conducted a live demonstration of the ICE website. She described the ICE timeline: the site was launched in March 2017 and updated in July 2017. Further updates are scheduled for January and March 2018.

1) BSC Discussion

Dr. McMartin introduced a board discussion period covering the entire session.

Dr. Barlow was the first BSC reviewer. He asked Dr. Behl about the battery of DNT tests she had discussed, and how it would be determined. She replied that determining the best combination of tests would be the next step in the process. Dr. Barlow asked Dr. Behl how the challenge represented by the blood-brain barrier would be addressed. She said the issue had been extensively discussed at the workshop, and that there are some blood-brain barrier models that could be incorporated. Dr. Barlow asked her how the various types of toxicities would be split to determine whether a substance is specifically a neurotoxicant. She said that the idea is to zoom out from neurotoxicity or DNT to allow the other types of toxicities to be considered, in possible systems toxicity...
scenarios. Dr. Barlow asked about the concentrations used in the battery versus those used in vivo with known DNTs, inquiring how they lined up in terms of what has been seen in the assays versus what is known. She discussed the IVIVE elements, and said the information overlapped quite well. The exercise was part of the workshop.

Dr. Barlow asked Dr. Germolec about the weighting of the 54 different models in the skin sensitization studies. He wondered if there was more weight put on the fact that a substance may be more lipophilic, passing through the skin more easily and potentially generating an allergic response. Dr. Germolec said that was not a specifically weighted element. Dr. Kleinstreuer added that it was a combinatorial approach, with the biology coming through. The lipophilicity of the compound turned out to be the most important physicochemical characteristic and was included in all of the highest-performing machine learning algorithms. Thus, when there is a data-driven approach with a well-characterized feature set, it does reproduce the biology, she noted.

Dr. Barlow said he found REACT to be an interesting project. He approved of its non-linear approach. He asked Dr. DeVito about the in vivo studies available, and how it would be determined that additional in vivo studies would be needed. Dr. DeVito replied that the program had not yet gotten to that point. He noted that going forward, it would largely depend on the chemistry involved, and that would be the element that would slow the process. He said that it was difficult to synthesize the 75 chemicals needed. He said he awaits the final list from EPA. He felt that the process would be trial and error and the first iteration would perhaps not be as rapid as desired, but that over time with ready tools, the process will be quicker.

Regarding ODS, Dr. Barlow asked Ms. Holmgren what was being superseded, and whether there had been no coordination previously. She replied that there had been numerous prior efforts around data at NIEHS, conducted at the individual office level. Those efforts coalesced into the need for and creation of ODS. Dr. Bucher addressed why ODS was positioned within NTP, noting the track record of NTP dealing with large data sets, including the CEBS database. Ms. Holmgren added that a lack of metadata associated with legacy data was making its incorporation into the Commons more challenging. Regarding ICE, Dr. Barlow approved of the concept of a centralized, user-friendly system, and noted the importance of including the appropriate tools, with a user interface to be adapted and adjusted according to feedback received from users themselves. Dr. Kleinstreuer emphasized that it was to be considered just one element of a broader system of interlocking parts. She noted that all of the data in ICE are also in CEBS, so there is 100% consistency among the NTP data systems.

Dr. Ramos was the second BSC reviewer. Regarding the DNT project, he felt that the importance of the project could be overstated, as an essential investment by ICCVAM and NTP. He said it is a good start, but that some significant fine-tuning is required, most importantly its focus on DNT. He said he believed that the developmental part of the assessment is weak, lacking the rigor to differentiate a DNT outcome from a neuro outcome and from outcomes associated with other tissues. He recommended working to answer questions that truly cater to the most important contribution of the program — to establish a screening paradigm for DNT outcomes. He did approve of the progression
of the models, in particular the medium-throughput models such as the zebrafish, representing a good investment. He said the most important contribution the program can make relates to behavioral outcomes. "The more you can do to provide data that’s going to inform behavioral outcomes in the context of developmental neurotoxicity, the stronger the program can be," he observed. He also felt that the program could benefit from placental/blood-brain barrier insight. He commended the program as a good initial effort, although it is underdeveloped at this point.

Regarding the dermal hypersensitivity project, he praised the write-up and the slide presentation. He agreed that more attention would be needed to differentiating an acute irritancy response relative to a hypersensitivity response.

Regarding REACT, Dr. Ramos noted the huge gaps in data, with a poor existing data set from which to build. Thus, it would be an uphill battle in the space — a very important project, but facing many challenges. He recommended better prioritizing where the energy and effort would be put for the project. He felt the project is very ambitious, posing a risk of under-delivery. He said that the concept of "rapid" needs to be better defined and described the value of read-across as "huge."

Regarding ODS, he recognized that NIEHS had been considering it for a long time, and said that much of what had been proposed "makes perfect sense." He felt that the office needs to spend more time on deliverables and outcomes.

Regarding ICE, he said he struggled with identifying the uniqueness of the project, with 3 or 4 sister agencies doing the same thing in different forms. He felt that ICE needs to define its niche. In many ways it seems to be "trying to answer a question that hasn’t been asked."

Commenting on the overall program, Dr. Ramos said he was gratified to see the progress on what has been done with ICCVAM. However, it will be important to identify the problem the program is trying to solve. There is a dichotomy between the effort to improve technology for toxicity assessment for its own sake and the bigger question of human risk assessment. The dichotomy creates problems with perception of ICCVAM’s value.

Responding to Dr. Ramos’s last comment, Dr. Bucher said that it is important for ICCVAM to better understand the needs of its customers.

Regarding the 6-pack and ICCVAM, Dr. Sass said that sensitivity should be the highest priority, with the danger of false negatives, particularly given the prioritization procedures under the Toxic Substances Control Act (TSCA). "It is really important to be able to use these tests to call something a problem, and not to put something in low priority when it shouldn't be there," she observed. Regarding ICE, she speculated that it was importing conclusions only, which would not be valuable. She said the database needs to also take the data. Dr. Kleinstreuer said that the primary ToxCast and Tox21 data are there, but some additional studies may not be represented for some chemicals. Dr. Sass was particularly concerned with access to Endocrine Disruptor Screening Program (EDSP) data.
Dr. Stevens expressed his support for the DNT and skin sensitization efforts. Regarding skin sensitization, he felt that substantial progress could be made, eventually leading to conducting the tests in silico, without cell data. He endorsed the strategy of dividing resources between pursuing the “quicker wins” and the more long-term, difficult efforts. He cautioned against duplication of effort.

Dr. McMartin noted that the board was very appreciative of the efforts in the wide variety of different strategies discussed during the session.

**VII. Report on the Peer Review of the Report on Carcinogens (RoC)**

**Draft Monograph on Haloacetic Acids Found as Water Disinfection Byproducts**

Dr. Gloria Jahnke from the Office of the RoC briefed the board on the peer review meeting, which was held July 24, 2017.

She provided background information about the RoC and the process for its preparation, as mandated by Congress. She described water disinfection byproducts and levels of U.S. exposure.

Thirteen haloacetic acids were identified and considered, using read-across approaches to arrive at overall cancer hazard evaluations and preliminary listing recommendations. The peer-review panel was charged with commenting on the accuracy of the draft monograph, and voting on whether the scientific evidence supported the NTP’s conclusions. The panel agreed unanimously with the NTP conclusions, she reported. There were no major scientific disagreements with the draft monograph. The panel concurred with the assertion that haloacetic acids could not be evaluated as a class or as subclasses, although with more mechanistic data that may be possible in the future. Some reviewers added suggestions for substantial revisions and comments outside the scope of the RoC monographs.

The next step in the process is to finalize the RoC monograph. After all substances for this edition of the RoC are reviewed, their substance profiles will be sent to the NTP Executive Committee and to the HHS secretary for approval for adding to the report.

Dr. McMartin related written comments from Mr. Daniel Kass, who was the BSC liaison to the peer review meeting. Mr. Kass found the staff presentations to be excellent, demonstrating the technical and translational expertise of the NTP staff. He noted that the panelists agreed with the NTP’s conclusions. They suggested adding additional references, and that instances of absence of data should be acknowledged. Overall, he said, the peer reviewers praised the completeness, objectivity, methodologic soundness, and presentation of the draft monograph.

Dr. Gamboa noted that the Center for Drug Evaluation and Research (CDER)(FDA) had voiced concerns about some of the interpretations of the mouse data in the report. He asked about the mechanism for comments from the FDA to be conveyed to the peer review panel, and whether the comments from CDER were considered. Dr. Wolfe replied that the draft monograph is shared with the interagency partners, which is
considered to be an internal, deliberative communication. The comments are considered, but are not made available to the public or the peer reviewers. Interagency comments are not considered to be public comments. The panel is provided with all public comments received on the draft monograph. Dr. Gamboa concluded that public comments are taken with more consideration than interagency comments, where they are not provided to the peer review panel. Dr. Bucher said there are steps where technical experts’ comments on various drafts are incorporated, and that interagency comments are considered in the development of the final draft. Dr. Jahnke added that there is an internal review by NTP staff and those comments as well as interagency comments are considered and incorporated as appropriate into the draft.

Dr. Gamboa said he found that procedure strange, and could not see why it should be that way. Dr. Wolfe said that with many of the comments received from the agencies, they prefer to share them with NTP staff as part of the internal process of open dialogue with the agency partners.

Dr. Ramos asked Dr. Jahnke whether the fidelity of the metabolic pathway in rodents is preserved in humans. Dr. Jahnke noted that human microsomes were used.

Dr. McMartin adjourned the meeting for the day at 5:30 PM.

December 8, 2017

Dr. McMartin reconvened the meeting and asked BSC members and other attendees to introduce themselves. Dr. Wolfe read the conflict of interest policy statement.

VIII. Report from the NTP Associate Director

Prior to Dr. Bucher’s presentation, Dr. Birnbaum referred to the earlier discussion of tissues-on-a-chip, and described one NIEHS-funded project, a 3D model testing the effects of chemicals and drugs on the female reproductive system. The product, called Evatar is a miniature 3D model of the ovaries, fallopian tubes, uterus, cervix, and vagina that also mimics human metabolic processes that the liver would maintain in a living person.

Dr. Bucher updated the BSC on recent developments at NTP. He recognized the upcoming retirement of Dr. Paul Foster, and recent awards to Dr. Angela King-Herbert and Dr. Kristen Ryan. He described a recent publication on maintenance of metabolic capability in HepaRG cells, which are increasingly being used in in vitro studies.

He discussed several recent NTP Reports publications. He described a recent National Academy of Sciences (NAS) meeting, “Understanding Pathways to a Paradigm Shift in Toxicity Testing and Decision Making,” held in November 2017. The workshop allowed NAS participation in development of the strategic roadmap. He provided details about keynote addresses and case studies presented at the meeting, as well as the workshop’s final session, “Motivating Change at the Institutional Level.”

Dr. Birnbaum commented that the NAS meeting was sponsored by the group that NIEHS funds, and that a summary paper would be forthcoming.
Dr. Stevens noted that often scientists call for more data when they seek to shift behaviors and opinions. He asked Dr. Bucher how scientists can do better when communicating decisions that can already be made, as opposed to always wishing for more data. Dr. Bucher replied that scientists can no longer take as much time as they used to in reaching decisions. “People want answers now. You have answers at the tips of your fingers, and if we can’t provide those answers, we have a very short window in which to be able to give to the public and actually influence what happens,” he observed. He noted that toxicology is a probability science.

**IX. Peer Review of NTP Technical Reports on Dietary Zinc, 2,3-Butanedione, and p-Chloro-α,α,α-trifluorotoluene**

Dr. Chad Blystone briefed the BSC on a recent peer review meeting for the three draft reports. He provided background information about NTP Technical Reports and the level of evidence criteria used to evaluate the strength of carcinogenic activity in the studies, and identified the peer review panel.

For dietary zinc (TR-592), the panel voted unanimously to accept the NTP conclusions.

For 2,3-butanedione (TR-593), four of the six panelists voted to approve the conclusions, with two votes opposed, asking for a “clear evidence” conclusion for male rats and a “some evidence” conclusion for female mice.

For p-chloro-α,α,α-trifluorotoluene (PCTFT) (TR-594), the panel voted unanimously to accept the NTP conclusions.

Dr. Blystone mentioned upcoming chronic toxicity and carcinogenicity Technical Reports on an ingredient found in sunscreen and other personal care products, and on PFOA, a widespread “legacy” PFAS. Four Technical Reports on prenatal developmental toxicity studies and a Technical Report on dermal irritancy and hypersensitivity study are also expected in 2018, as are several subchronic toxicity studies (TOX Technical Reports).

**1) Questions for Clarification**

Dr. Barlow asked whether the intent of the short-term toxicity studies is to not proceed to carcinogenicity studies. Dr. Blystone confirmed that is the case.

Dr. Markowitz asked what the National Institute of Occupational Safety and Health (NIOSH) would do with the results of the PCTFT report. Dr. Blystone replied that they would use it in risk assessment. Dr. Birnbaum elaborated on how OSHA and EPA use RoC listings. Regarding the PFAS chemicals, she noted that some are breakdown products that are still present in the environment.

Dr. Wolfe noted that the new level of evidence criteria developed for developmental and reproductive toxicity and for immunotoxicity would be applied in the new report series for the studies mentioned by Dr. Blystone.
Dr. Bucher mentioned that Dr. Blystone has also been preparing for a March 2018 peer review meeting on radiofrequency radiation (RFR) studies. He added that in April there will be a peer review meeting for a portion of the CLARITY Bisphenol A (BPA) Program as carried out at the National Center for Toxicological Research (NCTR).

Dr. Sass was the BSC liaison to the peer review meeting. She felt that it was a well-done meeting. She pointed out that 2,3-butanedione is diacetyl and also a flavoring used in vaping. Dr. Birnbaum said that there are many compounds used in flavorings for vaping liquids.

Dr. Walker mentioned to Dr. Markowitz that in addition to NIOSH and OSHA, several other industrial hygiene groups use NTP reports in their work.

X. New Approaches to Hazard Characterization and Risk Assessment

Dr. Bucher introduced the session, which dealt with efforts to bring genomic assessments into the alternatives arena.

A. Tox21 Phase 3: High-Throughput Transcriptomics and the S1500+ Initiative

Dr. Richard Paules, acting chief of the Biomolecular Screening Branch, updated the BSC on Tox21 developments.

He provided background information about the Tox21 federal partnership program, and noted that Phase 3 concentrates on improving biological coverage and human relevance, by incorporating high-throughput transcriptomics (HTT). To achieve a rapid and affordable quantitative high-throughput transcriptomic measurement of expression levels of genes for large numbers of samples, the group will employ

- Low-depth coverage, whole transcriptome targeted gene expression analysis of approximately 22,000 genes, led by EPA
- Targeted gene expression analysis using a set of representative or “Sentinel” genes, S1500+, to determine pathway and network perturbations, led by NTP

Dr. Paules described the S1500+ gene set in more detail, including listing the desired attributes. He provided data on evaluation of the Human S1500+ gene set’s extrapolation performance in independent tests using the BioSpyder TempO-Seq platform. He also discussed an HTT proof-of-concept study with an in vitro human liver organotypic model, using HepaRG cells in a 384-well format. The study of 24 compounds yielded 25 million data points.

Dr. Paules described the effort to move Tox21 toward quantitative systems toxicology:

- Hypothesis: Transcriptome profiling of in vitro treated human cells can provide an approximation of human in vivo responses to chemical exposures.
- Goal: To evaluate HTT analysis of in vitro cell models for providing Bench Mark Dose (BMD) information relevant to human BMD values and begin to address best practices.
NTP and its Tox21 partners have developed the BMDExpress 2.0 informatics tool to analyze HTT data to provide quantitative dose response information that can be used toward risk assessment evaluations. Dr. Paules provided several examples.

In future directions, the S1500+ gene set that has been developed for humans, is nearing completion for the rat and the mouse, and has been initiated for zebrafish. Dr. Paules noted that NTP is very interested in using the platform for screening for prioritization, particularly for the classes of compounds now being nominated. The intent is to integrate it with high-content imaging to facilitate phenotypic anchoring, and to integrate metabolomics data in consultation with the NTP Laboratory Branch. Also, it will be applied to biomaterial from NTP rat and mouse studies.

1) Questions for Clarification

Dr. Sass asked how the technology is being made publicly available by the BioSpyder team, a private company. Dr. Paules noted that the gene set has been published, and any vendor is free to develop a platform using it.

Dr. Stevens noted that Dr. Paules had said that 1650 genes contained all of the information, and asked whether that was information or variability. Dr. Paules said it was variability. On another slide where Dr. Paules had not touched on random gene performance, Dr. Stevens asked if he was reading the data correctly that randomly selected genes had done as well as the selected genes in imputing behavior. Dr. Paules explained that when the gene set approaches 3,000 genes, many very informative genes would randomly be included. Dr. Stevens asked whether after getting past a certain number of genes, a randomly selected set is as good as a selected set at imputing behavior of the entire chip. Dr. Paules said it would be, with the exception of the false error, which he had highlighted on the data slide. Dr. Stevens wondered if it might be possible to get more pathways without preselecting and biasing the set toward a particular subset of pathways. In other words, how do you know pathways are false as opposed to representing information not captured in the selected subset? Dr. Paules said it was because the comparison was based on the observed Affymetrix measurement of the whole transcriptome, which picked up 15 perturbed pathways.

Dr. Waters said she was confused by the stated goal of the program. She felt that the hypothesis had not been proven, and asked if there were plans to do so. Dr. Paules said it is a long-term hypothesis, and acknowledged that the pilot program has not proven it. She asked if statistics from the accumulation curves would be used to make judgement calls on particular compounds and their activity, or whether the minimum BMD value from a gene or pathway would be used. Dr. Paules noted that there had been an expert panel meeting to discuss those issues, which are being worked on.

Dr. Stevens clarified that the hypothesis was intended to estimate the exposure at which a human will respond, as opposed to human response concordance at the pathway level. The latter implies mechanistic and physiological similarity, whereas the exposure at which human tissues respond does not necessarily require concordance in the biological information. Dr. Paules agreed.

Dr. Scott Auerbach briefed the BSC on the peer review meeting that took place at NIEHS October 23-25, 2017.

He provided background information about genomic dose-response (GDR) modeling and its importance — it can quickly query a wide swath of biological space to identify an effect level that approximates the potency of traditional toxicological endpoints. NTP is pursuing in vivo and in vitro transcriptomics in dose-response format for determining screening-level biological potency and for identifying molecular processes that are altered by test articles. Data from these studies are intended to support margin of exposure-based assessments that can help in prioritization and for setting interim exposure limits. The expert panel meeting was held to review the proposed NTP GDR modeling approach to generating and analyzing the data from GDR studies.

The meeting was preceded by four webinars designed to inform attendees on several topics prior to the meeting. Dr. Auerbach described the expert panel, which was chaired by Dr. Carole Yauk from Health Canada, as well as several other important contributors. It was comprised of six sessions:

- Overall approach to genomic dose response studies
- Study design
- Filtering of measure features
- Fitting features to dose response models
- Determining gene set level potencies
- Biological interpretation

Several outside speakers addressed the three-day meeting, with considerable time set aside for in-depth discussions.

Dr. Auerbach went through each of the meeting sessions in more detail, and presented revisions to the proposed NTP approach based on comments from expert panel members, who voted on each of the session outcomes. He also acknowledged the contributions of several people and organizations who had helped to develop the BMDExpress 2.0 software, the platform upon which the GDR modeling approach is based.

Dr. Waters was the BSC liaison to the meeting, and presented her comments. She said the meeting was well-organized and well-executed, with the workflow components effectively laid out. Having researchers engaged in the process from other federal agencies and academic institutions provided rich input and much opportunity for lively discussion and data sharing. Many members of the panel commented about the ambitious nature of the project, but ultimately saw the workflow as do-able and manageable. She praised Dr. Auerbach’s summary and for his flexibility and open-mindedness in accepting the feedback and suggestions from the participants.
C. **ECHA Workshop: Accelerating the Pace of Chemical Risk Assessment**

Dr. Bucher described a recent (October 10-11, 2017, Helsinki, Finland) meeting that he had attended, which sponsored by the European Chemical Agency (ECHA). It was attended by personnel from several global regulatory agencies and academic institutions. The intent of the gathering was to accelerate the pace of chemical risk assessment and the use of alternative assays. The purpose was to “make the science of new approach methodologies (NAMS) work for common regulatory challenges,” and “to bring together international regulators to discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.” The U.S. TSCA reform act and the European REACH experience were the legal drivers propelling the meeting.

He discussed the NTP’s contribution to the group’s initial proposed case studies. NTP’s contributing hypothesis was that the point of departure (PoD) for changes in hepatic gene expression is predictive of the PoD for biological effects in any organ in any length study. He described the study design used and went over some of the data from the p-toluidine, N,N-dimethyl-p-toluidine 5-day genomics study conducted in male F344/N rats. The liver was the organ used for transcriptomic assessment.

Dr. Bucher said there were many issues to be addressed with these kinds of studies:

- What kinds of substances do we miss? Why?
- Do kinetic adjustments adequately accommodate bio-accumulative substances?
- Non-toxic substances will produce gene expression changes. Do we care?
- Can this approach be used for more than prioritization?
- Can this bridge to in vitro transcriptomic-based risk assessment?

Another case study to be pursued involves examining the utility of in vitro bioactivity as a conservative PoD. NTP will partner with several other agencies to work on the case study. The study flow is still being developed.

The workshop’s take-home message, according to Dr. Bucher, is that “we’re no longer in a situation where test developers are developing things and then the regulators are looking at it and saying, well, maybe. We’re now at the stage where the regulators around the world are saying, we need these tools and these are approaches that we think are of interest.”

1) **Questions for Clarification**

Dr. Davis referred to Dr. Bucher’s “provocative” hypothesis regarding the liver, and asked whether the study protocol would incorporate assessment of other tissues. Dr. Bucher said the study would do both, include the liver and other predicted target organs. The idea is that the liver would be seen as a sentinel organ, signaling that something is wrong with the animal. Dr. Davis asked whether to test that hypothesis by starting with, or at least incorporating into the strategy, a chemical for which it is known that other organs will be adversely affected, adding in a positive control to the experimental protocol. Dr. Auerbach described a 20-chemical study under development.
to address that question. Dr. Birnbaum asked whether the 20 chemicals included compounds for which there is good developmental information. Dr. DeVito provided further details about the study, and a companion study.

Dr. Stevens suggested a study looking at gender-specific P450s, an example where the liver is sentinel for something that is occurring elsewhere. Dr. Birnbaum agreed with the idea, and stressed that looking at development should be included.

2) BSC Discussion

Dr. Waters was the first BSC reviewer. She said she had heard three different goals outlined in the session’s presentations: one that focused on identifying transcriptome signatures that could be used to associate chemical effects with disease, one that wanted to use the transcriptome profiles to identify a PoD for biological activity, which could be used for prioritization, and a third focused on identifying points of departure that could be associated with any organ target toxicity, potentially using only a single organ, extrapolating that to risk assessment. She was not convinced that use of the transcriptome process is fit for purpose as an assay. She noted that if everything looks bad, the transcriptome assay may not be helpful in determining prioritization. She found the accumulation curves that had been depicted to be compelling. She recommended that NTP devote more thought to the purpose and goal of the approaches.

Dr. Stevens was the second BSC reviewer. He complimented Dr. Auerbach on the GDR modeling meeting, where he had been a panelist. He said that he agreed with the proposed approaches, but “the devil is in the details.” He felt that Dr. Auerbach had responded well to the constructive criticism cautioning against trying to do too much and the recommendation about demonstrating proof of concept with gene ontology (GO) terms. He said it was critical to separate the screening function for hazard identification from the formal risk assessment for a particular chemical. The audience will continually conflate those two activities, he observed. He suggested that NTP leverage the in vivo component, as it is still a very important part of risk assessment. He had no comment on challenges using NTP data beyond urging very efficient use of scarce IT resources to prevent duplication of efforts. In terms of suggestions for an effective communication strategy, he said it would be important to refine the overall message, including presenting the tiered strategy being taken across the NTP first. He recommended being clear in communication regarding mode of action and adverse outcome pathway (AOP) requirements, fitting with hazard identification. He urged clarity in telling the story, particularly with Tox21. He recommended moving from exemplars to real case studies involving more complex chemicals.

Dr. Sass found the session to be exciting and helpful. She said she was convinced that there are many uses for the new approaches outside of the regulatory area. She said her concern is that the tools (such as the 5-day liver assay described by Dr. Bucher) not be used in a regulatory framework to exonerate something, raising the issue of false negatives. Dr. Bucher said he felt that exonerating a chemical meant never studying it. If a short-term study can be done in an animal, which regulators will accept more readily than in vitro studies, and it shows biological effects at a measurable dose along with pathway information, it is “an enormous leg up from what you would have had without
it. Dr. Sass said she understood the point, but that it would be difficult for the public to do so. She cautioned that NTP should stay engaged along the entire process, and “be a little humble.” She expressed concern about the amount of public monies being expended on the entire enterprise, citing the BioSpyder platform as an example. Dr. Bucher noted that data from the BioSpyder platform is publicly available in NTP’s Chemical Effects in Biological Systems (CEBS) database, and acknowledged that dealings with public companies should be scrutinized carefully.

Dr. McMartin passed along comments from Dr. Ramos, who listened on the phone to the second day’s proceedings. Regarding the GDR modeling meeting, he noted that the rationale for selection of the expert panel was not discussed by Dr. Auerbach, with the appearance that the panel was weighted toward technical aspects and was somewhat underpopulated in the area of biological interpretation and end user perspective. He felt that future iterations should include more experts in genomic science. Dr. Ramos agreed with many of the revisions made by the experts, but disagreed with the suggestion that both sexes be screened, with the most sensitive sex being tested subsequently. He felt that dose selection should be guided by environmental relevance and not where the effect is seen. He noted that little attention had been given to species differences. Overall, he found the project to be technically sound, but needed expansion of the biological interpretation component, which is ultimately the major deliverable to come out of the efforts.

Dr. Auerbach responded to Dr. Ramos’s comments. He said that the panel was in fact “technical-heavy,” because the concentration was on the components of the modeling. With respect to biological interpretation, it was a very significant debate in the meeting, he noted, and there is always the possibility of misinterpretation when there is no immediate certainty of what a gene set means. Thus, the focus was more on safety and a dose that produces no biological effect.

Dr. Birnbaum asked Dr. Auerbach if it had been considered to look at areas where little or no apical effect was seen, which can occur with some mixtures.

Dr. Stevens wished to defend the strategy. If the desire is to extrapolate across species in order to understand human risk, and to understand whether biological effects in one system translate into another system, there is a need to understand the underlying physiological mechanism of the action, and whether the networks are conserved across species. In a given biological system, differential gene expression has a high effect size for association with biological responsiveness and adversity, he noted. Stratifying based on whether a chemical is potentially hazardous and should be studied further is one example of where communication is continually a challenge. He said the field is “on the tail end of a 15-year transcriptomic effort.” The current message is to do transcriptomics differently, in a more focused way, with impact. He recommended staying focused on the strategy, with it being incumbent for NTP and the BSC to really understand the strategy and how it is intended to be applied.

Dr. McMartin briefly summarized the discussion. He said the board was strongly supportive of the overall efforts. The comments focused on communicating what is being done in a meaningful way to end users and the general public. The board noted
that there are a number of other uses of the approach in addition to just doing regulatory risk assessment.

**XI. Update on NTP Studies of Glyphosate**

Dr. DeVito updated the board on NTP studies of glyphosate and glyphosate formulations.

He provided background information about glyphosate, a broad-spectrum herbicide. He noted that it has been listed as probably carcinogenic to humans by the International Agency for Research on Cancer (IARC), but that EPA and the European Food Safety Agency (EFSA) believe it is unlikely to be a human carcinogen. NTP has been asked to help resolve that disparate understanding. Challenges include the issue of glyphosate vs. formulations, and lack of mechanistic data. He described previous NTP toxicity studies on glyphosate in rats and mice, from 1992. Current specific aims of NTP glyphosate studies include:

- Compare the effects of glyphosate to the effects of glyphosate formulations using measures of genotoxicity, oxidative stress, and cell viability.
- Compare the dose response relationships between oxidative stress, genotoxicity, and cell viability.
- Determine whether there are other adverse effects of glyphosate and its formulations that require further evaluation.

Initially, cell-based systems will be used for the studies, including HaCaT, HepaRG, and TK6 cell lines. Dr. DeVito described the assays being used. Thus far, positive and negative controls have been evaluated in the three cell lines. Formulations and actives have been run in HaCaT and HepaRG cells three times, and data are being analyzed. A data analysis pipeline and a visualization tool are being developed. When studies are completed, an NTP Research Report will be published, sometime in late spring or early summer, 2018.

Dr. DeVito also described genetic toxicity testing of glyphosate and formulations, in both *in vitro* and *in vivo* assays (based on *in vitro* results).

To help identify other endpoints of concern, NTP is conducting a screening-level analysis of existing literature using text mining and machine learning approaches. This will provide an overview of the available literature for all human health outcomes related to glyphosate exposure. The Office of Health Assessment and Translation (OHAT) is actively monitoring the literature for health effects studies.

1) **Questions for Clarification**

Dr. Stump asked whether there were any thoughts to look at formulations without glyphosate. Dr. DeVito said there had been efforts in that direction, but it had proven difficult to purchase such agents. He noted that formulations are approved for local use by EPA, due to different plants and weather in different regions. NTP chose 13 of the most-used formulations, and 9 have been purchased, supplementing them by purchase
of some over-the-counter products for lawn and garden use. Dr. Stump noted that literature review was difficult, since it is often challenging to determine what agent was actually used in a study. He asked whether that was a difficulty in the literature review being conducted by NTP. Dr. DeVito said the initial review was keyed to any study using the word “glyphosate” and/or formulations. There have been challenges trying to describe the dose of formulations.

2) BSC Discussion

Dr. Sass was the first BSC reviewer. She said that most of her questions had been answered by Dr. DeVito’s presentation. She asked how NTP’s results, whether negative or positive, would fit into IARC’s decisions and regulatory decisions. Dr. DeVito said it would be a challenge, particularly since the animal data had been seen as sufficient. Dr. Birnbaum pointed out that IARC’s call was based on studies with glyphosate formulations. She speculated that if it was seen in current research that much more activity was seen with formulations than glyphosate, it would be a very important understanding. Dr. Sass agreed that the formulation issue is important, and that NTP studies would be quite helpful regardless of what is seen. She approved of NTP also studying lawn and garden formulations.

Dr. Markowitz was the second BSC reviewer. He asked Dr. DeVito if the genotoxicity tests are better, different, or complementary in a way that will add to the literature. Dr. Stephanie Smith-Roe replied that NTP had carefully reviewed the same literature that IARC had reviewed for the genotoxicity of glyphosate in formulations, and felt that in many cases the studies were inadequate or difficult to interpret. She felt that the NTP studies were better-controlled, and include comparison of glyphosate with AMPA, the only known metabolite of glyphosate. Dr. Markowitz noted that the IARC studies had considered the animal studies to be “sufficient,” but the Europeans looked at them differently. He asked whether there is a role for the NTP to weigh in on the issue. Dr. Bucher said that IARC had looked at the animal literature as hazard identification, while EFSA’s review looked at whether there was a carcinogenic risk associated with glyphosate. Thus, the reviews were “apples and oranges” with respect to the way they looked at the data. He said that if a 2-year study were initiated, it would be at least 5 years until completion, well past the glyphosate re-registration period. Dr. Markowitz said he understood the distinction between risk and hazard, but noted that the interpretation of the animal literature was very disparate in terms of hazard. If that is true, he asked, is there a role for NTP? Not necessarily in a 2-year study, but adding to the interpretation. Dr. Walker asked Dr. Markowitz if he was asking for a RoC-type review to look at the data again. Dr. Markowitz noted that “NTP is the premier federal organization that addresses these issues.” With a considerably different interpretation by different experts, he wondered if there was a role for NTP to get involved. Dr. Birnbaum noted that some other groups are conducting animal studies, and that the results of the NTP in vitro studies would help inform the decision whether to proceed with further in vivo work.

Dr. McMartin said the board generally supported carrying on the glyphosate studies, and approved of studying formulations with positive and negative controls. There were
questions about how the added studies would fit into the existing dichotomy of risk assessment interpretations.

XII. Adjournment

Dr. Bucher thanked all participants for their comments, and thanked Dr. McMartin for chairing the meeting. He also thanked Dr. Wolfe, Dr. Walker, and the entire staff. Dr. Birnbaum added her thanks, noting that it had been a very positive meeting with much great science.

Dr. McMartin adjourned the meeting at 12:30 pm, December 8, 2017.
Summary Minutes December 7-8, 2017
NTP Board of Scientific Counselors

Dr. Kenneth McMartin
Chair, NTP Board of Scientific Counselors

Date: 1-30-18