National Toxicology Program

Board of Scientific Counselors

June 8, 2021

National Institute of Environmental Health Sciences
Research Triangle Park, NC

Summary Minutes

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1. Abbreviations and Acronyms

AIDS	Acquired immunodeficiency syndrome
BMD	Benchmark dose
BSC	Board of Scientific Counselors
cART	Combined antiretroviral therapies
CEM	Combined Exposures and Mixtures
CPSC	U.S. Consumer Product Safety Commission
CPT	Consumer Products and Therapeutics
DNTP	Division of the National Toxicology Program
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HIV	Human immunodeficiency virus
MoA	Mode of action
NAM	New approach methodology
NCATS	National Center for Advancing Translational Sciences
NCTR	National Center for Toxicological Research
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NTA	Novel Tools and Approaches
NTP	National Toxicology Program
OFR	Organohalogen flame retardant
OAR	National Institutes of Health Office of AIDS Research
OECD	Organisation for Economic Co-operation and Development
Tox21	Toxicology in the 21st Century

2. Attendees[1]

Board of Scientific Counselors

Chair: David Eaton, PhD, University of Washington
David Berube, PhD, North Carolina State University
Eric Blomme, DVM, PhD, AbbVie (*ad hoc*)
Weihsueh Chiu, PhD, Texas A&M University
Susan Felter, PhD, Proctor & Gamble
Kathleen Gray, PhD, University of North Carolina, Chapel Hill (*ad hoc*)
Pamela Lein, PhD, University of California, Davis *(ad hoc)*
Matthew Martin, PhD, Pfizer, Inc. (*ad hoc*)
David Michaels, PhD, George Washington University
Devon Payne-Sturges, DrPH, University of Maryland, College Park (*ad hoc*)
Mark Russi, MD, Yale University (*ad hoc*)
Anne Ryan, DVM, PhD, Act 5 Ventures, LLC
Veena Singla, PhD, Natural Resources Defense Council (*ad hoc*)
Susan Tilton, PhD, Oregon State University

National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP) Staff

Rick Woychik

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

Danica Andrews
Brian Berridge
Ian Chen
David Crizer
Julie Foley
Rachel Frawley
Kamel Mansouri
B. Alex Merrick
Georgia Roberts
Andrew Rooney
Sheena Scruggs
Vicki Sutherland
Kyla Taylor
Gregory Travlos
Kristine Witt
Mary Wolfe

Other Federal Agency Staff

Gonçalo Gamboa da Costa, U.S. Food and Drug Administration (BSC liaison)
Christina Lawson, National Institute for Occupational Safety and Health (BSC liaison)

Contract Support Staff

Sarah Colley, ICF
Ernie Hood, Bridport Services
Jeanne Luh, ICF
June Mader, GOFORWARD LLC
Samantha Snow, ICF

[1]The meeting was webcast with the listed individuals attending by Zoom. NIEHS/DNTP staff are limited to those with a role in the meeting. Public attendees are not listed.

3. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened on June 8, 2021 via Zoom for identified attendees noted above and webcast for public attendees. Dr. David Eaton served as chair. Dr. Sheena Scruggs served as the Designated Federal Official.

Dr. Eaton called the meeting to order at 12:30 p.m., welcomed everyone to the meeting, and asked BSC members, Drs. Rick Woychik, Brian Berridge, Sheena Scruggs, Gonçalo Gamboa da Costa, and Christina Lawson to introduce themselves. Dr. Scruggs read the conflict-of-interest policy statement and briefed the attendees on meeting logistics.

4. Introduction to the Meeting Agenda

Dr. Berridge, Associate Director of NTP and Scientific Director of the Division of the NTP (DNTP), introduced the meeting's agenda.

He reviewed the agendas of the previous 2020 and 2021 BSC meetings and discussed the agendas of upcoming 2021 BSC meetings.

He reflected upon the feedback from the April 23, 2021 BSC meeting, in which board members were asked the following three questions in a survey:

- Was BSC engagement at the right strategic level to enable valuable input to DNTP's direction and work?
- What went well, specifically?
- What can we do better next time?

Survey responses showed that all respondents felt that the engagement met or exceeded expectations. Respondents endorsed the new discussion format and broader team member participation. Therefore, the NTP BSC planning committee intends to continue the format.

Dr. Berridge reviewed the four strategic areas of focus in the DNTP portfolio and described the highlights of the current meeting, focusing on the Consumer Products and Therapeutics (CPT) program and the Novel Tools and Approaches (NTA) program. He identified emerging themes for future BSC discussion, including: output/outcome metrics; diversity, equity, and inclusion; capability building; and communication/stakeholder engagement. Dr. Berridge emphasized stakeholder engagement and communication as a topic of particular interest to DNTP.

Dr. Eaton noted that there were no clarifying questions from the BSC members.

5. Consumer Products and Therapeutics Program

Ms. Julie Foley and Dr. Vicki Sutherland briefed the board on the CPT program.

Ms. Foley introduced the CPT program team, which consisted of Ms. Foley and Ms. Danica Andrews as well as Drs. Kamel Mansouri, Andrew Rooney, Vicki Sutherland, and Kyla Taylor.

Ms. Foley began by presenting background information about DNTP's research history associated with CPTs. Although consumer products and therapeutics were combined to form the CPT program, the program team considers them as separate categories given the differences in

their uses, exposures, and regulatory structures. Ms. Foley presented content related to consumer products and Dr. Sutherland presented content related to therapeutics.

The traditional chemical-by-chemical testing paradigm is not well-suited to the immense number of chemicals present in consumer products. There is a clear need to explore and apply a new strategy for toxicology testing. As such, Ms. Foley introduced the first objective of the CPT program, which is a focused testing approach related to consumer products:

- Objective 1: Within the next five years, evaluate whether class-based methodologies are an effective framework for assessing potential human health effects of chemicals in consumer products by considering in silico and empirical toxicity data.

Organohalogen flame retardants (OFRs) will be used as an exemplar of the class-based approach. OFRs are present in numerous consumer products and pose issues of bioaccumulation, daily and chronic exposures, and high-risk exposure groups; advanced toxicity testing will be used in this class-based approach. The U.S. Consumer Product Safety Commission (CPSC) will serve as a primary stakeholder due to their previous work in the field of OFRs and their work with the National Academies of Sciences, Engineering and Medicine Panel on OFRs.[2] Ms. Foley provided additional details about the class-based approach and summarized the first objective's short-term (within 1 year), mid-term (2–3 years), and long-term (4–5 years) milestones.

Dr. Sutherland then presented on the therapeutics portion of the CPT program. Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) therapies are the primary focus of therapeutics research within DNTP. The CPT program recognizes two primary questions for DNTP in the area of HIV/AIDS therapeutics: 1) how to best address concerns associated with HIV combination therapies and the long-term impacts due to these exposures across a patient's lifespan, and 2) whether there are cross-cutting issues of mutual interest with the wider community where DNTP can provide information. The first question originates from the priorities of the National Institutes of Health (NIH) Office of AIDS Research (OAR), which provides annual funding to DNTP and the National Institute of Environmental Health Sciences (NIEHS). The current DNTP testing portfolio includes assessments of combined antiretroviral therapies (cART) for use by HIV-positive individuals during pregnancy or as a prophylactic to prevent transmission.

Dr. Sutherland introduced Objective 2 of the CPT program:

- Objective 2: Partner early with appropriate stakeholders to provide impactful gained scientific knowledge on therapeutics

Under Objective 2, the CPT program will continue to support the NIH-OAR initiative to assess potential toxicities of cART and will engage with stakeholders to share capabilities in toxicity evaluations unique to DNTP. Dr. Sutherland summarized milestones related to Objective 2.

Both aspects of the CPT program need to build new partnerships and strengthen existing ones, leading to Objective 3:

[2]National Academies of Sciences, Engineering, and Medicine. (2019) A Class Approach to Hazard Assessment of Organohalogen Flame Retardants. Washington, DC: The National Academies Press. https://doi.org/10.17226/25412.

- Objective 3: Strengthen and build new partnerships across federal and other nongovernmental organizations to contribute value-added research for the CPT program and facilitate a broader dissemination of information to guide public health concerns.

Dr. Sutherland also described milestone priorities related to Objective 3.

Ms. Foley identified current primary internal and external stakeholders, as well as stakeholders the CPT program hopes to engage with in the future. She discussed several ideas for building and expanding stakeholder interest and engagement, as well to ensure connectivity with other DNTP programs. DNTP is at a pivotal point in toxicity testing and maintains a defining leadership role in advancing toxicology testing. Consumer products present an opportunity to redefine individualized examination of single chemicals. Therapeutics can address unforeseen research needs on health effects of HIV therapeutics. The CPT program presents an opportunity to build rewarding partnerships with multiple organizations.

Ms. Foley concluded the CPT program's presentation by providing the following challenge question to the board: "How [do we] address translation of animal/NAMs [new approach methodologies] consumer products research to humans, given that people are exposed to poorly characterized consumer product mixture and experimental studies test single chemicals?" Consideration of this challenge question occurred during the third discussion topic (see Section 5.2.3).

Clarifying Questions

Dr. Eaton noted that producers of consumer products are an important stakeholder group and producers frequently have their own toxicology and toxicity testing programs; he wondered how to maximize the value of the CPT program by including the producers of consumer products. Ms. Foley said that mutual communication will need to occur between DNTP, consumer product producers, and other stakeholders to share knowledge and techniques. Dr. Berridge added that the next BSC meeting will include the Safe and Sustainable Alternatives program, which will lead to more conversation on this topic.

Dr. David Berube asked how the class-based approach differs from the concept of "banding." After Dr. Berube clarified the definition of banding, Ms. Foley said that the class-based approach is similar, in that it takes "like things" (e.g., similar chemical properties, similar biological function) and groups them to evaluate if they will fit in a class-based approach for testing. Dr. Sutherland agreed that banding was likely another name for the class-based approach. She noted that regardless of the approach's name (e.g., class-based, read-across, banding), the overarching concepts are largely the same.

Dr. Susan Felter said that quantifying exposures is a challenge with many types of consumer products. She asked how CPT will quantify exposures (e.g., data from biomonitoring, modeling migration of chemicals from consumer products) and what role DNTP has in understanding exposure versus toxicology of chemicals in consumer products. Ms. Foley said understanding exposures will begin with building an evidence map, which involves a scoping review to identify and assemble various exposure data. This will achieve a first-glimpse approach of exposures and identify potential data gaps.

Dr. Devon Payne-Sturges asked for clarification on how the CPT program defines "class" within their class-based approach, noting there are multiple ways to group chemicals. Dr. Mansouri

agreed there are different ways to define a chemical class; many are based on the principle that chemicals with similar properties and similar chemical structures are generally associated with similar biological activity or toxicity. Dr. Mansouri noted there are two primary types of similarities: general similarity (i.e., similarity based on chemical structures) and specific similarity (i.e., similarity based on the endpoint of interest). Dr. Taylor added that another approach is to group similar consumer products, such as grouping based on similar consumer uses or common chemical ingredients. Dr. Payne-Sturges wondered if it might be helpful for the group to clarify in their Program Concept document that there are different thoughts about grouping chemicals. Dr. Sutherland noted that there are plans for the CPT program to work with other DNTP program management teams, such as the Combined Exposures and Mixtures (CEM) program, which will assist the CPT program in addressing questions about class definitions. Dr. Mansouri added that another consideration is the fact that some classes are information-rich while other classes are not.

Dr. Matthew Martin asked the CPT program to expand on comments related to Dr. Payne-Sturges' question about class definitions and to discuss the intended resolution of class definitions. He noted that the banding approach often assigns a singular value to a class of chemicals without fully understanding the dynamics within the class, citing the contemporary example of nitrosamines. He asked how the CPT program would approach the issue of depth versus breadth in relation to class definitions. Dr. Sutherland noted that CPSC has a categorization method that would be a good way to start the process.

Dr. Eric Blomme observed that in drug development, small variations can lead to considerable differences in biological activity. He reiterated that one of the CPT program's milestones is assessing the effectiveness of the class-based approach and he asked about the criteria for assessing whether the class-based approach is successful. Dr. Blomme also wondered how early lessons learned would be applied to future classes of chemicals. Dr. Mansouri said that as new methods are developed, they will guide future testing and prioritization efforts as needed, in a circular process of refining, developing, prioritizing, and assessing. Dr. Blomme suggested that the CPT program is therefore assuming the process will work and the program is instead interested in how to improve the process. Dr. Mansouri agreed with this assessment and noted that even if a process does not work for a specific chemical, the results can be used to guide and improve future processes.

Dr. Veena Singla asked the CPT program to elaborate on criteria for assessing methods' effectiveness in providing translatable health effects information. Dr. Mansouri returned to the concept of activity cliffs, noting that a small difference in the structure of similar chemicals can sometimes make a substantial difference in biological activity (i.e., toxicity). Such differences may be more readily identified in information-rich classes; these classes could be refined or split into smaller classes based on these differences.

5.1. Public Comments

Dr. Eaton noted that there were no written or oral public comments for this section.

5.2. BSC Discussion

Dr. Eaton introduced Dr. June Mader as a facilitator for the BSC discussion section. Board members were then asked to consider three discussion topics.

5.2.1. First Discussion Topic

Consider the Problem Statement, Objectives, and Value Proposition in the Program Concept document:

Share your insights regarding whether there is clean alignment among the three. For example, do the Objectives align with the Problem Statement? Does the Value Proposition match what is being stated in the Problem Statement?

Dr. Anne Ryan asked whether the therapeutics component of the CPT program had considered expanding beyond HIV/AIDS therapies to encompass other areas of therapeutics. Dr. Sutherland said that there are one or two other active areas in the CPT program that are not associated with HIV/AIDS, although they primarily focus on their stakeholders' questions in the area of therapeutics. Dr. Berridge added that DNTP receives directed funding to support HIV/AIDS drug-related research, which guides DNTP's therapeutics research priorities to a certain degree. He added that a partner of NTP, the National Center for Toxicological Research (NCTR), also conducts research in therapeutics.

Dr. Pamela Lein asked if there was an interaction or overlap between the CPT program and NCTR. Dr. Sutherland noted that NCTR is part of FDA, and DNTP, FDA, and the National Institute for Occupational Safety and Health (NIOSH) are all part of the broader, interagency NTP, so they share many similar interests. Dr. Sutherland briefly explained the liaising process between the DNTP, FDA, and NIOSH. Dr. Lein added that NCTR also emphasizes NAMs and the entities would work well together as a team. Dr. Sutherland agreed and said that DNTP hopes to continue this very strong relationship.

Dr. Eaton indicated the elements of the first discussion topic align fairly well for the CPT program, although he wondered about the role of DNTP's staff and time in performing consumer product safety testing, versus developing state-of-the-art protocols and approaches that would allow others to appropriately conduct such tests. That is, he felt it is the role of DNTP to develop validated methodologies that are transferrable to other stakeholders, such as producers of consumer products. Ms. Foley agreed with Dr. Eaton's comment, noting that DNTP's role is to develop new testing methods for others to implement and to share their expertise.

Dr. Felter was glad to see the close working relationship between the CPT program and CPSC, particularly given the CPT program's emphasis on OFRs and CPSC's experience in understanding consumer exposures to OFRs. There is likely information that DNTP could obtain from manufacturers and producers who are also interested in understanding these topics. She felt there is good alignment related to the first discussion topic, but she would like to see a greater connection between understanding and quantifying exposures from consumer products to help drive priorities. Ms. Foley noted that the CPT program is relatively new, and they will work with many stakeholders who have expertise in exposure science, such as CPSC and the Developmental Neurotoxicology Health Effects Innovation program within DNTP. Dr. Taylor mentioned a pilot study conducted in collaboration with the U.S. Environmental Protection Agency (EPA), which uses biomonitoring data, environmental sampling data, and exposure questionnaires to explore personal care product exposures from several different angles. Ms. Foley added that the group's first preference is to leverage and strengthen existing partnerships with federal agencies.

Dr. Singla noted that the biggest strength and added value of the CPT program relates to the paradigm shift in thinking about hazard characterization and toxicity testing. There is a need to understand how class-based approaches can be applied to assessing relevant human health effects and understanding how that hazard and toxicity information can inform better policy decisions. The CPT program's objective statement frames it as a question of whether a class-based approach is applicable, but Dr. Singla expressed that it should be a question of how a class-based approach is applicable. This is a more nuanced question. Dr. Singla is very supportive of the direction of the CPT program. Ms. Foley thanked Dr. Singla for her support.

Dr. Eaton added that mode of action (MoA) data need to be central to the class-based approach, because very small differences in a molecule can fundamentally change toxicity. MoA is critical in understanding which members in a class may or may not share toxicity. Dr. Mansouri agreed and said it will be very important to define similarity in specific terms and it should be specific to a study's endpoint.

Dr. Berube commented that if the CPT program intends to collect exposure information from the public, it would be better to use diaries instead of surveys. He added that the CPT program will probably encounter several of the problems that occurred in his research activities associated with nanoparticles, such as identifying the characteristics that need to be class variables and considering the level at which classifications are made. He noted that although the class-based approach will likely work at the macromolecular/compound level, the literature shows that similar approaches (e.g., banding) are problematic at the nano level, where it gets exceedingly complex. Dr. Berube added that the CPT program might need to eventually undertake the class-based approach at the nano level, such as addressing nanopharmaceuticals and the blood-brain barrier. Dr. Taylor noted that the team had used daily diaries as well as questionnaires to collect exposure information from the public.

5.2.2. Second Discussion Topic

Consider the Problem Statement, Objectives, and Value Proposition in the Program Concept document:

Share your insights on whether there is sufficient focus to deliver the intended value to stakeholders.

Dr. Eaton reiterated his assertion that the companies that make the consumer products are among the biggest stakeholders for the CPT program. When evaluating the Value Proposition, it is important that the methodologies, approaches, and new science generated are disseminated and effectively used by the manufacturers. The DNTP is well-positioned to contribute leadership and consistency in testing among the wide variety of consumer product types.

Dr. Susan Tilton expressed that the CPT program's objectives appear to primarily fill data gaps that exist for consumer products by class. She asked if that is the CPT program's goal and the goal of the stakeholders, versus developing the approaches for moving forward in testing by class. Ms. Foley said that the CPT program is working to do all of those things, but the primary goal is to find the new advanced method of toxicology testing that will provide impactful data to stakeholders and shift the existing testing paradigm. Dr. Mansouri added that the main goal is to develop and establish the approach so that it can be used for other classes, such as personal care products.

Dr. Martin noted that the area of quantitative structure-activity relationship modeling has been investigating class approaches for a long time and many other fields are using read-across approaches. From the perspective of the Value Proposition statement, he asked for more information about what is unique about the CPT program's approach and how DNTP is uniquely positioned to challenge some of the existing dogma about read-across approaches. Dr. Mansouri agreed that there are misconceptions about read-across approaches and the class approach in general. He acknowledged that the read-across approach is gaining popularity within the scientific community and among regulators globally. He emphasized that the class approach the CPT program is proposing is not the classical read-across approach, in which chemicals are categorized based on the same properties for all endpoints. In their proposed approach, class similarity will be very endpoint specific.

Dr. Singla indicated there is typically a distinction between the types of testing conducted by consumer product manufacturers and the types of testing conducted by chemical manufacturers. Consumer product manufacturers typically do not conduct a lot of chemical hazard testing; however, hazard information emerging from the CPT program will certainly be of great interest to consumer product manufacturers given their interest in using safer chemicals. Ms. Foley agreed with the distinction offered by Dr. Singla. Dr. Eaton felt that the new approaches developed and validated by DNTP will lead the way for consumer product manufacturers to do a better job.

Dr. Felter noted that labeling or grouping chemicals—as is done in the class-based approach—can lose important context related to potency and can create misconceptions about hazard or safety. Grouping a chemical into a certain class might create an improper perception of hazard and lead to the use of an alternative that could ultimately be more hazardous to human health. Hazard assessment can be misleading without also understanding exposures and potency. For example, programs evaluating "safer choices" often focus on hazard endpoints rather than conducting full risk assessments. She underscored the importance of communicating the nuances of findings from class-based approaches. Ms. Foley felt that an advantage of the class approach would be the ability to assess replacement chemicals through high-throughput testing and other novel methods to better assess MoA characteristics. Dr. Sutherland emphasized that the CPT program will engage with stakeholders to address some of the questions that have emerged in the discussion. Dr. Felter added that she has had concerns about the use of high-throughput testing that use protocols that go beyond the limits of what a human could be exposed to. She said it would be important for DNTP to be cautious about defaulting to methods used historically and using maximum doses in testing, because a chemical could be labeled as a hazard that may not be relevant to consumer exposure levels. Ms. Foley remarked that the value of high-throughput testing is the ability to test more chemicals and doses more aligned with human exposure. Dr. Sutherland emphasized that testing at human-relevant doses is of interest to DNTP.

Dr. Lein reaffirmed comments from Dr. Felter on the concept of hazard versus safety. Dr. Lein then indicated there may not be sufficient focus on mixtures and asked for more information on how the CPT program will approach this topic (e.g., mixtures within a class versus mixtures across classes). Dr. Sutherland replied that the CPT program recognizes that people are exposed to a variety of chemicals—not just chemicals in one class, but chemicals across classes. The CPT program plans to work with the CEM program on such issues, as there has been much work done by DNTP on mixtures. Integrating and translating human-relevant mixtures data from NAMs, *in*

vitro approaches, and *in vivo* approaches will be a major challenge for the CPT program, and the program welcomed any advice or guidance from the board. Dr. Lein added that it would be helpful to frame this issue along the lines of Dr. Sutherland's response, since the Program Concept document currently seems a bit vague. She advised establishing the appropriate criteria in advance. Dr. Sutherland commented that the CEM program has already established many of these criteria, which is a primary reason for their collaboration with that program.

Dr. Weihsueh Chiu expressed that it was still somewhat unclear how the CPT program's framework would fit with the approach suggested by the National Academies of Sciences, Engineering, and Medicine Panel on OFRs, particularly because some policy decisions will need to be made. Policy making is more likely in the purview of CPSC rather than DNTP. He was uncertain how the CPT program's objectives and milestones align with policy making. Ms. Foley noted that DNTP's mission is to provide health hazard assessment data that helps inform regulatory agencies. Dr. Mansouri added that DNTP would help with the science—by developing approaches and establishing methods—and work closely with CPSC to guide them in their regulatory process.

Regarding comparative assessment, Dr. Chiu suggested that the CPT program look at data from the United Nations Life Cycle Initiative, which may relate to consumer product exposures. This initiative has a hierarchy of toxicity data used in life cycle analysis. Ms. Foley responded that the CPT program will look into this.

5.2.3. Third Discussion Topic

Looking ahead, what do you see as the top opportunity or challenge in this Program?

Dr. Mader read the question and introduced the board to the online tool MURAL, which functions as a virtual whiteboard. BSC members were given five minutes to post their individual responses in the MURAL platform, which was visible to meeting attendees in real time.

BSC members' written responses from the MURAL activity are provided below (see Attachment A for actual MURAL output). The CPT program also posed a question directly to the board, noted below and in Attachment A.

- CPT program: How to address translation of animal/NAMs consumer products research to humans, given that people are exposed to poorly characterized consumer product mixture and experimental studies test single chemicals?
- Dr. Berube: Primary concern: We know much about banding (good to review literature) and we have found this approach problematic at the nanoscale. Borrowing a concept (like banding) comes with a history of knowns that need to be integrated to preclude wheel rediscovery.
- Dr. Blomme: Top challenge: Defining scope, application domain and limitations of class-based approach.
- Dr. Chiu: Challenge: Evaluating "effectiveness" for the class-based approach, because unless we test everything (or have extensive epidemiological data) we will never have "validation" data. So it will always involve expert judgement, policy calls, and likely "default" assumptions. Opportunity: Providing data where there are none for consumer product exposures.

- Dr. Eaton: The top opportunity is to bring state-of-the-art approaches to both exposure assessment and MoA-based *in vitro* toxicity assessment by class. The challenge is to ensure that MoA is understood enough to discriminate the "high hazard" from "low hazard" members of a class and then convert to relevant human dose from exposure assessment.
- Dr. Felter: Characterizing exposure from consumer products; ensure focus on risk versus hazard, especially when focus is on chemical classes.
- Dr. Lein: Challenge: mixtures and evaluating how well the class-based approach is working. Top opportunity: characterizing exposures to consumer products.
- Dr. Martin: As an organization not directly tethered to existing regulatory frameworks yet have a large role in developing the science to inform on future regulation and policy, the focus on highly science-based class-based read-across that may break the mold is a great opportunity. The challenge will be to show additive value over default approaches and understanding/quantifying the uncertainty.
- Dr. David Michaels: Several: understanding the effects of exposures in real life–of mixtures, to people with co-morbid conditions and susceptibilities; assisting regulatory agencies in moving from evaluating and regulating individual chemicals to classes of chemicals. Relatedly, I'd also like to see control banding better developed (recognizing it may not work for nanomaterials).
- Dr. Payne-Sturges: An important challenge is addressing chemical mixtures where the chemical components are dissimilar yet together may enhance toxicity. This is the issue with pesticide formulations (active ingredient and "inerts" that are added intentionally to enhance toxicity of the product).
- Dr. Mark Russi: With respect to HIV therapeutics, identify key side effects occurring among very long-term medication recipients and explore mechanisms.
- Dr. Ryan: Moving beyond the exemplar–capture learning and apply to the next consumer products group. Are there learning[s] from similar activities with environmental contaminants and pharmaceuticals?
- Dr. Singla: Opportunity: Paradigm shift of toxicity testing and much more relevant to how people are actually exposed to chemicals in the real world–huge opportunity to update assessment methods to incorporate current science and ultimately inform better decisions to protect public health. Challenge: focus is on chemicals used in consumer products, but consumers are not the only people exposed to the chemicals. Ensure results are also relevant/considered in the occupational context.
- Dr. Tilton: Challenge of mixtures and understanding exposure. Opportunity to fill data gaps and developing testing paradigm for consumer products by class.

After all responses were received from the board, CPT program team members internally discussed the responses while other attendees were on a break. Dr. Mader then reintroduced the CPT program and invited team members to share their thoughts about the board's responses.

Ms. Foley initiated discussion of the third discussion topic and the program management team's question directed to the board.

Dr. Michaels remarked that consumer products are largely unregulated, and consumers can be exposed to many different types of chemicals. CPSC is investigating brominated flame retardants as a class; however, it is impossible to understand all individual chemicals within the class, given the substantial number of chemicals. Similarly, there are more than 6,000 perfluorinated compounds, although good epidemiologic data are available for only a few of the compounds. The big question will be how to move into thinking about such chemicals as a class and then protecting people from harmful exposures. Substitutes are also a challenge, as a substitute chemical may be even more dangerous than the original. Ms. Foley agreed with the stated challenge. She also noted the similarity in challenges within the pharmaceutical realm.

Dr. Eaton commented that he had not yet heard discussion related to the tools of metabolomics and the exposome. This is an area the CPT program should closely watch, because these tools will soon allow for more accurate, quantitative measures of human exposures—including a variety of consumer product exposures and the identification of previously unknown exposures. He asked where the CPT program is in approaching this fairly new area of metabolomics and the exposome. Dr. Sutherland replied that this presents an opportunity for the CPT program to collaborate with other DNTP programs that have expertise in this area. Although the CPT program has not previously targeted their work to this area of research, Dr. Sutherland noted that the program hopes to work with Dr. David Crizer of the NTA program. Dr. Eaton said this approach could potentially narrow the list of thousands of chemicals to identify those of the highest concern. Ms. Foley commented that the next presentation from the NTA program will likely expand on this topic.

Dr. Lein agreed that the CPT program should consider the exposome. There are several centers of exposome research around the United States that work in this field, are NIEHS-funded, and also evaluate consumer products. These centers would be extremely helpful resources for the CPT program. With respect to the first part of the CPT program's question to the board (i.e., how to address the translation of animal/NAMs research to humans), Dr. Lein urged the CPT program to reach out to the Organisation for Economic Co-operation and Development (OECD), which has been actively working in the area of translational research and regulatory science. The OECD is also developing relevant guidance documents on this topic. Dr. Rooney noted that differences in data present considerable challenges, particularly in consumer products research; for example, animal studies frequently use single-chemical exposures, rather than mixtures and product use categories. Dr. Lein recognized this problem and alluded to the fact that OECD is screening consumer product mixtures through *in vitro* batteries.

Dr. Chiu reaffirmed previous comments about the importance of exposomic data, in addition to testing consumer products in *in vitro* systems. *In vitro* systems also need positive controls, such that a positive response is interpretable and meaningful. There is a need to leverage current knowledge of individual chemicals and use high-throughput techniques to rapidly test mixtures, guided by exposomic data or other untargeted analyses. Pursuing fully mechanistic techniques in this space is not yet possible.

Dr. Blomme commented that there are similar considerations throughout the field of biology; for example, developing new pharmaceuticals requires translating animal data to humans and typically starts with an understanding of human disease. He questioned if there might be a cheaper, faster way to evaluate the exposome, such as leveraging biomonitoring studies using fish models. Dr. Mansouri asked Dr. Blomme to clarify his question. Dr. Blomme replied that he

was referring to exposure data collected from monitoring studies to estimate human-relevant exposure levels. Dr. Berridge appreciated the board's focus on understanding exposures. He noted that historically DNTP has been reliant on other organizations to generate exposure data, as DNTP is not an exposure science organization, but rather a hazard assessment organization; DNTP has frequently used data from the National Health and Nutrition Examination Survey and other epidemiologic and biomonitoring studies. Dr. Berridge thought that Dr. Blomme might have been referring to ecotoxicology biomonitoring data that could represent human exposures, which would be interesting to consider. Dr. Berridge noted that the exposome was a major topic in the NIEHS Council meeting that occurred the previous week. NIEHS supports exposomic work and will increase that support in the future. He expressed that developing a better sense of exposures is critical for DNTP and NTP to perform real-world-relevant hazard assessments. This will require partnering with organizations like the rest of NIEHS, NIOSH, EPA, and others. Dr. Berridge would like to see toxicology studies driven more by a fundamental understanding of human exposures, as opposed to the single chemical, high-dose approach.

Dr. Woychik noted that NIEHS has embraced the exposome concept. NIEHS plans to develop improved definitions of the concept, methods for collecting exposomic data, and data infrastructure. This is an integral part of the future direction for NIEHS/DNTP and it is very important to continue these discussions.

6. Novel Tools and Approaches Program

Dr. David Crizer briefed the board on the NTA Program.

He introduced the NTA program team, which consisted of Ms. Rachel Frawley and Ms. Kristine Witt as well as Drs. Alex Merrick, Ian Chen, David Crizer, Georgia Roberts, and Greg Travlos. He also acknowledged former members Drs. Warren Casey and Rick Paules and Ms. Vickie Walker. The NTA is one of the DNTP Strengthening Capabilities Programs. Unlike previously introduced programs, the NTA program does not focus on a specific type of disease or exposure. It is one of two programs charged with providing special capabilities to DNTP. Specifically, the NTA program is tasked with identifying new and novel testing approaches that may improve DNTP science by:

- Increasing testing throughput
- Increasing speed of data acquisition from years to weeks
- Increasing data accuracy and precision
- Providing more in-depth analyses: molecular MoA and benchmark dose (BMD)
- Enhancing human relevance of DNTP studies

Existing NTAs frequently lack the throughput, translational relevance, and human health predictivity required to meet public health needs and expectations. The NTA program aims to identify, evaluate, and implement NTAs that address these shortfalls. The rationale for the NTA program includes the paradigm shift in toxicology (i.e., a desire for more rapid, predictive, and human-relevant data), DNTP's history of developing innovative methodologies, and the fact that DNTP is positioned to lead. The NTA program will address the need for human-relevant, actionable data by developing and validating *in vitro* assays, building confidence in new

approaches, and combining different data streams, such as BMD analysis and MoA data to be able to translate observations to human exposure.

The NTA program is mindful of the need to balance risk and reward in pursuing NTA-related projects. The NTA program's current portfolio of 28 projects fall into two main categories: 1) bioassays and biological systems, and 2) novel technologies. Both project categories have projects the NTA program considers "lower risk and lower reward" and "higher risk and higher reward." Dr. Crizer provided examples of projects under both categories and risk/reward profiles. He then described one of the program's more developed projects using the 3D (three dimensional) HepaRG spheroid liver model.

Dr. Crizer summarized the NTA program's stakeholders and the flow of information between internal and external stakeholders.

He listed the objectives of the NTA program:

- Objective 1: Identify and apply promising new technologies and approaches that enhance the efficiency and translational relevance of DNTP hazard assessments.
- Objective 2: Ensure that novel capability development is aligned to contemporary problems that DNTP is attempting to solve.
- Objective 3: Increase confidence in and adoption of NTAs, and foster development when need exists.

There are three areas of future focus and development for the NTA program: 1) spheroids and organoids, 2) microphysiological systems, and 3) high dimensional data streams. Dr. Crizer provided examples of projects in each of the three development areas.

He examined capability development of eight current projects over near-term (available now or in the near future), medium-term (available in 1–2 years), and longer-term (available in 3–5 years) timeframes. Dr. Crizer described internal connections between the NTA program and other programs and branches within DNTP, in addition to connections between the NTA program and external stakeholders; he used several example projects to illustrate these connections.

Dr. Crizer concluded the NTA program's presentation by providing the following challenge question to the board: "How would the BSC suggest the NTA [program] go about identifying promising new technologies that appear to have direct application(s) to DNTP areas of investigation?" Consideration of this challenge question occurred during the third discussion topic (see Section 6.2.3).

Clarifying Questions

Dr. Eaton asked about the fundamental challenge of converting a concentration in an *in vitro* system to a dose in an *in vivo* system, citing lipid partitioning and protein binding as complicating factors. He recognized that the NTA program might be well-positioned to address this challenge. Dr. Crizer mentioned that all of the Toxicology in the 21st Century (Tox21) cross-partner projects exist inside the NTA program, and one of these cross-partner projects is focused on addressing that very question. Dr. Roberts said that the NTA program is also aware of the need to extrapolate as the program develops new *in vitro* systems.

Dr. Tilton reiterated comments from Dr. Eaton regarding the importance of translational relevance from *in vitro* to *in vivo* models.

Dr. Chiu asked if there is a pipeline between the NTA program and various commercial platforms. That is, how much of the NTA program addresses testing and evaluating off-the-shelf systems versus more of a development pipeline. Dr. Roberts replied that the NTA program spends significant time discussing the right balance between those elements. The program currently leans toward applying more developed approaches, but there are instances for which the NTA program is also interested in assisting with the development or evaluation of less-mature approaches. Dr. Chiu mentioned the National Center for Advancing Translational Science (NCATS) tissue chip consortium and a similar consortium at Texas A&M University. He asked how the NTA program envisions itself interplaying with microphysiological consortia. Ms. Witt noted that there is significant, ongoing effort in the area of *in vitro* to *in vivo* extrapolation and she briefly described a collaboration with EPA. She thanked Dr. Chiu for mentioning the NCATS program and confirmed the NTA program has extensive and ongoing collaborations with NCATS through Tox21. Dr. Berridge mentioned that DNTP is a member of the Texas A&M University Tissue Chip Validation Consortium and reaffirmed that DNTP is active with the NCATS tissue chip consortium. As a follow up to Dr. Roberts' earlier comments, Dr. Berridge stated that DNTP's intent is to follow the progress and maturation of NTA technologies and to be strategic about when to engage with them, evaluate them, and help build confidence in them.

Dr. Martin asked about next steps after NTA technologies can be scaled up economically. In particular, he identified potential challenges related to data volume, management, analysis, and integration—even at moderate scales of implementation. Dr. Roberts replied that the NTA program has a small staff relative to the amount of data it generates, and the program executes much of its work under contracts. Their intent is to develop protocols such that external groups can produce consistent results and testing can be reliably subcontracted. The NTA program is also challenging themselves to focus on topics like data generation, management, and communication from the beginning of their projects. Dr. Merrick added that the program also looks at commercial availability as a measure of success. Ms. Witt recognized that communication was central to all the topics Dr. Martin mentioned. She discussed the NTA program's internal communications and ties with NCATS and other external stakeholders, noting there are many parties collaborating to move technologies from DNTP into a broader toxicological context.

Dr. Blomme asked how the NTA program selects projects to work on and how to allocate resources. Dr. Travlos responded that the program spends considerable time looking at the potential approaches for project selection and he cited several examples. The program has developed a consensus model by which they look at a set of weighted scoring criteria, using a semi-quantitative approach to evaluate elements such as risk, importance, and difficulty. Multiple experts in the NTA program provide input. It is not a simple question, and they sometimes require outside consultations before rendering a decision.

6.1. Public Comments

Dr. Eaton noted that there were no written or oral public comments for this section.

6.2. BSC Discussion

Board members were asked to consider three discussion topics.

6.2.1. First Discussion Topic

Consider the Problem Statement, Objectives, and Value Proposition in the Program Concept document:

Share your insights regarding whether there is clean alignment among the three. For example, do the Objectives align with the Problem Statement? Does the Value Proposition match what is being stated in the Problem Statement?

Dr. Tilton noted that the Problem Statement addresses building confidence in new approaches, which reminded her of earlier conversations the board had with DNTP about transitioning to new approaches. DNTP is in a unique position to provide the field with confidence on new approaches compared to historical animal data. She wondered whether the NTA program has projects in its portfolio that will leverage historical animal data for validation to build confidence in new models. Dr. Crizer cited recent work looking at 20 different chemicals using the five-day rodent study and comparing back to the BMD value resulting from the more traditional two-year cancer bioassays. Dr. Roberts expanded on this example, noting that the next step in this process is running the same set of chemicals through an *in vitro* system to evaluate similarities and differences in dose responses across short-term *in vivo,* chronic *in vivo,* and *in vitro* studies. Dr. Berridge noted that another advantage and opportunity for DNTP is integrated health assessments looking at human data. DNTP's extensive experience with *in vivo* animal studies is a clear strength, and DNTP is increasingly looking at human outcomes and relating them to *in vivo* and *in vitro* models.

Dr. Singla expressed that the effort to develop tools for more accurate and rapid hazard assessment is important, particularly in the context of chemical exposures and their effects on environmental justice communities and people of color. Nonchemical stressors also interact with chemical exposures to lead to adverse health outcomes. In relation to these elements, she asked how some of the new approaches can encompass population variability and vulnerability and the combined effects of environmental exposures and other stressors. Ms. Witt focused on the point about population variability and how it could be built into the new approaches. Ms. Witt noted the availability of the Diversity Outbred mouse model, which the NTA program—in collaboration with EPA—is using in an *in vitro* setting to evaluate potential genetic susceptibility to a set of developmental neurotoxicants. Dr. Roberts added that it is challenging to evaluate the effect of chemical exposures plus nonchemical stressors in an experimental setting, but there are several experts in DNTP who can look at those aspects from a literature assessment perspective and their input could be incorporated into the NTA program.

Dr. Felter observed that the Program Concept document references guideline studies and their historical importance in human health risk assessments. Historical approaches have focused on eliciting a toxicological response to identify hazards, although the question seems to be shifting toward safety assessments at human-relevant exposures. She asked whether DNTP sees the focus on safety assessment, where a legitimate response might be that nothing happens, as opposed to focusing on generating responses at levels that may not be consumer relevant. Given the current language of the Program Concept document, Dr. Felter was uncertain if that transition was really

occurring. Ms. Witt noted that there has been lively discussion in the NTA program about this topic. The Program Concept document's reference to NTP's gold-standard guideline studies, which are accepted by regulatory agencies, was to contextualize historical approaches and to recognize that improvements can be made. The goal is to improve the identification and prediction of health hazards to humans. Ms. Witt noted that there will likely need to be some tie-back to existing data and knowledge to validate new approaches and to facilitate acceptance of new approaches. It will be important for the toxicology community as a whole to move toward defining hazards and safety as they apply to human exposures. Dr. Berridge agreed that DNTP absolutely has an interest in doing toxicology studies that are more aligned to human-relevant exposures. The ability to induce a response that parallels what has been observed in an *in vivo* system builds confidence that the system is biologically and pathobiologically relevant.

Dr. Martin commented that spatial transcriptomics should be part of the NTA program. Dr. Merrick said that the NTA program is also focusing on lengthening the viability of *in vitro* systems (both at a cellular and a microphysiological level) to facilitate more realistic human exposures at lower levels. Dr. Berridge added that DNTP intends to push the envelope in terms of technology, while recognizing that such technologies allow for the generation of data that are more sophisticated than the questions DNTP traditionally asks. Therefore, part of DNTP's progress will be determining how to ask different, but still relevant questions, enabled by more sophisticated data. He noted that there have been discussions about where spatial transcriptomics would fit, but they first need to determine what question they would ask.

6.2.2. *Second Discussion Topic*

Consider the Problem Statement, Objectives, and Value Proposition in the Program Concept document:

Share your insights on whether there is sufficient focus to deliver the intended value to stakeholders.

Dr. Eaton remarked that Dr. Crizer did a good job demonstrating how central the NTA program is to the rest of the programs within DNTP. The NTA program is fundamental to the function of NTP, as the rest of the world looks to NTP to develop NTAs for hazard assessment and safety evaluation. Dr. Roberts was glad that that concept had been communicated effectively in the Program Concept document and presentation and she emphasized the importance of identifying internal stakeholders.

Dr. Eaton asked how NTA interfaces with NCTR, particularly in the areas of microphysiological systems and metabolomics. Dr. Crizer said that while the NTA program's interactions with stakeholders are currently project specific, there are some metabolomics projects that tie in with NCTR. Dr. Roberts described the NTA program's recent work with air-liquid interface exposure models and the importance of future collaboration with NCTR, given their experience in this area. Ms. Witt added that there is also interaction with NCTR related to NTAs in the field of genetic toxicology.

Dr. Singla raised the importance of capturing population variability and vulnerability in NTAs, rather than perpetuating weaknesses from traditional approaches. She noted that the public is ultimately a stakeholder. For the public to have confidence in NTAs, they must encompass real-world exposures and experiences and translate into actionable public health information. Ms.

Witt responded that efforts to generate more BMD data and MoA data could contribute to addressing issues of population diversity and genetic diversity, respectively.

Dr. Lein asked if the NTA program sees one of its roles as harmonizing NTAs across agencies and stakeholders. Dr. Roberts replied that it does, and cited several examples, many of which are currently project focused.

Dr. Blomme continued earlier comments from Dr. Singla. He noted that exposures are controlled in the field of pharmaceutical development, whereas exposures can be dramatically different in the field of environmental health. He asked if it is better to understand variability of people in an *in vitro* system, or to if it is better to understand the overall exposure. Dr. Berridge acknowledged the practice of using uncertainty factors in the field of environmental health, which are not used in pharmaceuticals. There is also the need to pay attention to susceptible subpopulations. With respect to susceptibility, Dr. Merrick discussed the exposome and epigenomics.

6.2.3. Third Discussion Topic

Looking ahead, what do you see as the top opportunity or challenge in this Program?

Dr. Mader read the question and asked the board members to provide their individual responses using the MURAL tool. BSC members' written responses from the MURAL activity are provided below (see Attachment B for actual MURAL output). The NTA program also posed a question directly to the board, noted below and in Attachment B.

- NTA program: How would the BSC suggest the NTA go about identifying promising new technologies that appear to have direct application(s) to DNTP areas of investigation?
- Dr. Berube: Not my area of expertise, nonetheless, there seems to be some translational issues which need to be resolved. Your stakeholder set is sophisticated and this is less a communication issue than a translational one. The only problem with translational fixes is that vested interests tend to dominate some methods over others which can make the hard work less productive as revolutionary approaches tend to be underreported.
- Dr. Blomme: Assuming that closeness to human tissue/physiological conditions (e.g., microphysiological systems) and that ability to dose at more realistic concentrations for longer periods of time is improving model translatability, models fitting these criteria should bring higher return on investment.
- Dr. Chiu: Challenge: Deciding on what systems to develop/test further, given the myriad available, and selecting appropriate positive (and negative) controls. Opportunity: Expanding substantially the "toolbox" of tools and approaches that NTP uses. Providing a "template" for best practices in evaluating these systems.
- Dr. Eaton: Top opportunity: To validate new technologies and approaches for hazard assessment that takes advantage of the wealth of legacy data available from previous *in vivo* studies. Top challenge: To ensure that *in vitro* doses used in new assays are "translatable" to in vivo human dose rates, including to relevant target tissues.

- Dr. Felter: How to set doses/concentrations; how to distinguish adverse from adaptive responses; extrapolation to guide human health risk assessment. How to communicate the paradigm shift (away from traditional tox testing at high doses to ensure toxicity is seen to relevant doses to ensure human safety).
- Dr. Kathleen Gray: I joined this discussion midway through; the comments that might benefit from more internal discussion related to population variability. Ensuring that susceptible populations are defensibly addressed in the identification, development, and assessment of these novel tools is important to adequately accounting for risk to these populations. Uncertainty factors are an imprecise approach, perhaps the best one, but it's worth this group considering their limits.
- Dr. Lein: Significant opportunities to begin to address the questions raised earlier about hazard assessment of the human chemosphere. Challenge–NAMs is like a kid in a candy store (at least for me) – how do you identify the most promising technologies to invest in?
- Dr. Martin: Great opportunity to continue to develop and influence development of novel systems like the TempO-Seq S1500+ but a big challenge in keeping up with an always evolving technology landscape that gets cheaper, better, faster (at least two of those, sometimes all three).
- Dr. Michaels: Hard to say, but clearly this would benefit from involvement of scientists – academic, corporate and others–nationally and globally.
- Dr. Payne-Sturges: The biggest issue to me is translation of these new technologies/methods to whole animal biology, including context. We are learning more and more how much social/physical environmental context matters in enhancing the toxic effects of chemical exposures. So, considering relevance to human population variability in co-exposures and/or responses should be included [as] a criterion for building confidence in these new methods. Similarly, an added value of this program is learning from your experience on how you build confidence in new tools and methods, and not just among your toxicology colleagues but also the public.
- Dr. Russi: Ensuring novel test systems are adequately grounded in actual physiological response.
- Dr. Ryan: Prioritization and making go/no go/stop decisions. 28 programs seems [like] a large portfolio (to me). How will you make room for the new technology that comes along, without getting entrenched in the earlier pursuits? I've seen an emphasis on publication/other communication options during these strategy reviews so how do you balance wrapping things up with taking on new efforts?
- Dr. Singla: Challenge and opportunity is to ensure that tools are developed to encompass population variability (like genetic differences) and vulnerability (life stage, co-exposures, other disease, non-chemical stressors, etc.). This would be significant and major advancement over existing approaches to hazard characterization which typically generate "brightline" concentrations of effect (like BMD) rather than reflecting the range of the population and capturing the most susceptible sub-populations.

- Dr. Tilton: Lots of opportunities: provide confidence in new approaches for regulatory purposes, improve translation of *in vitro* systems with pharmacokinetic models, evaluate/define uncertainties associated with new approaches to improve risk assessment.

After all responses were received from the board, NTA program team members internally discussed the responses while other attendees were on a break. Dr. Mader then reintroduced the NTA program and invited team members to share their thoughts about the board's responses.

Dr. Crizer started the discussion by requesting feedback on the NTA program's question. He identified that several board members' responses tied into the program's question, including prioritization, translation, regulatory use, and selecting the right model systems or exposures. Dr. Eaton observed that the NTA program is collaborating closely with NIH programs developing microphysiological systems. He recommended keeping in close contact with those programs, as well as monitoring progress in EPA and NCTR laboratories.

Dr. Chiu asked about the project portfolio's balance between capabilities supporting other DNTP programs and those of more use to the general community. Dr. Roberts said that the NTA program's portfolio largely consists of projects that complement other programs within DNTP, who they see as an initial stakeholder. Dr. Chiu asked if the NTA program had considered a nomination process for new technologies, perhaps as a part of external stakeholder engagement. Ms. Witt noted that the team had recently discussed ideas for processes to alert stakeholders outside DNTP who may not be aware of their efforts to foster new technologies. One idea was a workshop to bring in invited individuals with expertise in technology development. She cited the example of a successful Tox21 workshop and its role in establishing a bidirectional pattern of collaboration and communication. She asked if the board thought that kind of approach would be helpful. Dr. Eaton said it would be helpful since the area of new technologies is evolving quickly. He added that he was pleased to see references to biotransformation pathways, and he emphasized the importance of biotransformation in assessing toxicity. Dr. Lein supported the concept of holding a workshop and recommended that it focus on perceived knowledge gaps in the CPT program. She indicated workshops would also be useful for other programs such as the Developmental Neurotoxicity Health Effects Innovation Program. Dr. Eaton agreed that a workshop looking at the state of the art in NTAs would be beneficial. Dr. Berridge reiterated that a DNTP research principle is to develop novel capabilities in the context of contemporary problems they are trying to solve. This principle aligns with Dr. Lein's comment about identifying specific knowledge gaps and pursuing technology in those areas.

Dr. Crizer asked the board to comment on how the NTA program should prioritize techniques and technologies that will result in translatable information and will enable them to answer the specific questions they are asking. There were no readily available answers to Dr. Crizer's question. Dr. Travlos said that it would be helpful to have a workshop to create a collaborative group to identify and include other stakeholders.

7. Adjournment

Dr. Woychik noted that it would be important to involve developers of new chemicals and commercial products in the discussion of new technologies. He appreciated the robust discussion that had taken place. He also reinforced NIEHS's commitment to the exposome framework. He extended his thanks to everyone involved in the meeting and to Dr. Eaton for chairing.

Dr. Berridge also thanked Dr. Eaton. He said it was encouraging to see the maturation of engagement with the board and observed that the board's engagement has become increasingly strategic and meaningful. Dr. Berridge also endorsed the idea of workshops. Although DNTP has previously held workshops, he felt that DNTP has not fully leveraged its ability to convene people with common interests and they could consider emphasizing this in the future. He noted that the next BSC meeting will be in August and many of these conversations will likely continue then. He thanked the DNTP programs for a stellar job presenting and for their valuable feedback.

Dr. Eaton thanked Dr. Scruggs for her efforts. Dr. Scruggs added her thanks to the board, to Dr. Eaton for his excellent job chairing the meeting, and to Dr. Mader for her facilitation in partnership with Dr. Eaton. Dr. Scruggs noted that a survey would be going out to the board to gather its valuable feedback.

Dr. Eaton adjourned the meeting at 5:00 PM, June 8, 2021.

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

These summary minutes have been read and approved by the chair of the June 8, 2021 NTP Board of Scientific Counselors.

David Eaton, PhD, University of Washington

NTP BSC Chair

Date: September 12, 2021

9. Attachments

Attachment A

Consumer Products and Therapeutics Program

Looking ahead, what do you see as the top opportunity or challenge in this Program?

Program Management Team

How to address translation of animal/NAMs consumer products research to humans, given that people are exposed to poorly characterized consumer product mixtures and experimental studies test single chemicals?

David Berube

Primary concern: We know much about banding (good to review lit) and we have found this approach problematic at the nanoscale. Borrowing a concept (like banding) comes with a history of knowns that need to be integrated to preclude wheel rediscovery.

Eric Blomme

Top challenge: Defining scope, application domain and limitations of class-based approach

Weihsueh Chiu

Challenge: Evaluating "effectiveness" for the class-based approach, because unless we test everything (or have extensive epi data) we will never have "validation" data. So it will always involve expert judgment, policy calls, and likely "default" assumptions.

Opportunity: Providing data where there are none for consumer product exposures.

David Eaton

The top opportunity is to bring state-of-the art approaches to both exposure assessment and MOA-based in vitro toxicity assessment by class. The Challenge is to ensure that MOA is understood enough to discriminate the 'high hazard' from 'low hazard' members of a class And then convert to relvant human dose from exposure assessment.

Susan Felter

Characterizing exposure from consumer products; ensure focus on risk vs hazard, esp when focus is on chemical classes

Pamela Lein

Challenge: mixtures and evaluating how well the class-based approach is working Top opportunity: characterizing exposures to consumer products.

Matthew Martin

As an organization not directly tethered to existing regulatory frameworks yet have a large role in developing the science to inform on future regulation and policy, the focus on highly science-based class-based read across that may break the mold is a great opportunity. The challenge will be to show additive value over default approaches and understanding/quantifying the uncertainty.

David Michaels

Several: understanding the effects of exposures in real life – of mixtures, to people with co-morbid conditions and susceptibilities; assisting regulatory agencies in moving from evaluating and regulating individual chemicals to classes of chemicals. Relatedly, I'd also like to see control banding better developed (recignizing it may not work for nonomaterials).

Devon Payne-Sturges

An important challenge is addressing chemical mixtures where the chemical components are dissimilar yet together may enhance toxicity. This is the issue with pesticide formulations (active ingredient and "inerts" that are added intentionally to enhance toxicity of the product).

Mark Russi

With respect to hiv therapeutics, identify key side effects occurring among very long term medication recipients and explore mechanisms.

Anne Ryan

moving beyond the exemplar-capture learning and apply to next CP group. Are there learning from similar activities with environmental contaminants and pharmaceuticals?

Veena Singla

Opportunity: Paradigm shift of toxicity testing and much more relevant to how people are actually exposed to chemicals in the real world- huge opportunity to update assessment methods to incorporate current science and ultimately inform better decisions to protect public health.

Challenge: focus is on chemicals used in consumer products, but consumers are not the only people exposed to the chemicals. Ensure results are also relevant/ considered in the occupational context.

Susan Tilton

Challenge of mixtures and understanding exposure; Opportunity to fill data gaps and developing testing paradigm for CPs by class

Attachment B

Novel Tools and Approaches Program

Looking ahead, what do you see as the top opportunity or challenge in this Program?

Program Management Team

How would the BSC suggest the NTA go about identifying promising new technologies that appear to have direct application(s) to DNTP areas of investigation?

David Berube

Not my area of expertise, noentheless there seems to be some translational issues which need to be resolved. Your stakeholder set is sophisticated and this is less a communication issue than a translational one. The only problem with translational fixes is that vested interests tend to dominate some methods over others which can make the hard work less productive as revolutionary approaches end to be underreported.

Eric Blomme

Assuming that closeness to human tissue/physiological conditions (e.g., MPS) and that ability to dose at more realistic concentrations for longer periods of time is improving model translatability, models fitting these criteria should bring higher ROI

Weihsueh Chiu

Challenge: Deciding on what systems to develop/test further, given the myriad available, and selecting appropriate positive (and negative) controls. Opportunity: Expanding substantially the "toolbox" of tools and approaches that NTP uses. Providing a "template" for best practices in evaluating these systems.

David Eaton

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Susan Felter

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Kathleen Gray

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Pamela Lein

Significant opportunities to begin to address the questions raised earlier about hazard assessment of the human chemosphere. Challenge - NAMS is like a kid in a candy store (at least for me) - how do you identify the most promising technologies to invest in?

Matthew Martin

great opportunity to continue to develop and influence development of novel systems like the TempOseq S1500+ but a big challenge in keeping up with an always evolving technology landscape that gets cheaper, better, faster (at least 2 of those, sometimes all 3)

David Michaels

Hard to say, but clearly this would benefit from involvement of scientists - academic, corporate and others - nationally and globally.

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The biggest issue to me is translation of these new technologies/methods to whole animal biology, including context. We are learning more and more how much social/physical environmental context matters in in enhancing the toxic effects of chemical exposures. So, considering relevance to human population variability in co-exposures and/or responses should be included a criterion for building confidence in these new methods. Similarly, an added value of this program is learning from your experience on how you build confidence in new tools and methods..and not just among your tox colleagues but also the public.

Mark Russi

Ensuring novel test systems are adequately grounded in actual physiological response

Anne Ryan

prioritization and making go/no go/stop decisions. 28 programs seems a large portfolio (to me)-how will you make room for the new techthat comes along, without getting entrenched in the earlier pursuits? I've seen an emphasis on publication/other communication options during these strategy reviews so how do you balance wrapping things up with taking on new efforts?

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