National Toxicology Program

Board of Scientific Counselors

December 3-4, 2020

National Institute of Environmental Health Sciences
Research Triangle Park, NC

Summary Minutes

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1. Abbreviations and Acronyms

AOP	Adverse outcome pathway
BSC	Board of Scientific Counselors
COVID-19	Coronavirus disease 2019
CV	Cardiovascular
DNT	Developmental Neurotoxicity
DNT-DIVER	Developmental Neurotoxicity Data Integration and Visualization Enabling Resource
DNTP	Division of the National Toxicology Program
EPA	U.S. Environmental Protection Agency
FAIR	Findability, accessibility, interoperability, and reusability
HDP	Hypertensive disorders of pregnancy
HESI	Health and Environmental Sciences Institute
HEI	Health Effects Innovation
IVIVE	*In vitro* to *in vivo* extrapolation
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NTP	National Toxicology Program
PBPK	Physiologically based pharmacokinetic
PFAS	Per- or polyfluoroalkyl substances
QSAR	Quantitative structure-activity relationship
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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
Myrtle Davis, DVM, PhD, Bristol-Myers Squibb
Susan Felter, PhD, Procter & 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*)
Mark Russi, MD, Yale University (*ad hoc*)
Anne Ryan, DVM, PhD, Act 5 Ventures LLC
Jennifer Sass, PhD, Natural Resources Defense Council
Veena Singla, PhD, Natural Resources Defense Council (*ad hoc*)
Donald Stump, PhD, Charles River Laboratories
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

Scott Auerbach
Mamta Behl
Brian Berridge
Brandiese Beverly
Michelle Cora
Laura Hall
Alison Harrill
Nicole Kleinstreuer
Shagun Krishna
Scott Masten
Elizabeth Maull
Christopher McPherson
Arif Rahman
Sreenivasa Ramaiahgari
Sheena Scruggs
Robert Sills
Mary Wolfe

Other Federal Agency Staff

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

Contract Support Staff

Canden Byrd, ICF
Ernie Hood, Bridport Services
Jeanne Luh, ICF
June Mader, GOFORWARD LLC
Blake Riley, ICF
Samantha Snow, ICF

[1]The meeting was webcast on Day 1, with the listed individuals attending by Zoom. On Day 2, the meeting was via Zoom. NIEHS/DNTP staff listed are limited to those with a role at the meeting. Public attendees are not listed.

Day 1: December 3, 2020

3. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened on December 3, 2020 via Zoom for identified attendees noted above and webcast for public attendees. Dr. David Eaton served as chair. Dr. Mary Wolfe 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, Mary Wolfe, Gonçalo Gamboa da Costa, and Elizabeth Whelan to introduce themselves. He noted that board members Drs. Paul Brandt-Rauf and David Michaels would not be in attendance. Dr. Wolfe read the conflict-of-interest policy statement and briefed the attendees on meeting logistics.

4. Report from the NIEHS/NTP Director

Dr. Woychik, Director of the National Institute of Environmental Health Sciences (NIEHS) and NTP, welcomed everyone to the meeting. He commented on the honor of being selected Director of both NIEHS and NTP and noted the different missions of the two groups.

Dr. Woychik provided an update on the NIEHS budget. He focused on the FY2020 budget since the National Institutes of Health (NIH) is currently operating under a continuing resolution. The final FY2020 allocation increased the budget by 3.6% to just over $802 million. Superfund received a 2.6% increase to $81 million. He noted that NIEHS is hopeful there will be a modest increase this year, although that will not be known until Congress passes a budget. He reminded everyone that NTP does not receive a Congressional appropriation. The three organizations involved with NTP (NIEHS, National Institute for Occupational Safety and Health, and U.S. Food and Drug Administration) collectively fund the program.

Dr. Woychik described his vision for leading NIEHS, which he characterized as being supported by five pillars: a focus on prevention, leadership at all levels, innovation, collaboration, and a workforce including principles of diversity, equity, and inclusion.

He discussed the structure of NTP, which is an interagency partnership headquartered at NIEHS. There is an ongoing strategic planning effort to best position NTP for continued responsiveness and to enhance its effectiveness for addressing 21st century challenges.

Clarifying Questions

Dr. Eaton asked how the NTP budget is distributed among the different units. Dr. Berridge said that he would have a slide in his presentation that would address Dr. Eaton's question. Dr. Woychik noted that the budget planning process for NTP for the next five years is currently underway and reiterated that NTP is not funded through a Congressional allocation.

Dr. Pamela Lein asked about overlap of activities by NTP and U.S. Environmental Protection Agency (EPA). Dr. Woychik said that as the then-acting director, he attended his first NTP Executive Committee meeting in September 2019; EPA is a member of that group. He wants to

engage all members in the NTP strategic planning effort, to help work collaboratively to ensure that efforts are not being duplicated, while being able to take on big, bold projects with well-defined responsibilities.

Dr. Eric Blomme asked whether all NTP partners have a combined strategy related to data sharing. Dr. Woychik replied that he is personally passionate about developing better data architectures, databases, and information systems in order to facilitate machine learning and artificial intelligence. Well-structured data repositories are needed, with scientists agreeing to a common set of data elements, and data issues are an integral element of the strategic planning process. He emphasized the importance of effectively collecting, sharing, and archiving data.

Dr. Matthew Martin asked Dr. Woychik for his thoughts on how to leverage relationships in Europe and other related international agencies, including how to improve data sharing. Dr. Woychik noted that one of the pillars to enable the NIEHS vision is collaboration, and that toxicological and biomedical sciences do not stop at the United States borders. He is a strong advocate of reaching out globally and engaging partners. Science needs to become much more sophisticated and strategic with sharing data resources globally. Dr. Eaton asked about the current status of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, noting that NTP should be playing a critical role in that effort and Dr. Woychik agreed.

Dr. Woychik concluded by thanking the retiring BSC members: Drs. Brandt-Rauf, Myrtle Davis, Jennifer Sass, and Donald Stump, who had reached the conclusion of their appointments. Drs. Eaton and Berridge added their thanks to those members.

5. Introduction to Meeting Agenda and BSC Meetings 2020-2021

Dr. Berridge, Associate Director of NTP and Scientific Director of the Division of the NTP (DNTP), introduced the meeting's agenda and the plan for BSC meetings in 2021. The first day of this BSC meeting would consist of largely high-level material focusing on operationalizing the DNTP strategic realignment and discussing the DNTP strategic planning framework. The second day (December 4) would begin a series of DNTP program introductions, introducing two of the Health Effects Innovation (HEI) programs. The remaining DNTP program introductions will continue in 2021.

6. Operationalizing the DNTP Strategic Realignment

Dr. Berridge informed the BSC about efforts to operationalize the DNTP strategic realignment that has been in progress since he joined the organization. For context, he provided background about the NIEHS organizational structure, DNTP's mission and goals, the framework for the strategic realignment, and the translational toxicology pipeline.

Beginning in January 2018, three phases of the DNTP strategic realignment were set in motion. Phase 1 addressed the portfolio; Phase 2 considered ways of working, and Phase 3 worked on the organizational structure. There has been substantial progress toward achieving those milestones. Dr. Berridge noted that DNTP has evolved to incorporate testing, capabilities, and investigations into a more program-oriented operation. Part of the ongoing evolution is to increase diversity in the workforce.

Dr. Berridge relayed several of the points he had addressed in his first State of the DNTP, which he delivered to DNTP staff in October 2020. He broke down the FY2020 budget allocation by discussing the intramural funding as well as research and development funding via contracts and interagency agreements. DNTP currently has 113 federal staff. Adding contract personnel, the organization is roughly four times that size.

The division responded to the COVID-19 pandemic by widespread and effective adaptation and transition to largely remote work. Delineating NTP products, impact, and influence through journal and NTP publications, public health impacts, media attention, NTP website activity, and NTP databases, Dr. Berridge pointed out that DNTP has shown considerable innovation in products, capabilities, and partnerships and has been active in minority health research. Dr. Berridge concluded that over the next several months, DNTP would introduce a refined and strategic DNTP portfolio.

Clarifying Questions

Dr. Eaton asked how NTP addresses the issue of the precautionary principle when it comes to public health. Dr. Berridge said that one approach is to better contextualize the information NTP generates by adding exposure information and biological context. Also, there is a need for a better understanding of animal models. The field has not been transparent enough in making distinctions about when animal research represents human biology and when it does not. There is a need to better understand genetic diversity and how it impacts biological responses. Dr. Berridge also noted that human relevant modeling and biological systems are important.

Dr. Lein asked about the process for determining which projects are funded and how DNTP identifies personnel to lead these projects. Dr. Berridge described the evolution of the process over the years.

Dr. Kathleen Gray asked for an example of how health disparities and inequalities would be addressed. Dr. Berridge responded that the entire portfolio would be examined to determine how the projects relate to health disparities. Using the per-and polyfluoroalkyl substances (PFAS) initiative as an example, he discussed how DNTP was focusing on the association between exposure to these substances and maternal health. Another way to address this topic would be to identify specific issues related to health disparities. He cited the selection of hypertensive disorders of pregnancy as the model disorder being studied by the Cardiovascular HEI program.

Dr. Sass said it would be very helpful if NTP would assign weight to its use of animal models and conclusions in terms of their impact on human risk assessment in its publications. Dr. Berridge replied that this issue is related to NTP efforts to be more transparent by noting the strengths and limitations of the models. It was also part of an initiative to be more disease-focused and include more human context in NTP reports. Dr. Woychik elaborated on this point and noted that there was an effort to use rodent models with more genetic diversity, such as the Collaborative Cross, to mimic the genetic diversity in the human population.

Dr. Blomme asked how the current staff would be prepared to face the evolving science in context of the strategic realignment, and how hiring would be affected to ensure staff have the appropriate skills needed for future projects. Dr. Berridge said that it is important to have staff who are committed to lifelong learning, while being provided learning opportunities through training. Also, it will be necessary to hire personnel with the appropriate skills to help the institute move forward, particularly in the information technology area. He added that NTP must

present itself as a good partner and work with outside entities since they will never be able to hire enough people to meet all the needs.

Dr. Eaton noted that there were no written or oral public comments on this topic.

6.1. BSC Discussion

Board members were asked to consider two questions.

6.1.1. First Question

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been a stark reminder to significant vulnerabilities in our public health condition. What public health challenges has this pandemic revealed that we should consider within our sphere of influence and capability or how we operate as a scientific organization? More simply, how should the pandemic experience influence the way we think about our mission and operations?

Dr. Davis, the first discussant, broke her response into two parts. The first was focused on public health challenges that the pandemic revealed. Although this public health challenge is not necessarily squarely within the arena of the typical type of exposure science NIEHS/NTP are known for, there are aspects of the disease and susceptible populations that may involve exposures to known substances. The disease states associated with exposures may contribute to unique susceptibility to SARS-CoV-2. She speculated that there may be a place for NIEHS/NTP to draw some attention to those threads of evidence. Secondly, the question related to the workforce in terms of mission and operation. In terms of mission, it should include the interactive nature of environmental exposures and disease, as well as viral exposures, and how those elements interplay. Regarding operations, she was curious about how many people have been working effectively remotely, which presents an opportunity for NIEHS to expand its talent pool by accessing qualified people in other geographic areas.

Dr. Berridge responded that Dr. Davis "hit the nail right on the head." The ability to access talent unrestricted by geographic considerations opens a significant opportunity. The changeover to digital imaging in pathology is one example. Regarding susceptible populations, there is a project underway to understand how environmental exposures might sensitize someone to immune dysfunction. That is a new approach for toxicology, reflecting new thinking in the field.

Dr. Stump, the second discussant, noted that the public has come to expect scientific results quickly, and science can only go so fast to respond, which will be a challenge going forward. There has been a backlash in the case of COVID-19; in an effort to respond quickly, scientists released information that later had to be adjusted as new data became available. He asked whether NTP's goal is to inform other scientists, who can then make regulatory decisions, or inform the general public or Congress. "How do you balance those two?" Regarding remote work, he said it works well for distributing tasks, but the challenge has been that there is no longer the brainstorming that takes place among people gathered in a room. That type of creative interaction is more difficult in the virtual environment.

Dr. Berridge replied that there is a dual value proposition to be had, in that new approaches to predictivity and mechanistic understanding allow for more rapid responses. He agreed with the need to be a more responsive organization. Noting that NTP is evolving in its ability to have

effective interactions, Dr. Berridge observed that some people might express themselves in a chat box who would not necessarily speak in an in-person group setting. He added that it will be important to maintain solid investment in digital infrastructure to prevent distracting technical issues.

Dr. David Berube noted that from communication/social research on these online communication platforms, there are no data suggesting that they maintain or improve the quality of the communication products. He said it is not a science issue, but a "huge communication problem." NTP does great science but does not do a good job communicating about it with the public, legislators, and regulators. Dr. Berridge agreed and noted that NTP needs to pivot and get Dr. Berube on the preventive end of communication analysis rather than the responsive end.

Dr. Martin indicated that recruitment and workforce retention are two areas that should be considered moving forward, as the rapidly changing workforce dynamics now allow people to work for companies located elsewhere but continue to live in the desirable geographic area represented by Research Triangle Park. He also asked how onboarding of new staff was conducted during this time.

Dr. Berridge said that DNTP has had the good fortune to hire staff with prior experience from within NIEHS or the Research Triangle Park, NC area, making it easier to integrate them into DNTP. He noted it is more difficult to onboard people who are not familiar with the area or the organization.

Dr. Lein mentioned that one of the biggest challenges she has seen with COVID-19 is the public's trust in science and helping to rebuild that public trust represents a challenge.

6.1.2. Second Question

> ***A key theme of the NIEHS Strategic Plan is "Data to Knowledge to Action." As a research organization focused on hazard assessment, the "actions" we enable guide toxicology research and inform decisions by others including individuals and policy makers. We have shared with you our productivity over the past year and some outcomes of our work. We are interested in our work being effective and having impact. What other types of DNTP activities and products should we consider? How might they differ from the perspective of various stakeholders (decision makers, concerned citizens, scientific community)?***

Dr. Eaton asked Dr. June Mader to facilitate the exercise for board members. She read the question and said the group would break into three work groups representing various stakeholders: decision makers, concerned citizens, and the scientific community.

Following the groups' deliberations, Dr. Mader called upon the group leaders to report on their results, each responding to the question, "What other types of DNTP activities and products should we consider?"

Dr. Susan Felter provided input from Group #1's discussion, taking the role as "Decision Makers" (see Attachment A for slide presented). The group felt that as decision makers, they had to have confidence they were really understanding the data that were coming from new data streams and technologies and that DNTP needs to take a leadership role in developing training sessions on the tools that NTP offers. DNTP needs to consider ways to translate data into actionable knowledge and how to best communicate that actionable knowledge to stakeholders

and to the general public. This is critical since the challenges involved with science communication are tougher than ever. Dr. Felter added that since decision makers are usually presented with very large reports with a lot of data, being able to identify and quickly review the essential information via executive summaries is ideal. DNTP should offer risk of bias tools that decision makers and data generators can use to evaluate data and ensure confidence in the data, for example with mechanistic and computational data. Developing the confidence with new data streams will also be important. She mentioned that DNTP should offer or develop tools for evaluating external validity, particularly for mechanistic and computational approaches. Updating mailing lists will help DNTP ensure that their published reports are reaching the intended and interested audiences.

Dr. Veena Singla added that a lot of the group's discussion centered on tools and training to allow decision makers to evaluate data and use it to inform decision making. It is critical for DNTP to facilitate the outreach and connection directly to make sure these reports and publications reach the decision makers through the development of communication plans such as email distribution and webinars to interested agencies.

Dr. Sass provided input from Group #2's discussion, taking the role as "Concerned Citizens" (see Attachment B for slide presented). She noted the challenge government agencies and scientists face with the public in terms of credibility and trust, as they have been eroded over the last several years. It is important for DNTP to engage in trust building exercises, which include attending meetings organized by public groups, such as faith-based gatherings or other gatherings within communities, and report on the information using laymen terms. DNTP should work more with faith-based communities, who are trusted within the groups DNTP is trying to reach. The group also discussed the possibility of using social media campaigns to disseminate DNTP's message. Dr. Sass said that DNTP needs to have a two-way dialogue with members of the public, and ask them about their concerns and what NIEHS and DNTP can provide to them. DNTP needs to ask meaningful questions during these conversations that they can be responsive to.

Dr. Davis provided input from Group #3's discussion, taking the role as "Scientific Community" (see Attachment C for slide presented). The group indicated that a helpful product for the scientific community would be a more robust user interface that provides access to both data generated by DNTP and from other sources. DNTP should have some influence on the types of grants and opportunities there may be for scientific research and it is critical that the scientific community receive funding to do the work that is underpinning the understanding of these types of activities. There is a need to develop the molecular understanding of a mechanism of action, not only for the formation of adverse outcome pathways (AOPs) but also to provide clarity to AOPs so they can be used by the scientific community and those in regulatory agencies. DNTP and NIEHS should validate new approaches so the scientific community can use them immediately without needing to spend time on extensive validation of those approaches. Workshops for stakeholders to learn about these approaches once they are validated would be very helpful as a complementary event. It is critical to help with the interpretation of molecular and epidemiological datasets generated by NIEHS and the scientific community at large. DNTP and NIEHS should provide the right tools with the right type of communication messaging to help the scientific community explain their science and interface more effectively with concerned citizens.

7. DNTP Strategic Planning Framework

Dr. Scott Masten briefed the BSC on the DNTP strategic planning framework.

Strategic planning is a continuous process, as opportunities are assessed along with needs that DNTP is well positioned to address and lead. The aim is to build upon existing organizational strengths and identify research focus areas that align to the division's goals and strategic intent.

Strategic realignment activities include five elements: portfolio, processes, people, products, and structure. The purpose of the framework is to expand DNTP's value and impact by emphasizing innovative translational approaches to human relevance that increases confidence in decision-making.

The DNTP Research Principles include several key considerations that guide portfolio decisions:

- Complex public health concerns with recognized stakeholders that leverage DNTP's full spectrum of animal and non-animal capabilities
- Responsive to discrete knowledge gaps where actionable outcomes can be achieved
- Integrate and leverage existing knowledge in clearly defined and systematic ways
- Facilitate the adoption of novel tools and approaches to generate information that is more human-relevant and predictive
- Translational and mechanistic investigation supporting practical application in decision-making contexts

Dr. Masten provided several examples of portfolio elements aligned to these principles.

He discussed the areas of focus in the DNTP portfolio, which are designed to align to the following overarching strategic objectives:

- Address contemporary public health problems related to environmental exposures
- Improve DNTP's ability to carry out substance-based hazard evaluations that are more translational, innovative, and responsive
- Develop disease-focused environmental toxicology
- Provide an evidence-based approach to identify and understand potential environmental contributors to contemporary and common diseases
- Enhance DNTP's progress in becoming a more predictive science through the deliberate application of a translational toxicology pipeline of capabilities
- Leverage and improve upon existing strengths
- Selectively develop and apply novel capabilities that directly enable multiple scientific initiatives

Aligning the DNTP portfolio with the overarching strategic objectives results in a portfolio partitioned into four strategic areas of focus, with ten specific programs:

1. Health Effects Innovation (cardiovascular, carcinogenicity, developmental neurotoxicity)

2. Exposure-based Research (combined exposures and mixtures, consumer products and therapeutics, occupational and inhalation exposures)
3. Responsive Research (emerging contaminants and issues of concern, safe and sustainable alternatives)
4. Strengthening Capabilities (novel tools and approaches, scientific cyberinfrastructure)

For each research program, a DNTP staff-led team develops program-specific strategic objectives, explores partnership opportunities within and outside NIEHS, communicates to internal and external stakeholders, and manages a portfolio of projects within the program. The outputs of these strategic planning efforts are a progressive series of templated documents labeled Program Introduction, Program Concept, and Program Plan. The documents are continually revised, expanded, and used for internal decision-making and to facilitate external engagement with the BSC. Dr. Masten identified the components of the Program Introductions, Program Concepts, and Program Plans.

Engagement with the BSC is an important element of the strategic planning process toward development and execution of the Program Plans. It will incorporate:

- Focus on strategies, approaches, and products (SAPs)
- Understanding of DNTP's mission, goals, intent, and value
- Gaining perspective of the entire portfolio, how it is structured, and areas of focus
- Prospective advice during strategic program development
- Feedback on problems to be solved, realistic objectives, tactical approaches, and likelihood of success
- Assessment of progress against milestones and contemplation of strategic shifts in program direction or continuation

Future BSC engagement topics include cross-cutting strategic themes such as:

- Output and outcome metrics
- Diversity, inequality, and racism
- Optimizing stakeholder engagement
- Capability building
- Expanding DNTP's portfolio of products

Clarifying Questions

Dr. Eaton commented that duplication or replication of research efforts is not always bad, especially for very important questions.

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

7.1. BSC Discussion

Board members were asked to consider two questions.

7.1.1. First Question

We continue to refine our strategic intent, ensure that our research creates value for multiple stakeholders, and improve how we articulate that value. What elements of opportunity, merit, and value expressed in the Program Introductions are most compelling and match your expectations regarding DNTP's mission and strengths? What obstacles, risks, or blind spots are most important to consider?

Dr. Weihsueh Chiu, the first discussant, started by addressing the four focus areas and offering comments on the programs in those areas. He said that the HEI area is one of the strongest, and it will be important to leverage both intramural and extramural research. Responsive Research will also be important for topics such as emerging contaminants and issues of concern like Elk River and PFAS. He added that Strengthening Capabilities will be important for scientific infrastructure. He felt that the reference to novel tools and approaches was rather general and wanted to know whether this involved building new tools/approaches or helping with applications. For the Exposure-based Research area, there is long-standing expertise in combined exposures and mixtures, and on a broader scale, data on complex mixtures using untargeted approaches and whole mixture screening could offer new approaches. Dr. Chiu mentioned that non-chemical stressors should be incorporated on the exposure side, encompassing a broader range of stressors than just chemicals. For example, the long-term effects of COVID-19 may modulate chemical susceptibility in the future. Preexisting conditions or background disease might also be a factor that could impact susceptibility to chemical exposures. Consideration of these types of issues seemed to be missing, he noted. Looking at some of the individual programs, he felt that the overall focus for the consumer products and therapeutics program was unclear – whether it is a responsive research concern or more a methodological issue in terms of developing class-based approaches. He expressed similar misgivings about the occupational and inhalation exposures program and noted that other routes of exposure, such as dermal, as well as radiation exposure, exist. He was not certain that these exposures necessarily fell under occupational exposure. He felt that the lung models may belong in the HEI area. In terms of safe and sustainable alternatives, he was unsure how that would work and if it would be stakeholder-driven. He suggested a pilot project program for novel tools and approaches and noted that it is unclear whether this program involves building new tools, developing standard operating procedures for new tools, or achieving validation for these approaches.

Dr. Masten noted that the February 2021 BSC meeting will discuss combined exposures and mixtures in more detail. He felt that several of Dr. Chiu's comments addressed how broad some strategic areas of focus are, which is a result of combining legacy work with new directions.

Dr. Sass, the second discussant, divided her comments into strengths and recommendations. For strengths, she liked the continued emphasis on the use and development of whole animal models. She enjoyed the breakout sessions and hoped that DNTP would continue to set a high bar on how to integrate information in efforts such as systematic reviews. Guidance is needed on how to use the new high-throughput data, particularly how to use it to make health-protective decisions. For recommendations, she urged expansion of partnerships to include health-impacted communities, for example, groups like the Collaborative on Health and the Environment, as well as other affected community-based groups. She added that tools are needed to conduct cumulative hazard evaluations and risk assessments and recommended that DNTP and NIEHS keep sight of its prevention mission.

Dr. Masten agreed about the importance of a continued focus on prevention. He liked Dr. Sass's recommendation about expanding community-based partnerships and pledged to pursue it.

7.1.2. Second Question

Given there are many important things to work on that fall within the DNTP mission, what are factors to consider in maintaining a balanced, impactful portfolio? We are interested in your perspective along a continuum with respect to the dimensions of risk, timeframe, stakeholder responsiveness, etc.

Dr. Mader facilitated the zoom annotation activity for the board members. She read the question and asked the board members to mark each of the five continuums based on their impressions of DNTP priorities (see Attachment D for final annotation activity results).

Dr. Eaton summarized the results. There was a clear consensus that higher risk, novel approaches were preferred to lower risk, well accepted approaches. The second continuum, spanning actionable information to biological understanding, showed a slight preference for actionable information. The third, spanning stakeholder needs to scientific discovery, also had widely scattered responses. The fourth, spanning product focused to hypothesis driven, skewed largely toward hypothesis driven. The fifth, spanning short-term success to long-term payoffs, showed a clear preference for the longer-term approach.

Regarding the second continuum, Dr. Felter said that the two elements went together, as did some elements for other continuums. Dr. Lein felt the same about the third continuum; that the elements were not opposites and it was an odd continuum because the elements were so dependent on each other. Dr. Chiu observed that there should be a more portfolio-driven approach, rather than trying to center on the particular elements shown, as there is a distribution of projects mixing those elements. Dr. Davis noted that the actionable information versus biological understanding element called for that consideration to be made for every item in the portfolio independently. Dr. Singla felt that the questions were missing a focus on health disparities, with environmental exposures being "profoundly unequal." She said there is a need to better integrate those considerations into strategic planning. Dr. Sass noted that it was a valuable exercise and found it particularly interesting that the board largely agreed on the first and fifth continuums.

Dr. Eaton commented that it was a good exercise to end the day's proceedings. Dr. Berridge indicated that the day had far exceeded his expectations, with such high-level feedback and added that the board's thinking would certainly be integrated into future presentations.

Day 2: December 4, 2020

Dr. Eaton reconvened the meeting at 12:30 p.m. and asked BSC members, Drs. Rick Woychik, Brian Berridge, Mary Wolfe, Gonçalo Gamboa da Costa, and Elizabeth Whelan to introduce themselves. Dr. Wolfe read the conflict-of-interest policy statement.

8. Introduction to Meeting and Research Programs

Dr. Berridge introduced the day's proceedings. He provided context to the upcoming presentations on two of DNTP's HEI programs. The HEIs have two primary aims: to build

capability to characterize hazards in the different areas, and to invent a novel approach by modeling fundamental elements of disease to provide an understanding of where exposure might be exacerbating those diseases. That disease-oriented outlook is an innovative approach to toxicology.

He introduced Dr. Brandiese Beverly, presenter for the Cardiovascular HEI (CV HEI) Program.

9. Cardiovascular Health Effects Innovation Program

Dr. Beverly described the Problem Statement for the program:

- Chronic progressive cardiovascular (CV) disease is a primary cause of morbidity and mortality in the United States and globally
- Current approaches to environmental hazard assessment do not include specific assessments of CV bioactivity and hazards
- There is no defined approach to identify agents that might be contributing to contemporary and common CV diseases

The CV HEI program is structured around three objectives:

- Leverage existing knowledge to define key "failure modes" as a biological framework for modeling, link those modes to mediators of mechanistic bioactivity, and screen existing databases to identify putative CV hazards
    - CV failure modes are discrete ways in which the CV system responds to injury
    - Linking failure modes to mediators of mechanistic bioactivity leverages existing knowledge, e.g., using them as a framework to screen existing databases
- Develop a suite of assay/testing/modeling/knowledge management capabilities that aligns to the current DNTP Translational Toxicology Pipeline and apply it, in an integrated fashion, to provide an evidence-based approach to assessing CV bioactivity of environmental substances
- Develop and implement an innovative capability for identifying potential environmental contributors to specific and contemporary clinical CV diseases
    - This represents a shift from agent-based to disease-focused health effect assessments
    - The model disease state chosen for investigation is environmental contributors to hypertensive disorders of pregnancy (HDP).

Dr. Beverly discussed the progress to date in the project, including complete, ongoing, and pending milestones. She depicted the various activities associated with the project through its third year.

Clarifying Questions

Dr. Eaton asked Dr. Beverly whether it was the intention or plan to take compounds that have already been screened for various toxicity endpoints, such as the ToxCast list of chemicals, and assess whether they are potential environmental chemicals acting on a particular AOP.

Dr. Beverly said her group is identifying specific chemicals they want to test in the platforms they are using, adding that the existing chemical information has not yet been screened in the CV AOPs, although that is a possibility going forward.

Dr. Blomme asked about capability gaps. Dr. Beverly noted that many of the capabilities being considered had already been developed for other organ systems and can be applied to the CV system. She said her group needs to be smart about how to incorporate new CV endpoints into study design. Dr. Berridge commented that one of the gaps is physiologically relevant *in vitro* systems that bridge between basic mechanistic bioactivity *in vivo* and mentioned the possibility of leveraging secondary pharmacology screening in drug development, focusing on potential CV bioactivity. DNTP is working to build capabilities for employing *in vitro* systems to gain confidence that bioactivity will actually have an *in vivo* impact.

Dr. Lein asked how DNTP would ensure that a wide spectrum of individuals is being recruited to the various projects. Dr. Beverly replied that the personnel working on the projects have engaged their networks and had conversations with many stakeholders to ensure that the appropriate expertise is involved. Dr. Lein liked the transition to the biological hierarchy, but one thing missing in the AOP field is the cause-effect mechanistic data that allows linkage from one key element to the next. She asked if DNTP would consider developing those data that allows linkage from the molecular initiating event to the cellular effect to the organism effect. Dr. Beverly said there has been conversation about AOPs and how to achieve better understanding of the AOP framework, although the CV HEI is not actively working to develop AOPs. She felt that DNTP's work could ultimately inform AOPs. Dr. Lein considered that DNTP is uniquely positioned to bring the different models across different levels of biological hierarchy into one place and develop the cause-effect relationships that are the weakness of all AOPs. She further asked in what ways the goal of identifying how environmental exposures might exacerbate pre-existing conditions would overlap with the endpoints being measured. Dr. Beverly pointed out that this question focused on the project's third objective, which is focused on understanding the contribution of environmental exposures on the development or exacerbation of complex diseases. Current scoping efforts using HDP as an exemplar will identify relevant biomarkers of disease in humans and in animal models, the extent to which they have been evaluated in the context of environmental exposures, and ultimately, the feasibility of conducting *in vivo* studies, *in vitro* studies, and bioactivity screens in future work.

Responding to Dr. Martin's question about the CV quantitative structure-activity relationship (QSAR) screening tool, Dr. Beverly commented that it falls under the first-tier approach to evaluate chemicals that may have activity. Dr. Nicole Kleinstreuer added that a number of QSAR modeling efforts are planned and referred to several examples.

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

9.1. BSC Discussion

Board members were asked to consider five questions.

9.1.1. First Question

What are you most excited about?

The first question was a whiteboard activity facilitated by Dr. Mader. Board members filled in their own individual comments responding to the question (see Attachment E for whiteboard activity results).

BSC answers included:

- Connecting vascular disease with relevant environmental exposures in distinct populations
- Focus on health disparities
- Disease focused and computational/*in vitro* framework
- Opportunity for NTP to contribute to molecular pathway analyses for CV toxicity of environmental agents

9.1.2. Second Question

Please share your insights about the Program regarding:

a. How the objectives address the problem/opportunity

b. The boldness of the approach to achieve the objectives

c. The alignment of the metrics to the desired impact

Dr. Davis was the first discussant. She said there is general excitement about including a cardiac and vascular hazard assessment in the DNTP repertoire; however, the objectives are not well aligned with the problems. She commented there is no current approach to include CV bioactivity in an environmental hazard assessment and recommended including some of those measurements to define that bioactivity in a meaningful way. While the problem statement discussed how these bioactivities may contribute to CV disease, Dr. Davis failed to discern any alignment. She said that the bioactivity being measured right now may not assess the vascular response very well, adding that there is a huge gap in the vascular assessment. Although the approach of using cardiomyocytes instead of single point assays is not very bold, it is appropriate. The AOP is a bit different. In terms of the alignment of metrics to impact, she was unclear what the metrics were and wanted to hear more about them.

Dr. Sass, the second discussant, indicated that she had had difficulty answering the second question and had formulated three questions back to DNTP. First, she asked how this research would address air pollution and the clean air standards, since air pollution is a major contributor to CV disease. Avoiding the question could be viewed as dodging an important pollution driver, with projects not addressing it seen as creating delays for long-overdue health protective policies and practices. Dr. Sass also commented that there is a need to support the work of frontline communities and environmental justice communities, which are at high risk for CV disease resulting from chronic exposure to air pollution, as well as support legally enforceable standards. Her second question addressed concerns about the partnership with the Health and Environmental Sciences Institute (HESI), which she said draws its membership from business entities such as agricultural chemical manufacturers, pharmaceutical companies, and other corporate interests. DNTP needs to be transparent about its relationship to an organization that includes companies that contribute to air pollution and CV disease. She inquired about the potential influence wielded by these partners. Her third question asked whether this research

would contribute to the development of methods for addressing the cumulative impacts of complex multi-chemical, multi-sector air pollution for high-risk communities like Cancer Alley. That research is critical to those communities and to make the Clean Air Act more functional and more protective. Current approaches are inadequate, and NTP has a role to play in developing those methods. Dr. Sass wondered if the program could be used as a case study using key biomarkers of chronic CV disease and advanced statistical methods from social epidemiology to quantify the combined effects from exposure to multiple chemicals and vulnerability factors that are non-chemical stressors with relevance for health outcomes like CV disease.

Dr. Singla asked what kinds of exposures or disease processes would not or could not be tested in the system—for example, metabolites of substances. She also asked about attention to developmental toxicity. Dr. Eaton brought up the importance of biotransformation in assessing the toxicity of compounds, particularly metabolites since they usually drive toxicity, not the parent compounds.

Referring to the issue of cumulative exposures and how to evaluate them, Dr. Beverly said that the group is constantly looking at real-world scenarios of multiple exposures for which methods continue to evolve. Dr. Beverly fully agreed with Dr. Sass that stakeholders and impacted communities need to be engaged.

Dr. Berridge noted that the efforts presented are at different levels of maturity, so there are some elements not being shared, such as the vascular component mentioned by Dr. Davis. It has been considered, but no data have been generated yet. He appreciated Dr. Sass's comments on air pollution and her point about HESI. He cited his long involvement with HESI and said that they remain an important partner. Regarding cumulative risk, the field is starting from scratch in the environmental hazard assessment capability, and much of what will be done initially will replicate pharma's efforts.

Referencing the vascular component, Dr. Kleinstreuer cited collaboration with the National Center for Advancing Translational Sciences and the assay platform in the CardioToxPi work. There is also a project underway to develop a systematic evidence map of the literature, leveraging artificial intelligence approaches to semi-automatically screen the literature, with more than 200,000 potentially relevant papers identified in a keyword search, many of which are focused on air pollution.

Dr. Scott Auerbach asked Dr. Sass what she would consider actionable information on air pollution, both now and in the future. Noting support for NTP's work and its international reputation of its data as "the gold standard in the world", she said NTP's guidance is needed on how to use its studies to support prevention-driven public health action and regulatory standards. The data, analyses, and summaries feed into the chemical evaluations conducted by other programs and regulatory agencies that do not conduct their own studies.

9.1.3. Third Question

Considering DNTP's capabilities and expertise, what mechanisms do you suggest that we consider to be able to effectively execute against the objectives? With whom might we partner to ensure success?

Dr. Blomme, the first discussant, commented that the project is "extremely bold"; however, there are significant gaps. He enumerated three challenges. The first is the many steps involved to go

from biomolecular screening data to *in vitro* to humans. Second, small changes in metrics such as blood pressure can have a profound effect but are hard to tease out. Third, phenotypic endpoints have multiple indirect effects. He recommended going from a biased approach to a more unbiased approach using artificial intelligence, and the data structure must incorporate findability, accessibility, interoperability, reusability (FAIR) principles. He recommended partnerships based on those principles, particularly partnerships outside of the usual field, with entities such as Google because of the value from working with people with expertise in data analytics. He approved of the partnership with HESI and added that partnerships to develop appropriate *in vitro* models will be key. Regarding key capabilities, the challenge is to find the right balance. Dr. Blomme looked forward to hearing more about the QSAR modeling.

Dr. Martin, the second discussant, focused on specific technical items. He recommended examining the current Tox21 hERG assay and some of the non-pharma assays as a valuable exercise. He also thought consideration of other disease models such as inflamed or fibrotic models in the CV disease space would be of value. Dr. Martin endorsed establishing more collaborations with the epidemiology community.

Dr. Beverly agreed that leveraging the epidemiological community would be critical to understanding the impact of environmental exposures on some of the underlying diseases and co-morbidities.

9.1.4. Fourth Question

The disease-focused approach of the Health Effects Innovation Programs is novel in toxicology and hazard assessment. What unique challenges are we likely to encounter in taking that approach for CV disease? What near- and mid-term deliverables might reinforce our decision to take that approach?

Dr. Anne Ryan, the fourth discussant, complimented Dr. Beverly on the program's progress over time. She noted that one of the unique challenges of the disease-focused approach is that it is orthogonal to tradition, and there will be skeptics. Part of the challenge is that air pollution is comprised of mixtures, and HDP is a multifactorial etiologic disease. There will be skepticism by some that environmental exposures are related to CV disease. She urged careful selection of the first exemplar in order to build confidence in the new approach and to bridge to translation, perhaps focusing on a single mechanism or failure mode with appropriate positive and negative controls. She recommended focusing on a well-characterized test article with known effects, versus a mixture. She said it will be important to bridge the preclinical *in vitro* and *in vivo* data to human epidemiologic and exposure datasets.

Dr. Beverly indicated that DNTP is aware of the challenges discussed by Dr. Ryan and will address them, working in a stepwise fashion to gain acceptance and making sure to collaborate with the appropriate groups. Regarding the skepticism, she pointed to the availability of epidemiologists and toxicologists to aid communication, taking advantage of the breadth of epidemiological data that show associations between exposure to environmental chemicals and cardiovascular outcomes and linking mechanistic information to better understand observed associations. The next logical steps going forward will become clearer with the development of documents to define those associations.

9.1.5. Fifth Question

A key theme for the NIEHS Strategic Plan is "Data to Knowledge to Action." At what level of detail do we need to characterize CV hazards to enable public health-protective decisions by individuals, regulatory scientists, and policy makers? For example, at the level of bioactivity in the CV system, induction of adverse changes in morphology or function or at the mechanistic level?

Dr. Davis, the first discussant, suggested that the key question is--for what decisions would hazard identification be sufficient. Assuming that a hazard identification bioactivity is characterized well enough to define the attribute as a hazard, what decisions can be made with just a hazard identification, taking hazard identification forward into risk assessment, and then risk assessment forward into disease-based mechanistic connectivity. There is always a struggle with whether hazard identification is sufficient for regulatory decision making.

Dr. Berube, the second discussant, stated that the assumption in the question was incorrect; there are many variables that should be considered. It is also a questionable assumption that merely providing decision makers and regulators with more information will result in better decisions. He noted that the issue is not just hazard, but also encompasses exposure and, more importantly, the perception issue, noting that how we approach use of data is modified by the perception we bring. There are two worlds of thought on cardiovascular health communication. The old world of thought says you can get people to change their behavior by providing information about risk. Today's communication deals with the variables of severity, salience, and efficacy, whether dealing with an expert audience or a public audience. To make a real footprint in the world, attention should be paid to the concept of how to use positive reinforcement to move people forward, including both expert and inexpert audiences. Dozens of variables have been studied in past campaigns such as safe sex and smoking cessation, and they should be considered to detail those appropriate for incorporation; otherwise, there is the risk of coming up with a new tool that no one will use.

Dr. Beverly appreciated Dr. Berube's comments on how to create something that will be usable. She challenged everyone to help develop an effective communication strategy, with the public as a stakeholder. Dr. Berridge added that the communication and decision-making considerations make the job even more complex.

10. Developmental Neurotoxicity Health Effects Innovation Program

Dr. Mamta Behl reported to the board on progress in the Developmental Neurotoxicity (DNT) HEI Program.

Dr. Behl cited the following as motivating factors for developing a new framework for assessing DNT:

- Increased prevalence in neurodevelopmental disorders in the United States and globally
- Underdeveloped strategies to evaluate DNT
- *In vivo* DNT Guideline studies, which are time and resource intensive, remain the primary method of evaluation
- Compounds with unknown DNT potential remain untested

The program employs a three-pronged approach: (1) *in vivo* testing, (2) DNT screening, and (3) exposure assessment/clinical translation. DNT screening is being used to prioritize compounds for further testing and gain mechanistic insight to complement *in vivo* testing.

The program includes three objectives:

- Implement a DNT screening battery that covers key neurodevelopmental events
    - Initial assay selection includes 2D assays, 3D neurospheres, and zebrafish
    - Builds on DNTP's past experience, including DNT-DIVER (Data Integration and Visualization Enabling Resource)
    - Prioritizes compounds for further testing
    - Applied when animal studies may not provide the answer
    - Represents a global contribution to DNT
- Assess novel DNT assays and technologies *in vitro* and *in vivo*
    - Incorporates genetic diversity
    - Includes automated behavioral monitoring and neuroimaging
    - Linking mechanistic bioactivity to clinical endpoints
- Establish communication pipelines with stakeholders and public.

Dr. Behl described a number of stakeholders from government, industry, and academia, and noted that the partnerships will be expanded to include clinicians, advocacy, and more industry groups. She listed several program milestones and metrics, including milestones that have been accomplished and those still in progress. The program's ultimate goal is to more effectively predict DNT for unknown environmental chemicals to prevent neurodevelopmental disorders.

In summary:

- There is currently no comprehensive method to evaluate compounds with unknown DNT potential
- Compounds remain largely untested and susceptible populations continue to be exposed
- Our effort is an initial step in the long journey of preventing neurodevelopmental disorders due to environmental factors

Clarifying Questions

In response to a question from Dr. Blomme, Dr. Behl indicated that physicochemical properties are currently being considered and epigenetics, while a complex mechanism, will be part of future plans.

Dr. Lein requested additional details on the 24-hour activity assays and the modalities under consideration for the *in vivo* imaging. Dr. Behl indicated that both mice and rats will be used, including transgenic mice. The animals will be post-weaning age. Imaging will be conducted through local collaborations.

Dr. Gray asked what key stakeholders, in addition to those listed in the presentation, have DNTP engaged with that would fall into the categories of clinicians or advocacy groups. Dr. Behl

provided several examples and indicated that DNTP would be interested in suggestions for additional stakeholders.

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

10.1. BSC Discussion

Board members were asked to consider five questions.

10.1.1. First Question

What are you most excited about?

The first question was a whiteboard activity facilitated by Dr. Mader. Board members filled in their own individual comments responding to the question (see Attachment F for whiteboard activity results).

BSC answers included:

- DIVER, *in vitro* to *in vivo* extrapolation (IVIVE), harmonization of protocols
- Grouping chemicals together for regulatory assessment
- Multiplexing assays in 3D *in vitro*
- Zebrafish data linked to the *in vitro* data
- Timely evaluation of chemicals normally not studied
- Overall progress and maturity of assay development
- Many novel assays and endpoints – very integrative

10.1.2. Second Question

Please share your insights about the Program regarding:

a. How the objectives address the problem/opportunity

b. The boldness of the approach to achieve the objectives

c. The alignment of the metrics to the desired impact

Dr. Lein, the first discussant, stated that the overarching objective addresses the problem, but "the devil is always in the details." She questioned whether tools are actually being developed to allow the community to predict DNT and if the changes seen in simple 2D and 3D *in vitro* assays are truly predictive of *in vivo* DNT. For example, is it likely that issues such as *in vivo* regional specificity and compensatory mechanisms will be difficult to capture *in vitro*. Dr. Lein thought that the genetic issues should be integrated into the platform for analysis and she did not see the wealth of genetic mutation information that predisposes or increases susceptibility to neurodevelopmental disorders represented in the program. The program lacked quantitative endpoints as metrics. Overarching questions in the field are: By what mechanisms do genes and environment interact? Are the endpoints being measured *in vitro* actually occurring *in vivo*? Data analysis, particularly for imaging, would be a very important element moving forward.

Dr. Felter, the second discussant, was impressed by DNTP's shift to a disease-focused approach and the degree of collaboration with agencies and experts in the field. She questioned how the problem is being defined and recommended starting with a human DNT issue and then considering its major drivers, with environmental contaminants as just one factor. There is a lack of consensus within the field on where things stand. She also questioned if using a Diversity Outbred mouse population would be as informative for DNT as hoped. Dr. Felter suggested that a collaboration with 23andMe® might be more meaningful, without the need for translation from mouse to human. She asked if chemical metabolism was being considered and whether there would be a way to factor in a toxicant's ability to cross the placenta or the blood-brain barrier. She approved of the effort to use IVIVE and asked if biomonitoring data might be available to for connecting to human exposures. She requested more information about chemical prioritization and speculated about the need for more negative controls. Dr. Felter felt that employing toxicogenomics to identify pathways involved in neural processes would be a useful approach.

Dr. Behl agreed that there is a great deal of available data on gene-environment interactions. She cited the NTP program on botanicals as a good example of translation to the clinic. The team would investigate more about 23andMe®. She noted the importance of incorporating social behavior data.

Dr. Lein suggested that the team continue working from the bottom up and the top down. She agreed that the Diversity Outbred mouse population may be inadequate in terms of neurodevelopmental disorders and noted that there are good data available currently on genes that have a strong link to autism, as well as good animal models. She suggested delving into the clinical literature and letting that literature drive animal model development, while letting *in vitro* data drive the chemicals for testing in the *in vivo* models.

Dr. Woychik invited Dr. Alison Harrill, who has been conducting experiments using the Diversity Outbred mouse population, to provide additional comments. Dr. Harrill said that those models provide value by uncovering previously unknown genetic variants. It is an agnostic approach for which insights into the specific variants, which may be playing a role for a specific chemical or a specific outcome, are unnecessary.

Dr. Robert Sills said the team realizes that neurodevelopmental disorders are quite complex. He cited possible collaborations with other NIH institutes such as the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health, and acknowledged the importance of imaging to the study of neurodevelopmental disorders.

10.1.3. Third Question

> ***Considering DNTP's capabilities and expertise, what mechanisms do you suggest that we consider to be able to effectively execute against the objectives? With whom might we partner to ensure success?***

Dr. Susan Tilton, the first discussant, recommended relying heavily on strengths, particularly focusing on the linkages between the *in vitro* and the zebrafish data and the *in vivo* animal studies to achieve the program's objectives. She was impressed with the partnership plans but said it would be important to link existing data to clinical and epidemiological studies to more effectively address public health concerns. She suggested that physiologically based

pharmacokinetic (PBPK) models might be another area for expansion through partnering and added that non-chemical stressors and pre-existing disease should be considered. She was impressed with DNT-DIVER and suggested that it should include more data interpretation.

Dr. Gray, the second discussant, commented that as a social scientist, she was a little concerned about seeing a communications objective for a team that is composed primarily of scientists. She urged the team to take advantage of the strong communications resources available within the agency. While DNT-DIVER is exciting, it is not intuitive for a non-science-literate audience and recommended DNT-DIVER testing with the desired audiences. She found the reference to substitution chemicals compelling. Dr. Gray was impressed with the range of stakeholders that had been engaged and recommended tapping into a wider network of expertise to help with communication.

Dr. Behl said the team is working on including PBPK modeling and toxicogenomics, as well as addressing combined exposures and mixtures. She appreciated the feedback on DNT-DIVER and the board's other suggestions. Dr. Sills added that NIEHS and NTP have an excellent communication team, and the group would work closely with them.

10.1.4. Fourth Question

> ***The disease-focused approach of the Health Effects Innovation Programs is novel in toxicology and hazard assessment. What unique challenges are we likely to encounter in taking that approach for developmental neurotoxicity? What near- and mid-term deliverables might reinforce our decision to take that approach?***

Dr. Singla, the first discussant, commented that one of the challenges related to DNTs is that the burden of the disease is not evenly distributed in the population, with disparities in impact on Black and indigenous people of color. Another challenge is to balance the focus on known contributors to DNT risks with the need to identify unknown toxicants. Both areas need support. Hazard identifications feed into state and international requirements, so it is important to consider how the DNT HEI data can be most informative for authoritative hazard identification. She observed that it would be a challenge to message results in the context of the neurodiversity movement. In terms of deliverables, the question would be whether the data are being used in decisions that will ultimately reduce DNT risks.

Dr. Stump, the second discussant, stated that EPA has been developing DNT testing guidelines for 30 years, driven mainly by pesticides. A big challenge in testing is the question of exposing rodents to model human exposures, for example, making sure that testing is being conducted in the right developmental windows. Another is the relevance of identified rodent pathway insults for human health. Imaging, genomics, and microfluidics may be more predictive than some of the basic observational work. He wondered whether some of the biomarkers identified in the assays could be applied in the clinic for diagnosis.

Dr. Behl found these comments insightful and helpful.

10.1.5. Fifth Question

> ***A key theme of the NIEHS Strategic Plan in "Data to Knowledge to Action." At what level of detail do we need to characterize neurodevelopmental hazards to enable public health-protective decisions by individuals, regulatory scientists, and policy makers? For example,***

at the level of bioactivity in the developing central nervous system, induction of adverse changes in morphology or function at the mechanistic level?

Dr. Ryan, the first discussant, felt that the appropriate level of detail would be the weight of evidence approach.

Dr. Chiu, the second discussant, observed that the answer to the question would depend on the context of use. He was intrigued by the examples of flame retardants and Zika. He indicated that accepted positive controls could be used to look at what *in vitro* markers correlate with known *in vivo* hazards and recommended looking at positive controls to identify key agent-based characteristics as a way to help organize the large variety of endpoints. It should not always be necessary to wait for human data to identify hazards. Video and magnetic resonance imaging data are compelling forms of *in vivo* observations.

Dr. Eaton said that he could not think of an area of toxicology more important than DNT, and also more subject to false negatives and false positives from animal studies, given the complexity of human infant neurodevelopment, along with the species specificity of epigenetics.

Dr. Lein recommended reaching out to colleagues at the National Center for Toxicological Research for helpful *in vivo* imaging data. Dr. Behl said that those contacts had already been made.

11. Adjournment

Dr. Eaton turned to Dr. Woychik and Dr. Berridge for their closing comments.

Dr. Woychik thanked Dr. Eaton for his excellent job as chair. He appreciated the many good comments from the Board members and thanked them for their helpful input. Dr. Berridge added his gratitude for the hard work, and said he was looking forward to providing more information to the BSC at future meetings.

Dr. Wolfe added her thanks to the members, the staff, the outgoing Board members, and the *ad hoc* participants.

Dr. Eaton thanked everyone and adjourned the meeting at 5:00 pm.

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

These summary minutes have been read and approved by the chair of the December 3-4, 2020 NTP Board of Scientific Counselors.

David Eaton, PhD, University of Washington

NTP BSC Chair

Date: March 11, 2021

13. Attachments

"Data to Knowledge to Action"

Group #1: Decision Makers

What other types of DNTP activities and products should we consider?

- Have confidence to understand the data, so offer training sessions about tools that NTP offers (e.g., YouTube videos, webinars)
- Ways to translate data into actionable knowledge and best communicate that actionable knowledge to stakeholders and general public
- Executive summaries of data and research are important – can be reviewed quickly
- Offer risk of bias tools that decision makers and data generators can use to evaluate data and ensure confidence in the data (for example for mechanistic and computational data)
- Offer or develop tools for evaluating external validity particularly for mechanistic and computational approaches
- Ensuring that published reports are reaching the intended/interested audiences
  - Updated mail lists, etc.

Group #2: Concerned Citizens

What other types of DNTP activities and products should we consider?

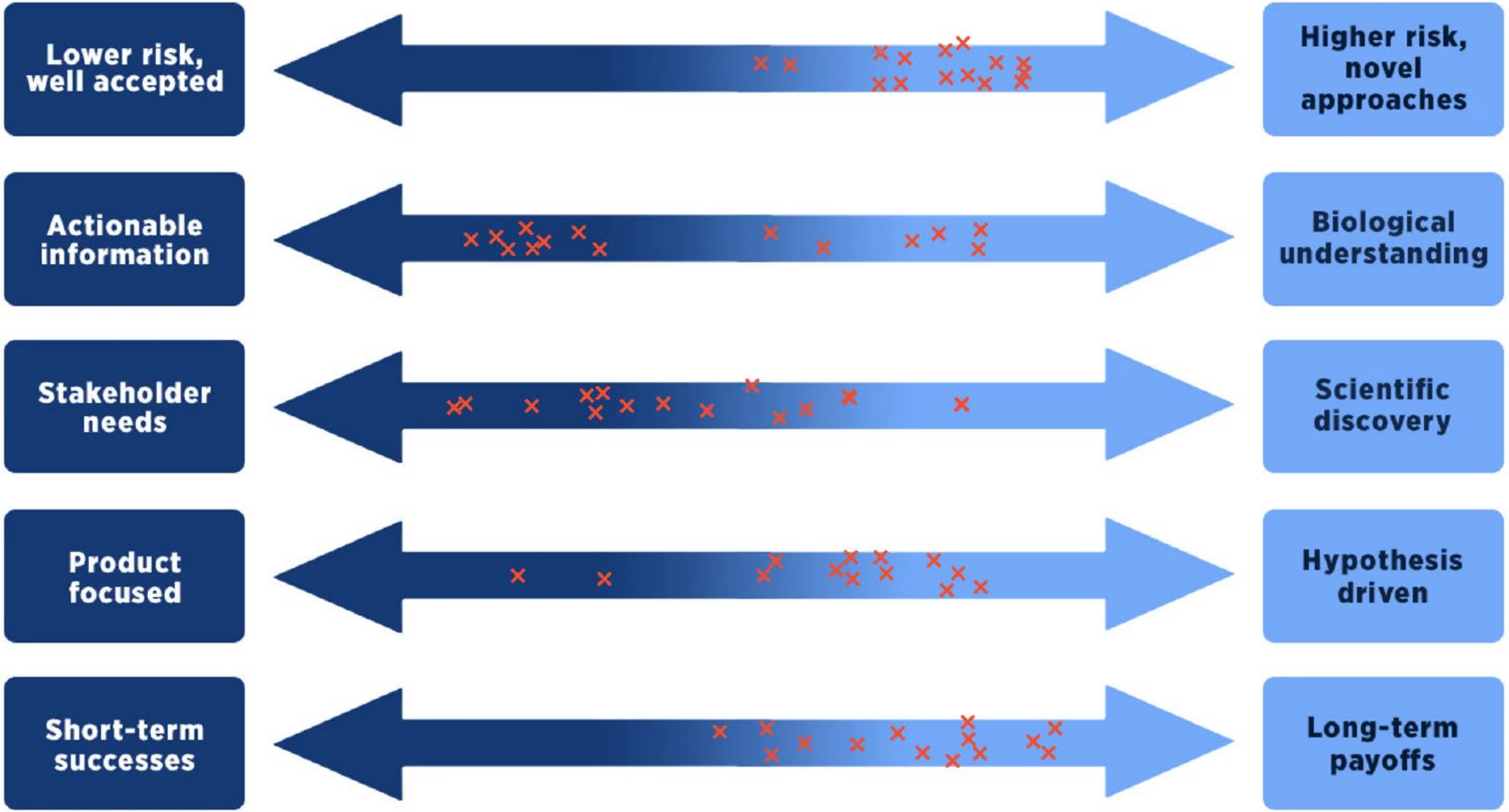
- Trust building exercises
  - Write reports in multiple registries (e.g., technical and laymen)
    - Critical that the technical expert not write the lay abstract
  - Ask the public what *they* want from DNTP (i.e., go to their meetings and where they are comfortable)
    - Be prepared to provide what they ask for
- Faith-based communities
  - They can reach people who might not otherwise be reached
- Social media campaigns
  - Determine the social media protocols (when do they come out, what do they say, what platforms?)
  - Planned platforms to transition information to the public
  - Build your own platform

Group #3: Scientific Community

What other types of DNTP activities and products should we consider?

- User interface that allows stakeholders to have access to data (e.g. along the lines of CEBS)
- DNTP play a role in who receives grants
- Developing the molecular understanding of MOA (cause and effect relationship between key characteristics of AOP) used in AOPs that can be used by regulatory agencies
- Validate new approach technologies
- Workshops consisting of stakeholders to learn about these new approach technologies
- Interpretation of molecular and epi datasets
- Facilitate interactions between the scientific community and concerned citizens

Attachment D



Attachment E

Cardiovascular Health Effects Innovation Program

Question 1

What are you most excited about?

coordination with academic

Tiered approach from bioactivity screening to

Connecting vascular disease with relevant environmental exposures in distinct populations

Opportunity for NTP to contribute to molecular pathway analyses for CV toxicity of environmental agents.

Opportunity to develop a communication project before the program matures.

from biomarker signals to in vivo human phane

novel/innovative approach to connec

Disease focused and computational/in vitro framework

disease-focused toxicology

from biomolecular activities to

The topic is great:

Disease focus - and leveraging work from pharma to environmental toxicants

Great topic

links to key characteristics wc

Connecting hazard ID with a more well defined and focused risk assessment based on

Assessing disease state in combination

application of computational approaches and tools

Focus on health disparities

focus on Black and Indigenous populations

Attachment F

Developmental Neurotoxicity Health Effects Innovation Program

Question 1: What are you most excited about?