National Toxicology Program

Board of Scientific Counselors

August 4, 2021

National Institute of Environmental Health Sciences
Research Triangle Park, NC

Summary Minutes

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1. Abbreviations and Acronyms

ADME	Absorption, distribution, metabolism, and excretion
AFFF	Aqueous film-forming foam
AI	Artificial intelligence
BSC	Board of Scientific Counselors
CEBS	Chemical Effects in Biological Systems
DNTP	Division of the National Toxicology Program
EPA	U.S. Environmental Protection Agency
FAIR	Findable, accessible, interoperable, reusable
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
ICE	Integrated Chemical Environment
NASEM	The National Academies of Sciences, Engineering, and Medicine
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PFAS	Per- and polyfluoroalkyl substances
SCI	Scientific Cyberinfrastructure
SSA	Safe and Sustainable Alternatives
Tox21	The Toxicology in the 21st Century Consortium
TRUST	Transparency, responsibility, user focus, sustainability, and technology
TSCA	Toxic Substances Control Act
UNC	University of North Carolina at Chapel Hill

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
Weihsueh Chiu, PhD, Texas A&M University
Susan Felter, PhD, Proctor & Gamble
Kathleen Gray, PhD, University of North Carolina, Chapel Hill
Pamela Lein, PhD, University of California, Davis
Matthew Martin, PhD, Pfizer, Inc.
David Michaels, PhD, George Washington University
Anne Ryan, DVM, PhD, Act 5 Ventures, LLC
Veena Singla, PhD, Natural Resources Defense Council
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
Brian Berridge
Bradley Collins
Jeremy Erickson
Stephen Ferguson
Jennifer Fostel
Kamel Mansouri
Scott Masten
Barry McIntyre
Suril Mehta
Charles Schmitt
Sheena Scruggs
Vickie Walker
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, GOFORWARDLLC
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 August 4, 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 2020 and 2021 BSC meetings, which focused on introducing DNTP programs categorized by strategic area of focus.

He reflected upon the feedback from the June 8, 2021 BSC meeting, in which board members were asked the following three questions in a survey:

- Was BSC engagement at the right strategic level?
- 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. Prior feedback from respondents has been successfully integrated into the meeting's format. Respondents continued to endorse the new discussion format and the 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 Safe and Sustainable Alternatives (SSA) program and the Scientific Cyberinfrastructure (SCI) program. The meeting previously scheduled for October 20, 2021 had been cancelled. The meeting scheduled for December 8, 2021 will aim to synthesize feedback and define a prioritized and strategic portfolio for DNTP.

After the presentation, Dr. Eaton asked if the December 8, 2021 BSC meeting would be virtual. Dr. Berridge confirmed that it would be virtual.

5. Safe and Sustainable Alternatives Program

Drs. Stephen Ferguson and Suril Mehta briefed the board on the SSA Program.

Dr. Mehta introduced the SSA program team, which consists of Mr. Bradley Collins and Drs. Susan Elmore, Stephen Ferguson, Scott Masten, Barry McIntyre, and Suril Mehta.

Dr. Mehta described ongoing public health concerns related to regrettable substitutions. There is a long history of replacing known hazardous chemicals with chemicals that have been marketed as "safer" or "better," despite limited information on the potential for toxicity or human health

effects. Dr. Mehta illustrated this point with several examples, including specific pesticides, plasticizers, flame retardants, and per- and polyfluoroalkyl substances (PFAS). The SSA program has identified a clear need to disrupt the historical cycle of regrettable substitutions. This cycle largely stems from the chemical-by-chemical approach traditionally used in environmental toxicology; DNTP's strategies should contribute to a metamorphosis in this field, including proactively contextualizing chemical hazards. He noted that DNTP has extensive experience evaluating chemical alternatives, although these studies are typically initiated after a chemical has already been in use. The key question for the SSA program is determining how DNTP can proactively help end the pattern of regrettable substitutions. This can be accomplished by enhancing the effectiveness of DNTP efforts, increasing efficiency, and fostering key collaborations.

The SSA program's Objectives include:

- Objective 1: Exploring and establishing stakeholder relationships and collaborations that identify critical gaps, opportunities, and strategies for proactive toxicological assessments of substances of public health concern.
- Objective 2: Identifying and qualifying effective tools and approaches through case studies that establish translational utility and refine proactive strategies for evaluation of alternative substances.
- Objective 3: Evaluating the relative potential for human health effects with exposures to select alternative substances.

Related to Objective 1, Dr. Mehta described the many opportunities for collaboration with regulatory agencies, international partners, non-governmental organizations, and industry. He cited the SSA program's initial interactions with the U.S. Environmental Protection Agency (EPA) Safer Choice program, which makes distinctions between "safer" and "unsafe." The Safer Choice program has also identified that many of these chemical classes are data poor, thereby presenting future opportunities for data generation by the SSA program. The non-governmental GreenScreen® project is another stakeholder identified by the SSA program. Notably, GreenScreen has created a framework for categorizing and prioritizing hazard endpoints, which can facilitate comprehensive chemical alternatives assessments; however, this framework does not explicitly consider a chemical's absorption, distribution, metabolism, and excretion (ADME) characteristics, internal exposures, or likelihood of biological persistence. Thus, DNTP has an opportunity to identify translational gaps and collaborate with key partners to further develop similar frameworks and prioritization schema.

Under Objective 2, Dr. Ferguson explained the SSA program seeks to use case studies that comparatively evaluate chemical alternatives and characterize the relative potential for human toxicity. The SSA program is actively collaborating with other DNTP programs (e.g., the Novel Tools and Approaches program) to identify key gaps in toxicology research strategies and to identify emerging areas of research that can address those gaps. Dr. Ferguson identified several existing research gaps, such as topics related to human bioaccumulation, ADME, and human internal exposures—particularly low-dose chronic exposures. Methods for closing these research gaps include *in vitro* and *in silico* screening, innovative combinations of tools, and the use of case studies to qualify and refine approaches. Dr. Ferguson illustrated these points with an example project involving aqueous film-forming foams (AFFFs), which are used in fire

suppression materials and contain PFAS. The presence of PFAS and its potential for human bioaccumulation was identified as a key research gap by the SSA team. This project aims to answer several key questions related to PFAS bioaccumulation resulting from AFFF exposure, including the ranking of "safer" AFFFs based on the potential for PFAS bioaccumulation. Data for this project are still under review but they have yielded promising and actionable preliminary findings.

The SSA program also seeks to enhance the human translation of DNTP investigations and seeks to determine the effectiveness of alternative toxicology methods in estimating potencies of toxicological response and in making inferences to *in vivo* outcomes.

Related to Objective 3, the SSA program will continue DNTP's history of identifying chemical hazards by evaluating data-poor chemicals and potential alternatives. Identifying the drivers of human health effects and health disparities will be central to those efforts. The current project portfolio consists of a diverse set of study designs and literature reviews related to PFAS, bisphenols, and ionic liquids, among others.

Dr. Ferguson listed several of the SSA program's short-, medium-, and long-term strategies under the three objectives.

Dr. Ferguson concluded the SSA program's presentation by providing the following challenge question to the board: "What factors contributing to regrettable chemical substitutions represent promising scientific opportunities that the SSA research program can effectively address?" Consideration of this challenge question occurred during the third discussion topic (See Section 5.2.3).

The SSA program members then introduced themselves; Dr. Elmore was not present for the meeting.

Clarifying Questions

Dr. Eaton identified the importance of the SSA program's partnership with EPA in addressing the issue of regrettable substitutions. He noted that revisions to the Frank Lautenberg Toxic Substances Control Act (TSCA) passed several years ago aimed to prevent regrettable substitutions by requiring industry to provide more up-front toxicity testing data on new chemicals. He asked how the SSA program might proactively work with EPA and with industry to identify new chemicals of potential importance, and how responsibilities related to predictive toxicity testing are distributed between these entities. Dr. Mehta noted that the SSA program is still in its beginning stages, although the program has had initial conversations with the EPA Safer Choice program. The EPA Safer Choice program had also emphasized the importance of the SSA program collaborating with key TSCA stakeholders. Dr. Mehta stated that collaborations will be defined as the SSA program progresses.

Dr. Eric Blomme asked, in reference to the SSA program's AFFF work, if they were able to determine the drivers of PFAS bioaccumulation. Dr. Ferguson acknowledged that these are complex mixtures and not all constituents could be defined or detected. For the compounds they were able to detect, however, their research has identified several constituents driving bioaccumulation and they identified that there are some PFAS that do not bioaccumulate under the tested conditions. This work is still under review, and it poses important questions for future research. Dr. Ferguson noted that having human-relevant *in vitro* systems that can assist in

teasing apart the characteristics that contribute to bioaccumulation will play a major role in improving the translation of the work.

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. David Berube asked why the phenomenon of regrettable substitutions recurs. Dr. Ferguson noted that toxicology is a very complicated process with degrees of severity. Sometimes solving one problem raises others, particularly when there is not appropriate due diligence. Dr. Ferguson identified a distinction between green chemistry research and pharmaceutical research—the latter involves intentional human exposure and requires more proactive research into the human health effects of replacements. Dr. Berube asked if the SSA program had tried to identify which classes of stakeholders might be key contributors to this problematic cycle. As a longtime member of the Society of Toxicology, he has observed a "lack of creativity" in some members with whom he has had interactions, noting that their proposed solutions to problems can exhibit "tunnel vision." Some problems associated with chemical replacements are unpredictable (e.g., DDT [dichlorodiphenyltrichloroethane]), although many problems could have been proactively identified (e.g., bisphenols). Dr. Mehta noted that there is a Society of Toxicology Specialty Section on alternatives, and that everyone in the field is working under the existing legal and regulatory framework.

Building on Dr. Berube's comments, Dr. Veena Singla observed that alternatives assessment is an emerging field of practice, and it has not been standard practice in industry. Health and environmental performance have not necessarily been a part of performance considerations for chemical substitutions. The entities considering substitutions often do not have training in toxicology or green chemistry and are thinking only about functional substitutions. Although alternatives assessments are attempting to address this, they are not necessarily standard practice in industry. This presents an important connection for the SSA program to make. Dr. Singla also did not see a strong emphasis on generating health hazard information in the SSA program's presentation or the Program Concept document, although that has been consistently identified as a major gap in alternatives assessment. Dr. Ferguson said that the SSA program has struggled with the question of how they fit in with other DNTP programs that may have a more central focus on consumer products or emerging contaminants of concern. The conversation has now shifted toward strategies to learn from the past and break previous cycles to enable intervention

higher up in the process. He noted that learning from case studies to identify gaps would be helpful. The underlying science behind characterizing human health effects is rapidly evolving, and the SSA program plans to survey and employ many of the new approaches to estimate human health effects (e.g., integrating *in vivo*, *in silico*, and *in vitro* tools to generate more powerful context and interpretations for human health).

Dr. Singla then asked the SSA program team to discuss characterizing health hazards versus estimating human health effects. Dr. Ferguson acknowledged that this is a struggle seen in various siloes of responsibility. He said that next generation risk assessments have produced a spectrum of biological responses (i.e., no observable effect level to clear adverse effects). The SSA program aims to create an interpretive context around hazard scenarios that are placed within that spectrum.

Dr. David Michaels expressed his support for initiatives within the SSA program. He noted that the cycle of regrettable substitutions relates to many of the issues identified by Dr. Berube. Dr. Michaels provided an example of this cycle from a worker safety perspective, given his tenure as the former Assistant Secretary of Labor for the Occupational Safety and Health Administration (OSHA). After OSHA issued exposure limits for methylene chloride, many small employers switched to the unregulated *n*-propyl bromide, rather than reducing exposures to methylene chloride through personal protective equipment or engineering controls. This substitution ultimately resulted in adverse health effects in workers. Dr. Michaels observed these problems relate to "regulatory whack-a-mole," with regulators regulating a substance, followed by users moving to a different, less-regulated substance. Although the SSA program cannot directly address this problem, they will need to work closely with various regulators and with industry to understand likely functional substitutions, to make recommendations based on toxicological evidence, and to proactively address this phenomenon. He remarked that data stemming from new TSCA regulatory requirements will help inform the SSA program about regulated chemicals and likely substitutions. Dr. Ferguson agreed that there is a need to proactively address the problems and not continue the cycles of the past. It will be important to identify data gaps and provide informative context for decision-making. These are complex problems involving numerous stakeholders, so DNTP must prioritize their involvement to make the most impact. Dr. Mehta added that urgency and timing are also important considerations, and it is critical to identify which data are most needed for timely decision-making. Dr. Michaels noted that regulatory agencies often do not think about substitutions and DNTP can provide an important service by providing pertinent information when substitutions are being considered.

Dr. Susan Felter raised the issue of how to consider hazard versus risk and noted there are challenges stemming from partnering with groups that approach this topic differently; for example, if a chemical is classified as a carcinogen by EPA's Safer Choice program, potency is no longer a consideration. This categorization can limit the available, and potentially nuanced, information related to human health. She supported the SSA program's work related to potency, which she views as more meaningful and relevant to human health. Dr. Felter asked how the SSA program's work might fit with other programs' work that does not focus on potency and only focuses on hazard. Dr. Ferguson agreed that a broader context is needed. He views the program's work as "hazard contextualization," and noted that decision trees, "safer" lists, and rankings should be employed. Dr. Felter asked why "safe" and "safer" had been put in quotation marks in the SSA program's presentation and if it related to the lack of context associated with

hazards. Dr. Mehta explained that the idea was to highlight that the terms needed to be defined, and that the term "safer" was relative to other chemicals.

Dr. Matthew Martin agreed with much of the content presented by the SSA program. He observed that DNTP is a government agency that works within a regulatory framework, but it is not a regulatory agency. In that context, he asked about the program's engagement with general merchandisers, which can influence products available to the public, and he asked if there could be strategic partnerships with those organizations. He also indicated there might be exposure information or efficacy of use information available from product producers (e.g., if a replacement chemical requires ten times the amount to achieve results similar to the original chemical). Dr. Mehta stated the SSA program is just entering this space and their initial efforts include partnering with EPA's Safer Choice program, which interacts frequently with those groups. Partnering with industry and industry-related groups will also be important for their program. Regarding Dr. Martin's point on exposure and product efficacy information, Dr. Mehta noted this is another area for which the SSA program will rely on key collaborations to help understand the broader context that companies and regulatory agencies must consider. Dr. Ferguson agreed with Dr. Martin's point related to understanding chemical efficacy, underscoring the importance of environmental hazard information and the SSA program's goal in making it a higher priority.

Dr. Weihsueh Chiu requested a better sense of DNTP's value-added, beyond the narrower perspective of refining traditional assays, metrics, or indicators for use in alternatives assessments. He suggested there may be a broader value-added with respect to methodological development, such as incorporating issues of potency and exposure into alternatives assessments. He recognized this may require additional partnerships, given the program's strengths in hazard identification rather than topics related to potency and dose-response. Dr. Chiu further commented that the key characteristics approach and mechanistic data could be adapted or integrated into the context of alternatives assessments. There is a range of value-added the SSA program could provide, although it is not explicitly clear from the presentation or Program Concept document. A menu of different options could be helpful as the SSA program enters into discussions with stakeholders. He added that the SSA program also seems to focus on analyses within chemical structural classes (e.g., "within bisphenols," "within PFAS"); however, alternatives analysis should focus on function-centric classes. This shift in perspective could change how chemicals are selected for analysis. He also offered the idea of creating substitution profiles, similar to substance toxicological profiles from the Agency for Toxic Substances and Disease Registry. Substitution profiles could draw on DNTP's expertise in systematic reviews and could provide the range of available alternatives and alternative assessment indicators for various chemical function classes (e.g., surfactants, lubricants). Dr. Ferguson thanked Dr. Chiu for his thorough feedback and indicated the SSA program will carefully reflect on the topics raised by Dr. Chiu. Dr. Ferguson also noted the SSA program is working to define its value proposition statement, although they must first understand which gaps they will address. The program has preliminarily identified the areas of ADME and bioaccumulation as clear gaps to address, but other areas will also emerge. The SSA program is centered on ideas of understanding environmental drivers of disease, so they will ultimately provide that context.

Dr. Kathleen Gray thanked the team for making stakeholder engagement its first objective, noting that this communicates a deep level of investment in the engagement process. She asked

the program to speak about health disparities and which stakeholders they view as particularly important within that context. Dr. Mehta said that proactive consideration of health disparities is an inherent part of the mission for National Institute of Environmental Health Sciences (NIEHS). These considerations will help improve DNTP work to better understand hazard, exposure, and potentially impacted populations. The SSA program will also proactively mention these considerations when communicating with stakeholders. Dr. Ferguson agreed with Dr. Mehta and added that each of the SSA program's three objectives have a specific intent, although each objective ultimately aims to help the most vulnerable populations and they hope to expand on this in more detail as their program develops.

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 commented that the "whack-a-mole" problem is almost intractable and asked how to prioritize "moles" among the many possibilities. In prioritization, hazard identification by itself will not provide enough information, and relative risk and potency should be considered. Hazard identification is certainly useful, he noted, but relative potency must be addressed in prioritization. The SSA program could provide value-added by developing approaches for clarifying what an *in vitro* concentration means relative to a target organ *in vivo* concentration. This type of semi-quantitative relative risk comparison will require characterizing numerous physical and pharmacokinetic parameters, but it could help the program prioritize. Dr. Ferguson replied that the team has certainly considered the importance of internal concentrations and those considerations have been key drivers in the program's thinking. Dr. Eaton cited PFAS as an important example for which differences in protein binding between species were missed.

Dr. Pamela Lein reiterated the importance of Dr. Eaton's comments. She also recognized this is an expansive field, but there is also substantial overlap between the SSA program and other DNTP programs. It would be useful to coordinate with them to leverage existing expertise and to avoid reinventing the wheel. She asked if they had conducted any focus groups or workshops with stakeholders to assess their needs as a way of identifying and developing the SSA program's priorities. Dr. Mehta agreed that leveraging expertise within DNTP is important and the recent strategic realignment would facilitate this. The program has also inquired about stakeholders' needs, although they would consider doing this in a more strategic manner, as Dr. Lein suggested. Dr. Ferguson said that DNTP is also often the customer or end-user, and efforts frequently fill specific needs within DNTP.

Dr. Singla felt she had a different perspective than several prior commenters. The community of practice associated with alternatives assessment has been deeply considering these issues for decades and developing frameworks to address issues of regrettable substitutions. It has emerged that alternatives assessment is not risk assessment—it is explicitly different in practice, principles, frameworks, and process. The National Academies of Sciences, Engineering, and

Medicine (NASEM) released a relevant report[2] in 2014. This report reviewed numerous alternatives assessment frameworks and developed a model framework in which hazard characterization is a critical first step and comparative exposure assessment is a later step. She expressed concern that the current focus of the SSA program is missing an opportunity to deliver value to the alternatives assessment community of practice. Much of their data to be generated is useful for risk assessment, as several of BSC members' have highlighted, but it does not fit into current alternatives assessment frameworks. She was glad to see the Program Concept document listed the Association for the Advancement of Alternatives Assessment as a stakeholder and she strongly recommended close engagement with that organization at this early stage in the SSA program's development. Dr. Mehta noted they have read the NASEM report, but they plan to review it in more detail. Collaborations will help the SSA program realize its full value.

Dr. Susan Tilton observed that the public has a role in driving replacement selection, and they have opinions about safer alternatives; however, there is public misinformation about replacements and it is extremely challenging to translate complex toxicological science for public use. She asked if there is a public outreach component of the SSA program or if the public is considered a stakeholder. Dr. Mehta said the public has been implicitly, rather than explicitly, identified as a stakeholder. He noted that the SSA program should perhaps more proactively consider how they communicate with the public, particularly because consumers play a role in driving alternatives assessments.

Dr. Felter said DNTP can play a unique role in this space by understanding that hazard identification is limited in its ability to inform human safety and protect human health. If the focus is limited to hazard, members of the public do not understand that a substance's classification does not necessarily mean it is a human hazard. This is a very difficult concept to communicate to the public. She supported the SSA program's focus on building context, which will help increase public understanding.

Dr. Gray commented that the terms "safe" and "safer" directly relate to the topic of public communication. When members of the public hear the word "safe," they assume it is an absolute.

5.2.3. *Third Discussion Topic*

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

Dr. Mader 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 SSA program also posed a question directly to the board, noted below and in Attachment A.

- SSA Program: What factors contributing to regrettable chemical substitutions represent promising scientific opportunities that the SSA research program can effectively address?

[2]National Research Council. (2014) A Framework to Guide Selection of Chemical Alternatives. Washington, DC: The National Academies Press. https://doi.org/10.17226/18872

- Dr. Berube: Risk and hazard [communication] are different challenges. Expert-expert vs. expert-inexpert have different dynamics as well.
- Dr. Blomme: Moving from a categorical to semi-quantitative assessment based on an optimized translational toolbox.
- Dr. Chiu: Working with stakeholders to 1) identify data gaps that NTP could routinely fill in a timely manner, and 2) develop assays/data analysis methods that are tailored for alternatives analysis. Challenge - ensuring focus (there is a lot of diverse work in this space ongoing, and very easy to become "mile wide, inch deep").
- Dr. Eaton: Developing semi-quantitative, robust approaches to extrapolating *in vitro* concentration to *in vivo* "target organ" concentration.
- Dr. Felter: Integrate potency considerations into decision-making, rather than a strict hazard-based approach (both an opportunity and challenge).
- Dr. Gray: Selection of chemicals to focus on: how to balance agency and stakeholder interests and functionality versus within class prioritization. Will also be challenging to meaningfully engage underrepresented stakeholders given the complexity of alternatives analysis.
- Dr. Lein: Top opportunity: contextualize hazard and provide tools to stakeholders to make better decisions about alternatives and leverage ongoing programs within DNTP with significant mission overlap. Top challenge: prioritization and focus and finding effective and efficient ways for integrating efforts with other groups within DNTP.
- Dr. Martin: Developing niche expertise and contributions across the larger landscape of alternatives research.
- Dr. Michaels: Identifying likely substitutes for chemicals facing regulation, assessing the hazards/risks associated, and then working with manufacturers and users to convince then to select safer substitutes.
- Dr. Anne Ryan: Opportunity-leverage case studies to develop and communicate an efficient, effective, and multidimensional screening paradigm to inform alternative selection.
- Dr. Singla: Top opportunity—to advance tools and systems for hazard characterization. Two recommendations of needs from NASEM 2014 report on alternatives assessment are particularly relevant: Moving beyond relying solely on traditional types of data associated with GHS [Globally Harmonized System of Classification and Labeling of Chemicals] or other benchmarking approaches and towards using data from novel high throughput and in silico approaches, for users with adequate scientific resources to do so. The committee specifically emphasizes greater use of available scientific information to fill data gaps when appropriate. The eventual development of a well-accepted classification scheme for novel types of data and in silico modeling, analogous to the GHS system, to enhance the use of this information. DNTP SSA could play an important and innovative role in this.

- Dr. Tilton: Opportunity to utilize the DNTP translational toxicology pipeline to support safer alternatives, particularly emphasis on ADME-TK [toxicokinetic] endpoints; Challenge of effectively communicating outcomes with public.

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

Dr. Ferguson re-read the SSA program's challenge question for the board and asked if the board saw specific opportunities for the program to contribute to breaking the cycle of regrettable substitutions.

Dr. Singla reiterated that the alternatives assessment community of practice has already thought quite deeply about these questions and has clearly identified that the risk assessment paradigm will not alleviate the regrettable substitutions problem. She said that the field's existing body of work will be important for the SSA program to learn from in order to maximize the program's value. Dr. Ferguson asked Dr. Singla if there are specific areas of the established frameworks that need methods development, or if it is mostly related to filling known data gaps. Dr. Singla responded that both aspects are needed, and both are related to the hazard characterization aspect. She said that DNTP could play a helpful role in integrating new approach methods into current hazard characterization frameworks, like the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), which form the basis of many hazard characterization approaches in alternatives assessment.

Dr. Ferguson stated that there are existing hazard characterization categories (e.g., EPA Safer Choice, GreenScreen). He asked if BSC members knew if any of these categories need additional human-relevant tools to address translational gaps.

Responding to the mention of integrating more human-relevant tools, Dr. Felter encouraged the program to consider translating *in vitro* concentrations to human-relevant exposures very early in the process—this consideration should be built into the original study designs. As new alternative methods are developed and the field moves further away from animal testing, the results must still be relevant to humans. Dr. Felter also noted that some endpoints in the GHS have potency built in (e.g., acute toxicity), whereas other endpoints do not have potency built in; the latter could be an area for improvement.

Building on his MURAL response, Dr. Eaton cited an example of an *in vitro* study of a dioxin analogue.[3] He wondered about translating the concentration of lipophilic substances in media to concentrations that could be expected at a receptor. This point illustrates the importance of being able to use modeling approaches to estimate *in vitro* concentrations and to approximate a reasonable concentration *in vivo*. Dr. Ferguson said that a core tenet of the SSA program's hypothesis is that the more physiologically relevant the *in vitro* models are—and the better they partition and transform chemicals faithfully to the tissues they represent—the better agreement there will be in the push toward physiological relevance.

[3]Dornbos *et al.* (2016) The Influence of Human Interindividual Variability on the Low-Dose Region of Dose-Response Curve Induced by 2,3,7,8-Tetrachlorodibenzo-p-Dioxin in Primary B Cells. *Toxicol Sci*. 153(2):352-360. https://doi.org/10.1093/toxsci/kfw128

Dr. Lein agreed with Dr. Felter and Dr. Eaton's discussion about the importance of translating concentrations *in vitro* to concentrations *in vivo*. With respect to specific gaps the SSA program might address in this translational work, she suggested leveraging the work currently being conducted by other DNTP programs, particularly work that focuses on developmental neurotoxicity.

Dr. Blomme referred to the SSA program's work with PFAS in AFFFs and the program's findings that some PFAS compounds demonstrated bioaccumulation, while some did not. He said that the answer may not be as simple as having physiologically relevant models. It might also be important to capture key characteristics that allow better prediction of what will *not* correlate with blood exposure, such as permeability, physiochemical properties, or transporter substrates. In addition to physiologically relevant models, which are necessary, there should also be a better understanding and categorization of molecules and their correlation with target organ concentrations *in vivo*. This approach has had success in the pharmaceutical field. Dr. Ferguson said the SSA program has discussed some of those issues, such as characterizing a chemical's ability or inability to arrive at a target site. They plan to develop case studies related to these topics, and he noted that many lessons-learned from pharmaceutical development apply to the field of environmental toxicology. Dr. Blomme added that some *in silico* models are fairly accurate for some classes of chemicals, and these could be used to improve extrapolation from *in vitro* to *in vivo*.

Dr. McIntyre asked if the board had resources to help communicate risk, given that mode of action is often unknown and the link to hazard may not be present. Dr. Eaton noted it was a challenging question and there were no readily available answers from the board.

Dr. Chiu referred to the previously mentioned key characteristics approach as one useful modality and remarked that it could be used in a contrapositive way. For example, if a chemical is screened against known key characteristics of carcinogenesis and it does not demonstrate any of the key characteristics, then that could suggest it is likely not carcinogenic. This negative predictive power could be useful in alternatives assessment, as compared to the positive predictive power typically used in risk assessment. Dr. Eaton noted that it is critical to have well-validated positive controls in a key characteristics model.

Mr. Collins observed that the board's MURAL responses frequently referred to the challenge of selecting alternatives to evaluate. He asked if there are particular groups or knowledge bases that the SSA program should recognize as potential stakeholders to help identify alternatives within chemical classes or use cases that should be considered. Dr. Singla suggested the European Union's SUBSPORT (Substitution Support) portal[4], which has information and industry case studies about substitution. She also mentioned ChemForward[5] as a group that is developing a portfolio of potential alternatives for functional applications and chemical classes. The European Union is also producing significant work related to the concept of safe and sustainable-by-design. She recognized the evaluation aspect is a challenging issue that exemplifies the intersection of data and values, and poses questions such as "how much safer is safe enough?" She reiterated previous comments from Dr. Gray related to engaging the communities most impacted by chemicals and their potential substitutions; she underscored the

[4] https://www.subsportplus.eu/subsportplus/EN/Home/Home_node.html
[5] https://www.chemforward.org/

importance of decision-making in the context of the values of and input from impacted communities. She mentioned a report[6] she had written in collaboration with Californians for a Healthy and Green Economy that explored values-based decision-making in alternatives assessments.

Dr. Mehta noted that most of the SSA program's stakeholders are within the scientific or regulatory communities, and those stakeholders are already well-versed in scientific or technical communication. He recognized it will be a challenge to communicate their work to the general public, given the complex scientific information involved. He asked the board for suggestions in this area. Dr. Gray appreciated the program's consideration of this topic and she suggested they utilize the extensive network of NIEHS research partners across the nation. As the SSA program begins to identify priority chemicals or classes of chemicals, there are existing groups—some engaged with university researchers—who have considerable experience and knowledge in those specific areas. She added that there are specific groups who should be part of the process given their exposure to particular chemicals, such as workers or communities with contaminated drinking water. She underscored the recommendation of focus groups previously suggested by Dr. Lein. She urged specific, formal engagement with vulnerable populations, which would help the team consider dimensions of exposure they might not otherwise consider.

6. Scientific Cyberinfrastructure Program

Dr. Jennifer Fostel briefed the board on the SCI Program.

She introduced the SCI program team, which consists of Mr. Jeremy Erickson, Ms. Vickie Walker, and Drs. Scott Auerbach, Jennifer Fostel, Nicole Kleinstreuer, Kamel Mansouri, and Charles Schmitt.

The program team consists of producers, consumers, and maintainers of SCI resources. The SCI program intersects and supports almost all aspects of DNTP work. SCI is distinguished from the other DNTP programs that have previously been introduced, in that SCI is one of two programs charged with providing cross-cutting capabilities for DNTP, the other being the Novel Tools and Approaches program.

Dr. Fostel defined scientific cyberinfrastructure as computing environments that support scientific data acquisition; support data storage and management; provide data integration, annotation, and analysis; and provide other computing and information process services. The staff supporting scientific discovery are also critical components of scientific cyberinfrastructure.

The SCI program includes five key areas:

- Core key area: coordinates basic solutions across common DNTP SCI needs.
- Data management key area: collects, manages, and publishes all DNTP data.
- Knowledge management key area: adopts standardized language, metadata, and data models within DNTP.

[6]Singla, V. *et al.* (2017) Selecting Safer Alternatives to Toxic Chemicals and Ensuring the Protection of the Most Vulnerable. Available at: https://www.nrdc.org/resources/selecting-safer-alternatives-toxic-chemicals-and-ensuring-protection-most-vulnerable

- ToxChem informatics key area: organizes, integrates, analyzes, and presents diverse toxicology-related data.
- Evidence informatics key area: evaluates and supports tools and methods for retrieval, extraction, and interpretation of evidence from scientific literature and external knowledgebases.

A fundamental challenge for the SCI program is fulfilling needs across various requestors and providers. The SCI program's responsibilities address both pragmatic needs and strategic needs. Needs are identified at various organizational levels, ranging from individual DNTP staff members to the overall program. The SCI program coordinates requests to ensure efficiency, to decrease risk, and to provide information to DNTP management to aid in prioritization. Providers of SCI resources include contractors, internal and external collaborators, and other NIEHS branches and laboratories. The SCI program provides oversight and facilitates cooperation, interoperability, and reuse of SCI resources between various entities.

The SCI program's primary Objectives include:

- Objective 1: Providing support for day-to-day and strategic needs (i.e., oversight).
- Objective 2: Engaging and coordinating stakeholders and partners (i.e., engagement and partnerships).
- Objective 3: Providing innovative tools and capabilities for the DNTP mission (i.e., strategic capabilities).

Oversight, engagement and partnerships, and strategic capabilities comprise the team's program plan. Objective 1 involves oversight of SCI generators, coordinating and collecting information for DNTP decision-making, providing advice on prioritization, and supporting DNTP compliance with National Institutes of Health (NIH) standards. Under Objective 2, the SCI program aims to maximize the impact of SCI resources across providers, stakeholders, and users by ensuring that needs are identified, projects are appropriately coordinated, and best practices are used. Under Objective 3, the SCI program aims to develop automated data management pipelines for the rapid collection and reporting of DNTP data and semi-automated pipelines for annotation and curation. The SCI program also intends to work on the standardization of metadata and to publish many of their SCI tools.

Dr. Fostel provided additional details about the plans under their Objectives and for each of the key area teams, including timelines for key area teams' expected milestones over the next 1, 2–3, and 4–5 years.

The SCI program members then introduced themselves. Dr. Kleinstreuer was not present for the meeting.

Clarifying Questions

Dr. Eaton noted that there is a substantial amount of toxicological data within the private sector, and it is usually proprietary data. He asked if there have been any efforts to acquire any of this data or efforts to coordinate access of this information. He remarked that pharmaceutical industries have historically had difficulties with data sharing, but he was uncertain about data sharing with chemical industries. Dr. Fostel said she came to DNTP from the pharmaceutical field, and that Johnson & Johnson gave its library of toxicants to DNTP. Dr. Fostel noted that Dr.

Auerbach also contacted the group associated with the DrugMatrix database and the SCI program has obtained TG-GATEs (Toxicogenomics Project-Genomics Assisted Toxicity Evaluation system) data. She added that DNTP works with the Health and Environmental Sciences Institute, which makes its data public. Dr. Auerbach remarked that the European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation is critical for making privately owned data available to the public sector. He also described relationships with stewards of proprietary and private data, such as the Toxicology in the 21st Century Consortium (Tox21) and EPA. Dr. Mansouri added that DNTP is a member of the Accelerating Therapeutics for Opportunities in Medicine Consortium, a group of pharmaceutical companies and national laboratories collaborating on several projects.

Dr. Lein asked if the SCI program is also curating *in vivo* imaging data. Dr. Fostel replied that the SCI program is planning to do so, but it has not begun that effort yet.

Dr. Martin was glad to see that science is integral to the cyberinfrastructure plan, rather than being primarily driven by information technology. He asked if the program had thought about how it would prepare for the era of digital pathology. Dr. Fostel said the DNTP pathology group is pioneering that effort, beginning with obtaining high quality scans before developing related artificial intelligence (AI) tools. The SCI program plans to bring Chemical Effects in Biological Systems (CEBS) and DNTP into better alignment with NIH Commons, so there will be a good place to store unstructured data. Dr. Martin asked about deep annotation of the images, rather than simply attaching high-level pathological terms, to facilitate deep learning approaches for automated image analysis. Dr. Fostel said that is where the CEBS resources would come into play and noted that DNTP recently received a grant to develop this capability over the next several years. This effort would involve putting the data into the cloud and developing a layer of tools for analysis within the cloud.

Dr. Eaton asked the SCI program to elaborate on the topics of AI and machine learning, particularly as they relate to image data analysis. Dr. Fostel said the pathology group is using an AI approach in image analysis and Dr. Ferguson (from the SSA program) is also working to characterize images of cells to determine viability. Dr. Auerbach added that there is significant interest in this area, particularly within the Imaging Sciences and Artificial Intelligence Group led by Dr. Ron Herbert. DNTP has the expertise and infrastructure, both internally and under external contracts, to support various machine learning efforts. For example, they are currently building simple classification models to automate the identification of cytotoxicity in *in vitro* analyses.

Dr. Singla was excited to see the emphasis on evidence informatics and support for systematic reviews within the Program Concept document. Noting the program's collaboration with the EPA Office of Chemical Safety and Pollution Prevention, Dr. Singla observed that the SCI program's work in this area could be particularly useful to them. She asked if the SCI program is closely collaborating with scientists working on the TSCA systematic review. Ms. Walker briefly revisited the topic of AI and remarked that AI technologies are being used in evidence informatics as well, particularly with respect to natural language processing. Answering Dr. Singla's question, Ms. Walker confirmed there is coordination between their program and EPA, and that their collaboration involves a complementary approach.

6.1. Public Comments

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

6.2. BSC Discussion

Dr. Eaton introduced Dr. Mader as a facilitator for the BSC discussion section. Board members were then 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. Martin commented that the Program Concept document contained all of the major components and aligned well overall. Given the small number of SCI program members, their larger pool of contract support will be instrumental in achieving their goals. He also remarked on the SCI program's reference to training; he recommended improving data literacy within the broader DNTP organization. This could involve setting up a core curriculum in data science or providing a type of basic training in coding. These efforts could increase appreciation for and awareness of basic data science principles. Dr. Fostel agreed and said one critical objective for their program is to determine a good way to engage DNTP staff so that they understand both the tools they are using and the larger value their data can bring to DNTP. The SCI program was hoping to receive input from the board on these issues.

Dr. Blomme said that the challenge is to transform data into knowledge. The culture of users is important, as is the user interface. "Superusers" are still needed—that is, users who can address very complex questions that connect data, structure, and science. There is a fundamental challenge of suboptimal use of many of these tools. Dr. Fostel agreed and described her experience with a spectrum of user types. The data management key area within the SCI program is attempting to provide different levels of data, while the knowledge management key area is trying to ensure data are not restricted by internal DNTP terminology. Regarding interfaces, Dr. Auerbach noted that they aim to deliver tools and data that span the range of possible users, including simple tools or simple units of data, advanced tools for superusers, and larger data caches. The Integrated Chemical Environment (ICE) might best exemplify a tool that engages a variety of stakeholders. Dr. Mansouri agreed and noted that ICE is a largely public-facing tool, but it also has internal tools under development for later public release. Part of the SCI program's long-term (3–5 year) plan is to develop an infrastructure that includes: 1) tools that will be user-friendly and have characteristics that will democratize their use, especially among non-coders, and 2) tools for more advanced users and programmers. Dr. Fostel remarked that Mr. Erickson builds Jupyter notebooks and other tools to leverage CEBS data for visualization and analysis. Mr. Erickson commented that the DNTP Office of Data Science team is also dedicated to providing training opportunities related to Jupyter, IPython, R, RStudio, and Shiny applications, among others. Separately, the Integrative Bioinformatics Support Group also provides training opportunities related to microarray analysis and Next Generation Sequencing.

Dr. Felter expressed her appreciation for the group's work to make user-friendly tools and interfaces, which are important to the many toxicologists who do not aim to become superusers; however, it will be critical for users to still understand the underlying limitations and assumptions. Understanding limitations and assumptions will help prevent misuse and misinterpretation, especially related to data and tools available to the public.

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 asked how DNTP and the SCI program are working on topics related to epigenetics. Dr. Auerbach said there is a group[7] at NIEHS focusing on evaluating epigenetic changes. This group focuses primarily on tumors and tumor epigenetic analysis rather than predictive, prepathological work. Dr. Auerbach is also personally collaborating on epigenetic studies of *in utero* arsenic exposure. Of all the nucleotide-based –omics, Dr. Auerbach suggested that epigenetics tends to be the most challenging to obtain reproducible results, particularly related to short-term effects and low-level exposures. It is, however, an outstanding resource for stable biomarkers and it is a maturing area of research. Dr. Eaton agreed with Dr. Auerbach's observations related to reproducibility. Dr. Woychik added that investigating how epigenetic mechanisms lead to alterations in gene expression following environmental exposures is a major focus of research at NIEHS. He noted that it is more complex than simply sequencing genomes; it is necessary to identify which cell types are responding to environmental perturbations, as well as how environmental exposures trigger epigenetic changes. Dr. Eaton underscored the importance of this topic and was glad to hear NIEHS and DNTP have invested in this area.

Dr. Singla supported the SCI program's plans to make data and tools more readily available to the public. She wondered how the data could be made most useful to the public and communities. Dr. Singla suggested that individuals working closely with communities, such as Dr. Gray, would be excellent resources for the SCI program. She further remarked that the Environmental Data and Governance Initiative[8] has worked extensively on issues related to data access and usability. Dr. Fostel identified that this is a potential gap in the SCI program, given that they work more closely with scientists than the general public. With increased public access to data, it will be particularly important that the public understands limitations of the data. Dr. Fostel appreciated Dr. Singla's recommended resources.

Dr. Tilton commented that concerns about data usage can sometimes prevent data sharing. She asked if there is a requirement for data submission or data sharing within DNTP. Dr. Fostel said that DNTP has embraced the FAIR (findable, accessible, interoperable, reusable) standards for data management. NIH also has a policy on data sharing that will go into effect at the beginning of 2023. The expectation is that most data generated by the federal government will be shared with the public. The concern, however, is that the conclusions from DNTP testing programs are based on committees' expert evaluations. For example, a statistically significant effect might be

[7]Molecular Pathology Group: https://www.niehs.nih.gov/research/atniehs/labs/lep/mole-path/index.cfm
[8]https://envirodatagov.org/

observed but based on considerable experience with a particular animal model or class of compounds, the finding might not be toxicologically relevant. These findings are particularly difficult to capture or convey. Dr. Schmitt remarked that the NIH Office of Data Science Strategy has put together FAIR standards in addition to TRUST (transparency, responsibility, user focus, sustainability, and technology) principles, which will apply to the development of responsible data repositories and data sharing. The expectation is that NIH will continue to put forward recommendations in this area. Dr. Auerbach reiterated the challenge of a spectrum of stakeholders and the varied data they might request. Tox21 has navigated this challenge well.

6.2.3. *Third Discussion Topic*

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

Dr. Mader 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 SCI program did not submit a challenge question to the board.

- Dr. Berube: This is not my field, but I do know something about overstanding. Having written in this area, overstanding can lead to lack of understanding by misdirecting emphases. For example, why is public access a substantive direction when the system is expert in nature? You have a conceptually fascinating project, and you must carefully control its excessively expansion capabilities.
- Dr. Blomme: This is a "need to have," so it's better to think of the top opportunity: development of a tool that will 1) generate operational efficiency by guiding "fit-for-purpose" experimentation, 2) reduce some testing, and 3) develop new knowledge faster.
- Dr. Chiu: Top challenge – the multitude of stakeholders with different needs and skill levels. Opportunity – enabling discovery through data integration.
- Dr. Eaton: Communicating both the strengths and the limitations of various cyber tools available to NTP investigators who are the ones generating the "raw data."
- Dr. Felter: Defining what is fit-for-purpose and how to define/identify (and make explicit) uncertainties associated with new tools based on big data. Helping with interpretation of what evaluations mean and what they don't mean (again – related to defining acceptable uncertainty).
- Dr. Lein: Top opportunity: to integrate data sets across multiple databases for enhanced application of tox data; Top challenge: training users to optimally leverage the databases and understand limitations.
- Dr. Martin: With the increased democratization of coding, an increased demand for comp scientists; maintaining quality of analyses and tools, preventing over-proliferation of tools all while balancing those challenges with incentivizing a high-level of data-centric culture through empowerment and strategic hiring and colleague development.
- Dr. Ryan: This is a universal need, across government, academia, and industry! Driven by increased capacity for data generation and at increasing levels of granularity. Tools, communication, and collaborations across these stakeholders, utilizing common

ontologies, and data standards are critical to leveraging the data, new insights and data exchange that can lead to collaborations across academia, industry, and government. The challenge is getting people to see the need to use common ontologies and standards to achieve this greater good.

- Dr. Singla: Big opportunity to deliver value to NTP, EPA, other partners, and the public with this work. Challenge is the wide range of stakeholders and the need to tailor products to meet different needs and doing so with limited resources.
- Dr. Tilton: Opportunity to develop an infrastructure to support predictive toxicology goals of NTP; Challenge to balance in-house development/management with outsourcing/leveraging of already developed tools and databases to meet needs of projects and stakeholders.

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

Dr. Auerbach commented that the "siloed mindset" is a challenge in transitioning from traditional science to science in the age of big data. Experiments are often done without considering the unification or datafication of the information generated. There is also a considerable amount of existing information (e.g., subacute data) that has not been turned into unified, usable data. He asked the board to comment on motivating people to shift these traditional mindsets.

Dr. Eaton said the issue is more about data integration across platforms, for example, interpreting gene expression data relative to an epigenetic change. Integration is a huge opportunity and a huge challenge.

Dr. Lein expressed that the effort must start with junior-level scientists, possibly by making data science training a requirement. This will demonstrate the value of these principles, help create buy-in from a new generation of scientists, and bring about cultural changes. Although senior-level scientists might appreciate the value of such efforts, they have different priorities at this stage of their career. Dr. Auerbach agreed that the point about a generational gap is reasonable.

Dr. Martin said that compulsory efforts are typically not effective because much of the problem is driven by culture. He suggested organizational changes can induce behavioral changes, such as embedding computationalists within groups to help them deal with data. The addition of even one such team member can influence a team's broader willingness and abilities in this area. Data science competency, in addition to scientific competency, could also be a hiring consideration for scientist positions; however, there are no "quick fixes" to this issue. Dr. Auerbach agreed that generational shifts could come about through the hiring process.

Dr. Berube responded from his perspective as social scientist and recommended the use of pretests to understand the way people work before proceeding. He also expressed there is the potential danger of "overstanding"—that is, so much data is generated that the process of using the data becomes the primary problem. There is a continuum between understanding and overstanding; the SCI program is extremely vulnerable to this issue, and they should keep it front of mind when evaluating priorities and processes. For example, providing data access to the general public may not be a high priority, given that most of the public will not use or understand

the data. Dr. Auerbach acknowledged the importance of this point and remarked the SCI program struggles with this. The general public is a clear beneficiary of their work, but there are questions related to the amount of data shared directly with the general public versus through other agencies that work more closely with regulations and communications.

Dr. Blomme shared his experience with the impact of these types of tools in his field. His field also generates an abundance of data without holistic considerations for its use. Smarter science, in his view, is designing experiments and using existing data in a way that proactively guides scientific progress. Dr. Auerbach agreed that it is important to have a clear goal and not just build tools for the sake of building tools.

Dr. Mader remarked that the SCI program had identified interrelated and interdependent themes within the board's MURAL content.

Dr. Fostel recognized the tremendous opportunity to develop curricula using DNTP data and tools to educate scientists. There is also a range of information produced by DNTP, such as conclusions by expert committees and more granular information that would be useful to modelers. There is concern about how the public could use and interpret the more granular types of data. This returns to the concepts of training and communication.

Returning to the discussion of generation gaps and the next generation of scientists, Dr. Eaton asked if the SCI program has engaged with local graduate students at the University of North Carolina at Chapel Hill (UNC) or Duke University. Dr. Fostel replied that there are training opportunities with those universities, and that SCI could further contribute to training opportunities in data science. She commented that they must deliver the message of how data science can improve future scientists' work (e.g., more findable, more usable, more collaborative). Dr. Berridge remarked that there are a number of formal programs engaging students and many DNTP staff members teach at local and nonlocal universities. Education is part of the fundamental mission for DNTP. Dr. Woychik noted that the DNTP chief data scientist, Dr. Schmitt, came from UNC and he maintains connections with the university. Dr. Schmitt said there are a number of connections with UNC, including a recent postdoctoral researcher who made great contributions in this area.

7. Adjournment

Dr. Woychik thanked Dr. Eaton for his leadership in chairing the meeting, BSC members for their participation, and DNTP staff for their excellent presentations. He particularly enjoyed conversations related to data sharing issues. The many valuable insights from the meeting will factor into future directions for DNTP.

Dr. Berridge noted that this meeting was the conclusion of six intensive BSC sessions that have been engaging and will help DNTP develop its strategic portfolio. He thanked Dr. Eaton for his excellent chairmanship, Dr. Scruggs for coordinating the logistics, BSC members for their engagement and feedback, and DNTP staff for their effort on the Program Concept documents and presentations. He recognized DNTP's unique role and opportunities. A number of themes have emerged from the meetings, including integrating health disparities into DNTP work and the importance of stakeholder engagement. Dr. Berridge also commented on the connectivity between programs and research areas. The next step will be integrating feedback to identify strategic priorities. He also noted that it would be important not to create new siloes within the

organization. The next BSC session in December 2021 will present the integration of the discussions into a strategic and prioritized portfolio.

Dr. Scruggs added her thanks to the board, Dr. Eaton, Dr. Mader, and support staff. She noted that a survey would be sent to the board members to gauge their thoughts about the meeting.

Dr. Eaton adjourned the meeting at 4:54 PM, August 4, 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 August 4, 2021 NTP Board of Scientific Counselors.

David Eaton, PhD, University of Washington

NTP BSC Chair

Date: October 12, 2021

9. Attachments

Attachment A

Safe and Sustainable Alternatives Program

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

SSA Program: What factors contributing to regrettable chemical substitutions represent promising scientific opportunities that the SSA research program can effectively address?

David Berube: Risk and hazard comm are different challenges. Expert-expert vs. expert-inexpert have different dynamics as well.

Eric Blomme: Moving from a categorical to semi-quantitative assessment based on an optimized translational tool box

Weihsueh Chiu:
Working with stakeholders to (1) identify data gaps that NTP could routinely fill in a timelymanner, and (2) develop assays/data analysis methods that are tailored for alternatives analysis. Challenge - ensuring focus (there is a lot of diverse work in this space ongoing, and very easy to become "mile wide, inch deep")

David Eaton: Developing semi-quantitative, robust approaches to extrapolating in vitro concentration to in vivo 'target organ' concentration

Susan Felter: Integrate potency considerations into decision-making, rather than a strict hazard-based approach (both an opportunity and challenge)

Kathleen Gray: Selection of chemicals to focus on: how to balance agency and stakeholder interests and functionality versus within class prioritization. Will also be challenging to meaningfully engage underrepresented stakeholders given the complexity of alternatives analysis.

Pam Lein: top opportunity: contextualize hazard and provide tools to stakeholders to make better decisions about alternatives; and leverage ongoing programs within DNTP with significant mission overlap; top challenge: prioritization and focus and finding effective and efficient ways for integrating efforts with other groups within DNTP

Matthew Martin: Developing niche expertise and contributions across the larger landscape of alternatives research

David Michaels: Identifying likely substitutes for chemicals facing regulation, assessing the hazards/ risks associated, and then working with manufacturers and users to convince then to select safer substutites.

Anne Ryan: opportunity-leverage case studies to develop AND communicate an efficient, effective and multidimensional screening paradigm to inform alternative selection.

Veena Singla: top opportunity- to advance tools and systems for hazard characterization. Two recommendation of needs from NAS 2014 report on alternatives assessment are particularly relevant: Moving beyond relying solely on traditional types of data associated with GHS or other benchmarking approaches and towards using data from novel high throughput and in silico approaches, for users with adequate scientific resources to do so. The committee specificallyemphasizes greater use of available scientific information to fill data gaps when appropriate.
ANDThe eventual development of a well-accepted classification scheme for novel types of data and in silico modeling, analogous to the GHS system, to enhance the use of this information.
NTP SSA could play an important and innovative role in this.

Susan Tilton: Opportunity to utilize the DNTP translational toxicology pipeline to support safer alternatives, particularly emphasis on ADME-TK endpoints; Challenge of effectively communicating outcomes with public

Attachment B

Scientific Cyberinfrastructure Program

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

David Berube: This is not my field but I do know something about overstanding. Having written in this area overstanding can lead to lack of understanding by misdirecting emphases. Ex: why is public access a substantive direction when the system is expert in nature? You have a conceptually fascinating project and you must carefully control its excessively expansion capabilities.

Eric Blomme: This is a "need to have", so it's better to think of the top opportunity: development of a tool that will (1) generate operational efficiency by guiding "fit-for-purpose" experimentation, (2) reduce some testing and (3) develop new knowledge faster

Weihsueh Chiu: Top Challenge - the multitude of stakeholders with different needs and skill levels. Opportunity - enabling discovery through data integration.

David Eaton: Communicating both the strengths and the limitations of various cyber tools available to NTP investigators who are the ones generating the 'raw data'.

Susan Felter: Defining what is fit-for-purpose and how to define/identify (and make explicit) uncertainties associated with new tools based on big data. Helping with interpretation of what evaluations mean and what they don't mean (again - related to defining acceptable uncertainty).

Pam Lein: Top opportunity to integrate data sets across multiple databases for enhanced application of tox data; Top challenge: training users to optimally leverage the databases and understand limitations

Matthew Martin:
With the increased democratization of coding, an increased demand for comp scientists; maintaining quality of analyses and tools, preventing over-proliferation of tools all while balancing those challenges with incentivizing a high-level of data-centric culture through empowerment and strategic hiring and colleague development

Anne Ryan: this is a universal need, across governement, academia and industry! Driven by increased capacity for data generation and at increasing levels of granularity Tools, communication and collaborations across these stakeholder, utilizing common ontologies and data standards are critical to lveraging the data, new insights and data exchange tha can lead to collaborations across academia, industy and governament The challege is getting people to see the need to use common ontologies and standards to acheive this greater good

Veena Singla: Big opportunity to deliver value to NTP, EPA, other partners and the public with this work. Challenge is the wide range of stakeholders and the need to tailor products to meet different needs, and doing so with limited resources.

Susan Tilton: Opportunity to develop a an infrastructure to support predictive toxicology goals of NTP; Challenge to balance in-house development/ management with outsourcing/ leveraging of already developed tools and databases to meet needs of projects and stakeholders