

Summary Minutes February 15, 2019
NTP Board of Scientific Counselors

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NTP Board of Scientific Counselors
February 15, 2019

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I. Abbreviations and Acronyms

ATSDR	Agency for Toxic Substances and Disease Registry
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
DNTP	Division of the National Toxicology Program
DOD	Department of Defense
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HESI	Health and Environmental Sciences Institute
NC3Rs	National Centre for the Replacement, Refinement & Reduction of Animals in Research
NCCT	National Center for Computational Toxicology (EPA)
NCEH	National Center for Environmental Health
NCTR	National Center for Toxicological Research
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
TSCA	Toxic Substances Control Act
UCSF	University of California, San Francisco
UK	United Kingdom

II. Attendees

Members in Attendance:

In-Person:

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

Via WebEx:

Cynthia Afshari, Janssen Pharmaceutical
Norman Barlow, Seattle Genetics
David Berube, North Carolina State University (*ad hoc*)
Weihsueh Chiu, Texas A&M University (*ad hoc*)
Myrtle Davis, Bristol-Myers Squibb
David Eaton, University of Washington (*ad hoc*)
Susan Felter, Procter & Gamble (*ad hoc*)
David Michaels, George Washington University (*ad hoc*)
Kenneth Ramos, Arizona Health Sciences Center
Anne Ryan, Pfizer (*ad hoc*)
James Stevens, Paradox Found Consulting Services, LLC
Donald Stump, Charles River Laboratories
Susan Tilton, Oregon State University (*ad hoc*)
Katrina Waters, Pacific Northwest National Laboratory

Government Agency Personnel:

Goncalo Gamboa, FDA, BSC liaison (in-person)
Elizabeth Whelan, NIOSH, BSC liaison (via WebEx)
Denise Hinton, FDA (via WebEx)

Invited Speakers (all via WebEx):

John Piacentino, NIOSH
William Slikker, Jr., FDA/NCTR
Gina Solomon, University of California San Francisco
William Cibulas, NCEH/ATSDR
Patricia Underwood, DOD
Syril Pettit, HESI
Fiona Sewell, NC3Rs
Russell Thomas, EPA/National Center for Computational Toxicology

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

Brian Berridge	Robbin Guy	Robert Sills
Linda Birnbaum	Michelle Hooth	Nigel Walker
John Bucher	Scott Masten	Mary Wolfe
Michael DeVito	Andrew Rooney	

Contract Staff:

Canden Byrd, ICF
Steve McCaw, Image Associates
Blake Riley, ICF
Kelly Shipkowski, ICF

Public:

Ernie Hood, Bridport Services

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened February 15, 2019, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC.

Dr. Kenneth McMartin served as chair. The other BSC members attended via WebEx.

Dr. McMartin welcomed everyone to the meeting and asked BSC members and invited speakers to introduce themselves. Dr. Birnbaum and Dr. Berridge also welcomed everyone to the meeting. Dr. Mary Wolfe, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Update on the Strategic Realignment and Introduction to the Meeting

Dr. Brian Berridge, NTP Associate Director and DNTP Scientific Director, began the meeting with an overview of *The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment*. He said that the intent of the meeting, with its series of invited speakers, was to gain a broad range of perspectives on what the future of toxicology looks like and how that fits in the context of the strategic planning taking place at NTP.

He noted that the program is sitting at an intersection between the evolving needs of science and society and the growing opportunity presented by rapid advances in technology and willingness to innovate. He described the NTP's aspiration, as well as the need to quicken the pace for meeting it, and delineated the current needs of the program:

- A need to address a rapidly increasing list of concerns.
- A need to respond to a broad stakeholder group with changing aspirations.
- A need to bring more human relevance and individual precision to NTP's hazard characterizations.
- A need to build confidence in a different approach to assessing hazards.
- A need to decrease NTP's dependence on animals as a primary modeling platform.

He discussed opportunities facing NTP including: the many advances in technology, willingness to innovate, and an ability to leverage prior experiences as prime opportunities.

Dr. Berridge said this meeting was a continuation of prior BSC meetings addressing the strategic realignment and related several instances of relevant BSC feedback. He went over the translational toxicology pipeline and described the evolution of the NTP scientific portfolio, with the goals of increasing impact and visibility and improving sustainability and complementarity. Part of that effort will involve three health effects innovation areas: (1) carcinogenicity testing for the 21st century, (2) developmental neurotoxicity modeling, and (3) cardiovascular hazard assessment in environmental toxicology. This represents a fundamental shift in the way NTP does business – instead of a sole focus on the biological impact of individual agents, there will be a shift towards specific diseases or areas of disease to understand what environmental agents might be contributing to them. In addition, he foresaw contextualizing hazard and enabling stakeholders, particularly the public.

As the BSC considers the changing toxicology landscape, he asked them to bear in mind the following questions:

- How might potential challenges of the future affect the NTP mission?
- How should the NTP position itself to be impactful in the toxicology and risk assessment communities?

Following Dr. Berridge's presentation, Dr. McMartin stated that NTP had received no oral or written public comments on the meeting.

V. The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

A. John Piacentino, M.D., M.P.H.

Dr. Piacentino, Associate Director for Science, NIOSH, presented background information about the long partnership between NIOSH and NTP, which is designed to:

- Characterize occupational exposure to agents of mutual interest and assess potential health effects
- Understand that worker exposure is greater than that of non-workers
- Capitalize on NIOSH access to worker populations and work sites to provide real-world context for toxicology studies
- Guide decision-making for NIOSH epidemiologic studies
- Provide toxicologic and epidemiologic evidence for guidance documents

He outlined strategies for smarter surveillance for the future, including improved direct reading and sensor technologies, and described the evolution of NIOSH's approach to assessing the immunotoxicity of workplace xenobiotics. He talked about the impact of the NIOSH-NTP collaboration internally, as well as the international impact beyond NTP, and noted that NIEHS influence has spurred NIOSH to develop occupational systematic review.

Dr. Bucher said that NTP's interactions with NIOSH over the years had been outstanding. He asked Dr. Piacentino whether he foresaw a future ability to further evaluate and provide nominations to the NTP for atypical exposure scenarios, which could be approached using different technologies or paradigms than are used presently to generate information that is helpful to understand occupational hazards. Dr. Piacentino said that nomination to NTP is a critical part of the partnership, and added that it is an opportunity to raise issues of concern to workers, particularly since some exposures occur exclusively occupationally.

B. William Slikker, Jr., Ph.D.

Dr. Slikker, Director, NCTR, began his presentation by outlining the FDA Predictive Toxicology Roadmap. The FDA Predictive Toxicology Roadmap, which was announced in 2017, was developed by the cross-agency FDA Senior Level Toxicology Working Group.

Dr. Slikker noted that the roadmap emphasizes qualification, context of use, and the importance of partnerships for accepting new technologies. He also pointed out the emphasis on training on new predictive toxicology methods for FDA regulators, setting up an agency-wide education calendar of events and seminar series to introduce new toxicology methodologies, ensuring ongoing communication across FDA and with stakeholders, and building collaborations, both nationally and internationally.

The roadmap's goals are to:

- Identify critical priority activities for energizing new or enhanced FDA engagement in transforming the development, qualification, and integration of new toxicology methodologies and technologies into regulatory application.
- Engage with diverse stakeholders and enable FDA to fulfill its regulatory mission today while preparing for tomorrow's challenges.

Dr. Slikker acknowledged the importance of the relationships between FDA and partner agencies within the NTP.

Dr. Felter asked Dr. Slikker whether a formal mechanism and process exist for regulatory bodies to provide input to NTP. Dr. Slikker said yes, through formal, biannual meetings of FDA centers with NTP and NIEHS staff and other *ad hoc* meetings during the year.

Dr. Bucher commented that the concept of safe harbor for genomic data had been very successful, and asked Dr. Slikker if he foresaw its wider use for generating alternative information streams for FDA. Dr. Slikker said he would like to see more of that type of activity in the future as it provides the opportunity to evaluate new and novel datasets and approaches to make sure they are useful, fit for purpose, and qualified for FDA application.

Dr. Pettit asked Dr. Slikker how FDA and NTP might work together to achieve broad international acceptance of new toxicological applications. Dr. Slikker described the 2011 formation of the Global Coalition for Regulatory Science Research, under the direction of the FDA Commissioner and NCTR leadership. The group, which is comprised of representatives from nine countries and the EU, holds an annual meeting and training courses during the year. He also mentioned several other international groups involved in the coordinated implementation of the new technologies.

Dr. Birnbaum asked Dr. Slikker to discuss the relationship between NTP and NCTR. He noted the long history of their interaction and said that continuing their relationship would be important in aiding future regulatory decision-making.

Dr. Berube asked about the effort to engage the public. He noted the importance of science communication in light of widespread misinformation. Dr. Slikker agreed. He said that FDA had invested heavily in science communication efforts and felt that development of new approaches to communication would be critical.

C. Gina Solomon, M.D., M.P.H.

Dr. Solomon, Clinical Professor of Medicine, University of California San Francisco, described the pathway-based toxicity testing approach from Tox21, and said that the challenge in risk assessment is how to effectively utilize early cellular information. She described gaps in toxicity pathway assays related to the key characteristics of carcinogens as an example, which led to the first of a series of recommendations that she presented:

- Recommendation #1: Systematically address identified gaps in toxicity pathways by developing and incorporating new assays.

She illustrated an effort undertaken by her group in California, where 50 chemicals were evaluated for their ability to affect five of the key characteristics of carcinogens. Many of the chemicals affected multiple key characteristics of carcinogens. Identifying the most active chemicals for the key characteristics and the biological pathways involved could aid in determining where additional information would be useful.

- Recommendation #2: Test hypotheses by following up with testing of chemicals that show markedly positive results on important pathways.

She pointed out that the key characteristics of carcinogens are not specific to cancer and that toxicity pathways may impact several endpoints. As an example, she highlighted chronic inflammation, which is an upstream effect of not only cancer, but also vascular disease, diabetes, asthma, and reproductive or neurodegenerative disorders.

- Recommendation #3: Move toward making decisions based on the pathway disrupted, not on each endpoint.

The ability to look at chemical classes is important in risk assessment. Figuring out how to use predictive toxicology to divide chemical classes into sub-classes, identify chemicals within each sub-class for screening, and use read-across to tie information on a class together, will be very important moving forward.

- Recommendation #4: Develop and implement strategies to group chemicals into classes and impute hazards across the class.

She discussed intrinsic and extrinsic stressors, factors which occur over a person's lifetime and may impact their propensity for good health or disability/death. She stressed the importance of determining how chemical and non-chemical agents interact and affect human health, and gave chronic inflammation as an example.

- Recommendation #5: Evaluate how multiple stressors, including non-chemical ones, perturb biological pathways.

D. William Cibulas, Ph.D., M.S.

Dr. Cibulas, Associate Deputy for Science, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry (NCEH/ATSDR) discussed how ATSDR fits with the changing toxicology landscape. He described the agency's mission and the steps necessary to achieve the mission. He said that predictive toxicology is recognized as very important to the work being done at ATSDR.

He detailed ATSDR's toxicology needs:

- Basic biological research on cellular pathways and mechanisms at environmentally-relevant concentrations

- Improved techniques for assessing harmful effects from co-exposures (mixtures) and cumulative exposures
- Improved methods for assessing cancer risks
- Improved understanding of risks for susceptible populations
- Harmonized approaches for developing health guidance values for emerging chemicals
- New and improved, validated tools for predictive toxicology
- Better use of probabilistic techniques for communicating “risk” to communities
- New methods for incorporating “big data” into health/risk assessments, especially human data (e.g., biomonitoring, epidemiology studies, surveillance, medical health records)

E. Patricia Underwood, Ph.D., DABT, M.B.A.

Dr. Underwood, Deputy Director for Risk Assessment, Office of the Deputy Assistant Secretary of Defense, said that she leads the Chemical Materials Risk Management Program, whose mission is to understand emerging chemicals related to the Department of Defense’s (DOD’s) operations, identify risks, and establish policies to address those risks.

She noted the increasing ability of the public to access information on hazardous chemicals and their expanding desire to understand the health implications of exposure to environmental chemicals. There is the expectation that government and regulators will assess and address those implications in a timely manner. This presents the most significant challenge faced by the field of toxicology and risk assessment.

To address the requirements for information that is better, faster, and cheaper, she felt that risk assessors should focus on four main areas:

- Support a transparent, purpose-driven prioritization for toxicity assessment that is informed by current public health and regulatory needs.
- Support the continued development of rapid hazard characterization methodologies and toxicity assessment.
- Advance risk assessment methodologies to address expanding public concerns.
- Revolutionize the way we communicate about health risk with the public, and take action by considering the development of an interagency risk communication action plan.

F. Syril Pettit, Dr.P.H., M.E.M.

Dr. Pettit, Executive Director, Health and Environmental Sciences Institute (HESI), provided background information about HESI, a 30-year-old organization that brings together scientists from around the world to ensure the health and safety of people and our environment.

HESI recently undertook an activity called Science Foresight, with the objective to create a broad picture of widely identified global and/or national science and health

priorities and align those with priorities identified by HESI's diverse stakeholder base. They arrived at a global health view by surveying the publications of national and international health and/or environment organizations and mining the opinions of HESI governance, leadership and scientific committee.

Dr. Pettit said she would focus on an overarching theme that emerged from the Science Foresight project: moving toxicology from defense to offense. Currently, toxicology currently reduces toxicity in order to avoid harms and "de-risk" compounds. In the future, toxicology will reduce toxicity in order to enhance quality of life and public health; moving the field from a "tox-centric" orientation to a "health context" approach. Part of that approach will require the generation of "real-world evidence".

Dr. Birnbaum asked Dr. Pettit to comment further on the real-world evidence concept, as opposed to epidemiology. Dr. Pettit said it is a term of art that has been adopted by the FDA, who is trying to implement it in clinical trial and post-market surveillance contexts. She said that although it is in fact epidemiology, it is being positioned as a new approach to evaluate long-term drug safety and near-term clinical trials and regulatory approvals.

Dr. Stevens said that the "real-world evidence" term was invented by the pharmaceutical industry to allow them to differentiate between data collected in a well-controlled clinical trial versus data collected in a less-controlled patient environment. He further commented that it will likely be the cutting edge of how new statistical approaches and big data are used.

G. Fiona Sewell, Ph.D.

Dr. Sewell, Programme Manager in Toxicology and Regulatory Sciences, National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), noted that global harmonization of regulations is key in this global marketplace. The 3Rs landscape has changed and is still changing, with large incentives to move away from animal use.

She provided background information about NC3Rs, an independent scientific organization established in the United Kingdom (UK) in 2004 to lead the their 3Rs agenda. She stated the NC3Rs' mission:

- To discover, develop, and promote new ways of replacing, reducing, and refining the use of animals in research.
- To work towards decreased reliance on animal toxicity tests in conjunction with improvements in the science and predictivity of safety assessment.

She described they have a large program in toxicology and regulatory sciences with an emphasis on changing policy, practice, and regulations. Data sharing and its role as an "honest broker" are key to building an evidence base for change.

Dr. Sewell discussed their short- and long-term goals, including an aim to engender a paradigm shift, with the ultimate goal of working toward implementation of non-animal

methods that are more predictive than traditional methods and improving safety assessment. She provided several examples of policies affected by NC3Rs' efforts.

Dr. Birnbaum asked Dr. Sewell whether her organization is working with the International Cooperation on Alternative Test Methods. Dr. Sewell replied that NC3Rs has had interactions with the Interagency Coordinating Committee on the Validation of Alternative Methods.

H. Russell Thomas, Ph.D.

Dr. Thomas, Director, National Center for Computational Toxicology (NCCT), U.S. Environmental Protection Agency (EPA), described the EPA's approach to applying changes in toxicology to decision-making.

He noted that early versions of toxicity testing left challenges for evaluating chemical safety, and that addressing those challenges would require scientific and policy advances including:

- Technology advances to comprehensively evaluate large numbers of chemicals across toxicological space.
- Strategies to incorporate new approach methods in regulatory decisions.
- Use of new approach methods to identify potential candidates for prioritization.
- Use of visualization and decision support tools to manage and integrate diverse data.

He summarized EPA's many scientific advances in toxicity testing, including innovations in high-throughput and high-content screening, and described the EPA strategic plan to develop and integrate new approach methods under the Toxic Substances Control Act (TSCA), with three main parts to:

- Identify, develop, and integrate new approach methods.
- Establish relevance, reliability, and confidence.
- Train, educate, and collaborate.

The plan delineates near-term, intermediate, and long-term objectives, with the long-term goal to "reduce and eventually eliminate vertebrate animal testing."

He characterized as "take home messages":

- Toxicology advancement to the new and improved version will require both scientific and policy advances.
- New technologies exist for rapidly and comprehensively covering toxicological space at significantly less cost.
- New strategies provide a blueprint for developing and applying new approach methods for regulatory decisions related to statutes like TSCA.
- New approach methods are a key component of the long-term strategy for informing priority candidate selection in TSCA.

- Data management systems and decision support tools will be increasingly important for interpreting and integrating the expanding and diverse landscape of chemical safety information.

Dr. Birnbaum asked Dr. Thomas about work with the EPA Office of Air or Office of Water. Dr. Thomas said his group had worked with the Office of Water to evaluate high-throughput systems for volatiles and aerosols.

Dr. Berridge asked Dr. Thomas about his thoughts on an approach for building confidence in novel data and novel approaches. Specifically, he asked whether it requires showing that the biological substrate has in vivo relevance, or maybe having a critical breadth of data, or demonstrating that the novel approach's outcome is similar to the traditional approach? -Dr. Thomas said that the answer is all three and more, depending upon the audience and decision context. Thus, there is no easy answer, and it is important to develop all three in parallel.

VI. BSC Discussion

Board members were asked to discuss the following questions:

- How might potential challenges of the future affect the NTP mission?
- How should the NTP position itself to be impactful in the toxicology and risk assessment communities?

Dr. Chiu had two comments based on the day's presentations. First, he noted that there is a subtle distinction between characteristics of compounds and characteristics of diseases, and said that in discussions about pathways, those two distinctions can get mixed up. He felt that there should be more focus on characteristics of compounds known to cause disease rather than getting too much into the disease characteristics themselves. Secondly, he talked about moving from hazard identification to dose response, and the challenges involved.

Dr. Berridge thanked all of the day's presenters and noted some consistent themes. There was good consistency in recognizing that getting to a more predictive posture is needed, with novel approaches and confidence that those novel approaches would allow the field to deal with the multiple issues facing it. There was a theme of real-world human relevance and good recognition that it will take a village was mentioned several times, particularly communication with novel stakeholder groups. He also detected a theme of confidence and confidence-building and noted that not too long ago, the conversation around novel methods was all about validation. It is now recognized that the need is much more than that, with attention on the need to build confidence, which is more difficult than analytical validation.

Dr. Thomas said it is important to distinguish between being predictive and also protective. In the current risk assessment framework, the endpoints upon which risk assessment decisions are based are fairly non-specific, such as body weight changes, etc., which are not necessarily predictive in humans. He felt that NTP should work to explore the protective space as well. For many chemicals, particularly those that are

promiscuous in their action, it may not be necessary to predict the mechanism, but rather identify the dose. Dr. Berridge said that it was an excellent point that should be discussed as to how NTP fits in.

Dr. Stevens said he felt that the properties of biological systems must be considered, particularly if NTP is going to take on chronic diseases. It is almost inevitable that disease progression becomes dominated by properties of the biological system. For example, if a broad category of chemicals causes inflammation, it can't necessarily be known whether the inflammation will lead to insulin sensitivity and diabetes, chronic cardiovascular disease, neurodegeneration, or cancer. However, it is known that inflammation is a component of the chronic disease progression process. He wondered whether in the future this type of information might be sufficient to create points of departure or define hazards of chemicals, and stressed the need to decouple those conclusions from requiring the link to absolute proof of an apical endpoint.

In response to Dr. Stevens' comment, Dr. Solomon noted there is some precedent for moving in that direction. She gave the example of cholinesterase inhibition, which can lead to a number of endpoints, and pointed out that there is precedent for regulating chemicals based on that inhibition instead of only on apical endpoints. She noted the benefits of looking at biological pathways both upstream and downstream of an observed effect. Dr. Stevens wondered whether risk assessment practices are too disease-focused, and whether the risk assessment field might ever shift to enable use of intermediate apical endpoints for decisions. Dr. Solomon said that their use would depend upon factors such as the risk-related language in statutes and their various legal and precautionary requirements.

Dr. McMartin said the meeting's presentations had highlighted the importance of communication, particularly communication to the public. He felt that explaining concepts such as intermediate endpoints and upstream markers is going to be very difficult, especially when the public is concerned about diseases like cancer. Dr. Chiu felt that clinical biomarkers might be a start for communicating this concept with the public and also targets for high-throughput screening.

Dr. Felter wanted to ensure that the context of dose is considered, whether in high-throughput screening or *in vivo* testing, and Dr. Solomon agreed.

Dr. Berube said that with regard to public health communication, there are data on why the public reacts as it does to health information. He offered to prepare a summary of what has been done over the past decade. He pointed out that the communication must address two points – maintaining public trust and debunking misinformation. Dr. Berridge said he would welcome that information.

Dr. Gamboa felt that using subapical endpoints as points of departure for risk assessment presents a "very substantial risk of overregulation." He agreed with Dr. Felter's point about contextualizing dose.

Dr. Stevens agreed that dose is important; however, in terms of chronic disease progression, he felt that the time course is as important, if not more so. He opined that

understanding a chemical's impact on biological processes and linking that to the probability of disease and its progression are important questions to probe.

Dr. Bucher agreed with Dr. Stevens. He felt that relating the initial events to the chronic disease situation in humans and looking at intermediate outcomes could be addressed in two stages. First, evaluate the relationship between the intermediate outcomes and the end outcome in humans using information from all chemicals and all sources, and second, examine the chemical-initiated event for the creation of the intermediate step. The information from both stages can then be used in conducting the risk assessment.

VII. Adjournment

Dr. Birnbaum and Dr. Berridge thanked all participants and staff for their efforts related to the meeting. Dr. Mc Martin adjourned the BSC meeting at 2:30 pm, February 15, 2019.

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Dr. Kenneth McMartin

Chair, NTP Board of Scientific Counselors



Date: 4-16-19