Summary Minutes

NTP Board of Scientific Counselors

December 14-15, 2016

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I. Frequently Used Abbreviations and Acronyms

BPA	bisphenol A
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
EPA IRIS	EPA Integrated Risk Information System
FDA	U.S. Food and Drug Administration
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
HHS	Health and Human Services
IAA	International Antimony Association
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ILS	Integrated Laboratory Systems, Inc.
NCTR	National Center for Toxicological Research
NICEATM	NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NORA	National Occupational Research Agenda
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
ORoC	Office of the Report on Carcinogens
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RoC	Report on Carcinogens
SOT	Society of Toxicology

II. Attendees

Members in Attendance:

Cynthia Afshari, Amgen
Norman Barlow, Johnson & Johnson
Paul Brandt-Rauf, University of Illinois at Chicago
Myrtle Davis, National Cancer Institute
Mary Beth Genter, University of Cincinnati
Daniel Kass, Vital Strategies

Steven Markowitz, City University of New York
Kenneth McMartin, Louisiana State University
Lisa Peterson, University of Minnesota (chair)
Jennifer Sass, Natural Resources Defense Council
James Stevens, Eli Lilly and Co.
Donald Stump, WIL Research
Katrina Waters, Pacific Northwest National Laboratory

***Ad Hoc* Members:**
Bruce Aronow, Cincinnati Children's Hospital
David Eastmond, University of California, Riverside
Tim Wiltshire, UNC Eshelman School of Pharmacy
Miyoung Yoon, ScitoVation, LLC

Other Federal Agency Staff:
Carl Cerniglia, FDA
Goncarlo Gamboa, FDA
Paul Howard, FDA, BSC Liaison
Elizabeth Whelan, National Institute for Occupational Safety and Health (NIOSH), BSC Liaison

National Institute of Environmental Health Sciences (NIEHS) Staff:

Scott Auerbach
Windy Boyd
Linda Birnbaum
Abee Boyles
John Bucher
Warren Casey
Mike DeVito
June Dunnick
Anika Dzierlenga
Steven Ferguson
Julie Foley
Paul Foster
Dori Germolec
Robbin Guy
Will Gwinn
Allison Harrill
Jean Harry
Ron Herbert
Cindy Innes
Gloria Jahnke
Grace Kissling
Nicole Kleinstreuer
Kelly Lenox
Ruth Lunn
Robin Mackar
Dave Malarkey
Scott Masten
Elizabeth Maull
Deborah McCarley
Alex Merrick
Dan Morgan
Esra Mutlu
Fred Parham
Julie Price
Sreenivasa Ramaiahgari
Cynthia Rider
Andrew Rooney
Kristen Ryan
Kelly Shipkowski
Keith Shockley
Robert Sills
Stephanie Smith-Roe
Diane Spencer
Kris Thayer
Molly Valant
Suramya Waidyanatha
Nigel Walker
Vickie Walker
Lori White
Kristine Witt
Mary Wolfe
Yun Xie

NIEHS Contractors:
Whitney Arroyave, Integrated Laboratory Systems, Inc. (ILS)
Ernie Hood, Bridport Services
Rachel McIntosh-Kastrinsky, Kelly Services
Les Recio, ILS

Public:
Elizabeth Baker, Physicians Committee for Responsible Medicine (by telephone)
Scott Belcher, North Carolina State University
Brian Berridge, GlaxoSmithKline
Craig Boreiko, International Antimony Association
Raymond Tice

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened December 14-15, 2016, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Dr. Lisa Peterson served as chair.

The December 14 proceedings were a review of the NTP Biomolecular Screening Branch. It was closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552(c)(6), Title 5 U.S.C., and section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

The board convened in a public session on December 15, 2016, with Dr. Peterson presiding. She welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. Dr. Lori White, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Report of the NIEHS/NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, briefed the BSC on recent developments at NTP and NIEHS.

In her update on budgetary matters, she noted that the federal government remains on a Continuing Resolution. She discussed the recent passage of the 21st Century Cures Act and what it would ultimately mean for NIEHS and NTP. Although there is little direct impact as the great majority of the funds are targeted to specific projects, she hoped that NIEHS and NTP would be able to participate in some of those projects, such as the Cancer Moonshot and the Precision Medicine Initiative.

Dr. Birnbaum related details about the background and history of NIEHS as she went over “50 Years of Informing Public Health Decisions.” She described several current major projects, such as Zika research, studies on perfluorinated chemicals, and findings related to cell phones. She provided a timeline of the many events that took place during the institute’s 50th anniversary celebration in 2016. She listed the distinguished speakers at the 50th anniversary celebration and the twelve recipients of the Champion of Environmental Health Research award.

She noted the recent recognition of NIEHS environmental justice efforts, as part of the Hazel M. Johnson Federal Agency Achievement Award, presented to the HHS secretary by the head of EPA.

Dr. Birnbaum highlighted three recent NTP scientific publications in the use of alternatives to animal testing.

She recognized the retirement of BSC members Dr. George Corcoran and Dr. Lisa Peterson, who each served four-year terms. She also featured the retirement of Dr. Paul Howard, who served for ten years as liaison between the BSC and the FDA National Center for Toxicological Research (NCTR).

Dr. Barlow asked Dr. Birnbaum what she saw as the biggest challenge facing NIEHS in the coming mid- to long-term, budget constraints aside. She said that NIEHS can contribute to healthier lives by investigating how the environment impacts human health. She supports efforts to make toxicology more predictive. She endorsed the systematic review approach developed by NTP, as interpretation is often just as important as the data itself. She added that current *in utero* rat studies are promising to help understand the impact of early life exposures, and that studies documenting multigenerational effects will prove to be important.

Dr. Stevens asked whether Dr. Birnbaum felt that current NIEHS and NTP training programs are adequate to produce the skill sets that would be necessary in a Big Data world. Dr. Birnbaum said that NIEHS has been leading the training component of BD2K, the NIH Common Fund Big Data effort. She listed several other NIEHS- and NTP-funded training programs.

V. Office of the Report on Carcinogens (ORoC)

A. Update on the 14th RoC

ORoC Director Dr. Ruth Lunn briefed the BSC on the release of the 14th RoC on November 3, 2016. She provided background information about the RoC, and noted that the new release included seven newly reviewed substances: trichloroethylene; cobalt and cobalt compounds that release cobalt in vivo; Epstein-Barr virus; human immunodefiniciency virus, type-1; human T cell lymphotropic virus, type-1; Kaposi sarcoma-associated herpesvirus; and Merkel cell polyomavirus. There was substantial media coverage of the report.

She described several substances currently under or proposed for evaluation, including antimony trioxide, the draft concept of which she would subsequently present in more detail. She delineated the revised process for the preparation of the RoC.

Dr. Howard said he wanted to applaud the staff for how they reached out to the other federal agencies for input, and encouraged the practice at even earlier stages of the process.

B. Draft Report on Carcinogens Concept: Antimony Trioxide

Dr. Lunn reported on the concept for antimony trioxide. She explained that a draft concept is a planning and communication tool that is used early in the RoC listing process.

She provided background information about antimony and antimony compounds, metalloids found in nature in over 100 mineral species. Antimony trioxide is the most commercially significant antimony form and is contained in a variety of consumer products. She described cancer studies of antimony trioxide, which led to its nomination for RoC review, and discussed existing databases of antimony and antimony trioxide. The database for antimony trioxide is considered to be adequate to evaluate the carcinogencitiy of antimony trioxide. There is also evidence of exposure to antimony trioxide in the United States, especially among workers.

Dr. Lunn discussed the scientific issues involved in the evaluation, and reviewed the objective and scope of the review and assessment of antimony trioxide. The major issue was whether the evaluation should be expanded to include other antimony compounds. She said the evaluation would culminate in a peer review of the draft monograph by a panel of experts.

C. Public Comment

Dr. Craig Boreiko spoke on behalf of the International Antimony Association (IAA), commenting on the proposal to move antimony trioxide onto the path for future listing in the RoC. He mentioned that many regulatory processes have acknowledged the limited utility of applying persistence to the prioritization of inorganic substances. He addressed the current convergence of regulatory processes in the U.S. and the European Union (EU). He noted that antimony and its compounds will shortly be evaluated in the REACH process in the EU. The IAA will embark on research to address some of the fundamental issues concerning hazard classification and risk assessment for antimony and its compounds. Thus, new information will emerge pertinent to some of the uncertainties that presently exist with respect to carcinogenicity and mutagenicity of antimony and its compounds. Dr. Boreiko noted that although the profile of antimony and its compounds may seem straightforward, the case for the listing of antimony is not so simple. He discussed questions and uncertainties related to the rat and mouse studies. He said that although hazard classification of antimony trioxide could be attempted, it would be difficult to translate to estimates of risk. With REACH and IAA research coming, he suggested that parallel efforts in different regions should be coordinated.

D. BSC Discussion

Dr. Barlow, first discussant, asked Dr. Lunn what drove consideration of listing antimony trioxide in the RoC. She clarified that it was only a concept at this point, without any commitment to listing it. She noted that the substance had been nominated in the early 2000s by NIOSH. Dr. Barlow asked how the other activities described by Dr. Boreiko were taken into account, and if they might lead NTP to delay the evaluation until some of the other data were available. Dr. Lunn proposed there was an adequate database of cancer studies to move forward. Dr. Bucher said when a major study is anticipated to be published, a delay is possible if it is clear that it would be a crucial piece of information for an evaluation. He noted there is always research going on that could further inform a listing decision; however, in this case, there is adequate data to move forward. Although new information could result in re-evaluation in some cases, in all cases the best science at any time is taken into account. Dr. Barlow recommended including robust exposure data in terms of the number of people exposed and levels. Dr. Lunn replied that it is rare to have that type of data available. Dr. Barlow said that his conclusion was that the overall significance of the proposal was moderate, and that his level of enthusiasm for the concept is “between the moderate and high level.”

Dr. McMartin, second discussant, said that the concept was well-crafted. He proposed the exposure data as decent and not definitive. He noted that there are a number of different studies, and a comprehensive review to reconcile the various studies would be important. He agreed that the largest exposures would be found in an occupational setting; however, the extent of exposure among the general U.S. population is unclear. He said although the animal studies database is adequate, the human cancer studies are small in number and difficult to assess. He agreed that there is not much information on mechanism of carcinogenicity. Thus, a thorough literature search is important. He concurred that the review should focus on antimony trioxide. He rated overall significance as moderate to moderate-to-high.

Dr. Stump, third discussant, said that the strongest support for the RoC evaluation is the two-year NTP cancer bioassays. He proposed the best existing data is for antimony trioxide. He said that the NTP Technical Report, with clear evidence of carcinogenicity in mice, provided strong support for pursuing the study further. He agreed that the overall significance is moderate, with most of the exposure being occupational.

Dr. Lunn agreed that it would be good to have more information on human exposure, and agreed with the focus on antimony trioxide.

Dr. Markowitz noted that worker exposure is important, with higher risk of developing disease due to high exposure than the general population. He noted that NIOSH has a database of historic exposures, and wondered whether NTP was able to use that data, given cancer latency. Dr. Lunn said that past exposures are considered.

Dr. Davis asked whether an investigation of mechanism that revealed gaps might push forward additional mechanistic research. Dr. Lunn said that it would. Dr. Walker provided the example of formaldehyde as a case of data gaps spawning additional research.

Dr. Brandt-Rauf asked whether there would be a vote. Dr. Peterson explained that there would not be a vote; the board would issue a recommendation. Dr. Bucher elaborated on the process. Dr. Brandt-Rauf supported proceeding with the evaluation after taking into account the total burden of disease that could occur.

Dr. Sass asked where public comments would be found on the website. Dr. Lunn explained where they were. Dr. Wolfe added that comments are initially posted to the board meeting's public website and then linked to RoC pages.

Dr. Sass showed enthusiasm about the concept. She mentioned the importance of knowing the data gaps, particularly the possible release of the substance from consumer products.

Dr. Peterson summarized the board's comments, stating that support for moving forward was "moderate-to-high," perhaps closer to high than moderate given some of the comments.

VI. A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century

A. Presentation/BSC Questions

Dr. Warren Casey, Director of the NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods (NICEATM), briefed the board on new efforts toward adoption of alternative testing methods. He provided background information about the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which NICEATM supports.

Dr. Casey described the 18-month effort, which has shown that communication is the most important aspect of the initiative, and will be the focus going forward, under the rubric "Modernizing Safety Assessment of Drugs and Chemicals in the U.S." He noted that it is challenging to highlight the need for change without condemning past methods or approaches. He said it would be vital to communicate clearly why the effort is being made, with the three major drivers being ethics, efficiency, and public health. Challenges include the difficulty of evolving institutional practices to keep pace with revolutionary advances in science and technology. Others include institutional resistance, the difficulty of harmonization, and reliance on animal models as reference standards.

He discussed progress in the effort to replace animals in acute toxicity testing by 2020, significantly reducing the use of animals in the EPA "6-pack" panel. He described upcoming events and key strategic projects related to the effort.

Dr. Davis asked Dr. Casey whether the effort is designed to establish whether the complete model system can be compared with an *in vitro* system, as opposed to whether a particular question that is asked of the model can be efficiently addressed by an *in vitro* system. Dr. Casey said that assertion was correct.

Dr. Whelan clarified that NIOSH is not a regulatory agency.

B. Public Comment

Speaking by telephone, Elizabeth Baker of the Physician's Committee for Responsible Medicine noted that there are opportunities to correct the current disconnect between scientific advances and their implementation. She said her group strongly supports Dr. Casey's call for a national strategy to modernize testing, and firmly believes that the strategy will help to correct the disconnect. They recommend that the roadmap focus on replacement, with consideration given to opportunities for reduction.

C. BSC Discussion

Dr. Waters, first discussant, said she found the presentation to be helpful, particularly the comments about barriers and challenges. She agreed that the process would need to be driven by the regulatory agencies, with consensus from the agencies being a major challenge. She proposed the initiative related to acute toxicity testing is a good place to start. She asked Dr. Casey how harmonization from the regulators could be achieved, given that they may have different purposes for why they are regulating chemicals or pharmaceuticals. Dr. Casey replied that identifying those opportunities is one of the central goals and purposes of ICCVAM, and that understanding how each agency uses animal testing is important. Dr. Waters asked if there were any lessons to be learned from the European approach. Dr. Casey said that the European situation is quite complicated, with each of the countries having its own regulatory bodies. He said one element to be learned is the EU's ability to identify an objective and organize efforts to achieve it. Dr. Waters noted that there is a very strong public motivation in Europe related to the ethics of animal testing; stronger in Europe than in the U.S. Dr. Casey said it would be important to get the American public more involved and to do a better job of communicating the value added by moving away from animal testing.

Dr. Afshari, second discussant, commended the work of NIEHS and NICEATM as a strong voice that communicates a combination of strong science and data with transparency about limitations. She approved of the emphasis on improved communications. In terms of efficiency, she warned that it may be premature to present a cost-saving method broadly. However, the efficiency value is the ability to get to

answers faster. Dr. Casey noted that efficiency is commonly included as one of the drivers for use of alternatives, although they are not always less expensive. Dr. Afshari said it would be important for the public to understand that adoption of alternatives will be an iterative science that is pushing the envelope, allowing for some failures along the way. She discussed the value of existing data, particularly as they inform mechanistic knowledge. She said there is a need for new tools to probe the biology in humans. New training programs in areas outside of traditional toxicology would help develop the necessary expertise.

Dr. Davis said the project needs more specifics in the future, particularly identifying areas where animal models do well and where they fall short in human predictivity. She cited *in vitro* assays currently being used to evaluate the risk of cytokine release syndrome as an example of an instance where such tests are being used in decision making about human risk. She suggested that the regulatory agencies may be able to provide examples of instances where in vitro alternatives to assess human safety are needed. Dr. Casey agreed, and added that it would be useful to identify instances where animal models do work and why.

Dr. Stevens noted that there are distinct differences between environmental testing and drug safety testing. He said that in pharmaceutical trials, drug candidates are tested in animals first to help determine starting dose and other factors, allowing for safe testing in humans. He added that in his opinion, ethics actually do drive decisions on animal use in the U.S., although there is a better balance of ethical and scientific considerations when considering animal testing.

Dr. Howard said he did not envy Dr. Casey's position of needing to respond to the Congressional mandate while dealing with a myriad of agencies and laws. He questioned Dr. Casey's assertion that costs have escalated with decreasing returns on investment in drug testing, and that adoption of alternative methods would reduce costs. Dr. Howard noted that more than three-quarters of the costs of bringing a new drug to market are in the human clinical trials. He encouraged Dr. Casey to keep the agencies involved in his efforts, particularly in terms of helping define relative risks. He said it would be important to choose strategically where to engage the agencies. Dr. Casey agreed that ethics is certainly a factor in the U.S., and the main selling point is human health.

Dr. Barlow noted that examples of ethics factors can drive public pressure that can be used to support alternative testing methods. Dr. Casey agreed, stressing the need for a simple, effective message.

Dr. Sass suggested more specifics in future presentations on the topic. She agreed with the focus on replacement of the EPA 6-pack. She approved of the use of descriptive

statistics in describing the alternative test methods, helping the agencies' ability to defend conclusions regarding toxicity. Dr. Casey said that understanding the variability of animal tests will help regulators put the data into context.

VII. Assessing the Impacts of Toxicants on the Microbiome

A. Presentation

Dr. Carl Cerniglia, Director of the FDA NCTR Division of Microbiology, spoke to the BSC about current collaborative projects with NTP to assess the impacts of toxicants on the microbiome.

He described microbiome research as one of the most exciting areas that has emerged in public health. He provided extensive backgrou nd information about the human microbiome and environmental exposures, as well as a history of microbiome research. He discussed a collaborative project with the NTP's Dr. Vicki Sutherland, "Assessment of the Role that the Microbiome May Play in the Toxicity of Xenobiotics." Aside from the specific experiments involved, a major part of the effort is to standardize approaches in methods development, collection of samples, and data analysis. The idea is to include microbiome analysis in the risk assessment toolbox. He noted that the tools for microbiome analysis are becoming more available and affordable, and they are being used in the NTP/NCTR project. The research aim is to integrate all of this information and try to have a lot more knowledge and understanding of the effects of these chemicals on the microbiome and on the human body.

He described the role of the gut microbiota in health and intestinal disease, and the host influences on gut microbiology ecology, along with the important role played by the human gut microbiota in the metabolism of xenobiotics. He outlined the methods for measuring the effects of xenobiotic compounds on the human gut microbiota. He listed the compounds currently being studied in animals: triclocarban and triclosan, bisphenol AF, arsenic, silver nanoparticles, and aloin/aloe vera. Despite the recent explosion in research on the microbiome, the field is still in the infancy of beginning to recognize the critical role the microbiome has in our health and wellbeing.

B. BSC Discussion

Dr. Birnbaum said she appreciated Dr. Cerniglia's slide depicting the varied microbial population within the gastrointestinal tract.

Dr. Davis asked Dr. Cerniglia what kind of changes in the microbiome could be associated with an adverse outcome. He replied that it is difficult to specifically determine those patterns from a microbial population standpoint due to interindividual diversity. However, the dysfunction of the intestinal barrier could lead to certain microorganisms, which are known to be pathogenic, to colonize the gastrointestinal tract. He said the field is more concerned with looking at the functional effects, such as

the gut associated immune responses and metabolism. He added that what constitutes a healthy microbiome is still being determined. More research is also needed to predict the changes in the microbiome that lead to a disease state.

Dr. Walker noted that the aloe vera story drove the development of the microbiome program. The observed increase in colon tumors in the animals led to a question of whether destruction of the microbiome was a factor in causing inflammatory responses in the colon of the aloe vera treated animals.

Dr. McMartin said there was a danger in doing studies where a substance is used to treat an animal, with changes in the gut microbiome looking like an effect, whereas the long-term functional aspect is more important. Dr. Cerniglia agreed, and observed that many of the disorders are actually multifactorial. Dr. Cerniglia also discussed the differences between the intestinal microbiomes in humans and other species.

Dr. Howard said there is very little existing information in this area, so developing the method to gather the information correctly across labs will be of paramount importance. Common methodology will be vital. Dr. Cerniglia noted that samples must be handled properly and that developing and standardizing methods in microbiome analysis is part of the NCTR/NTP project.

VIII. Report of the NTP Associate Director

Dr. Bucher, Associate Director of NTP, informed the BSC about developments at NTP since the last BSC meeting. He described recent publications, including the ICCVAM 2014-2015 Biennial Progress Report and the 14th RoC. He updated the board on the status of several NTP research projects, including the synthetic turf/crumb rubber research program, glyphosate studies, and investigation of the low-dose mixtures hypothesis of carcinogenesis.

Dr. Bucher discussed several recent meetings with NTP participation, and looked ahead to an upcoming ICCVAM meeting and an ICCVAM ontology webinar series scheduled for early 2017. He outlined current requests for data and information on zebrafish embryo chemical screening, technologies used for identifying potential developmental toxicants, technologies used to identify substances with the potential to cause acute systemic toxicity, and short-term alternative animal models or *in vitro* tests used to identify substance with the potential to cause excessive inflammation or exaggerated immune responses.

He reported that NTP staff members Ray Tice (retired 2015), Nicole Kleinstreuer, and Warren Casey were recent award recipients. Dr. Birnbaum received the 2016 North Carolina Award for Science. He noted recent hires by NTP, and recognized the

retirement of Dr. Lori White from the Office of Liaison, Policy, and Review. Dr. White has long been the BSC Designated Federal Official.

Dr. McMartin noted that Dr. Birnbaum had just received the SOT Distinguished Toxicology Scholar Award.

IX. Update on Current NIOSH/NTP Collaborative Research

A. Presentation

Dr. Whelan, BSC NIOSH liaison, briefed the BSC on the long-standing cooperation between NIOSH and NTP, focusing on the most recent projects that have been worked on over the past 5-7 years. She described the goals and impact of the NTP/NIOSH collaboration. She provided updates on seven current studies, including background information, findings, and current status:

- Use of and occupational exposure to indium in the United States
- Occupational exposure assessment of manganese fractions in welding fume
- Industrywide exposure assessment study of workers exposed to carbon nanotubes and carbon nanofibers
- Urinary bisphenol A concentrations among manufacturing workers in the U.S.
- Assessment of exposure to polycyclic aromatic hydrocarbons in coal tar sealant applications
- Assessment of occupational exposure to flame retardants
- Occupational exposure to 1-bromopropane

B. BSC Questions and Discussion

Dr. Birnbaum asked what measurement method was being used in the carbon nanotube study. Dr. Whelan replied that transmission electron microscopy (TEM) was used.

Dr. Bucher noted the long-standing relationship between NTP and NIOSH, which has benefited from the ability of NIOSH to access workplaces, helping NTP to focus nominations and studies. He said it has been an enormously successful collaboration over the years.

Dr. Walker thanked NIOSH for its contribution to moving the carbon nanotube studies forward. Dr. Birnbaum thanked NIOSH for its participation in the bisphenol A studies. Dr. Wolfe said she appreciated Dr. Whelan's reference to the impact of the studies, which often occurs long after the studies have been completed.

Dr. Markowitz, first discussant, asked Dr. Whelan to elaborate on the relationship between NIOSH and NTP and whether projects were chosen based on the association with NTP. Dr. Whelan replied that it is a back-and-forth process, with NIOSH and NTP both wishing to study high-priority chemicals. She said the relationship is not an overlap,

as NIOSH has the skills, expertise, and legal authority to go into workplaces and get records and take samples. She noted that NIOSH wants to conduct the studies that are of the highest priority to other federal agencies, including NTP. Dr. Markowitz asked whether NIOSH distributes NTP products to employers, industries, and unions. Dr. Whelan said that one way to accomplish that would be to disseminate NTP products through the Councils that are part of the NIOSH National Occupational Research Agenda (NORA) process. The councils, organized by industry sectors, include external stakeholders such as labor unions, trade associations, industry, and others. Dr. Markowitz asked Dr. Whelan why NIEHS conducted the BPA in cashiers study. Dr. Thayer explained NIEHS has resources from the Clinical Research Unit, which offers the appropriate mechanism to be able to recruit the cashiers.

Dr. Sass, second discussant, offered to connect NIOSH and NTP with the BlueGreen Alliance, a linkage of environmental groups and unions, to help disseminate findings from NTP and NIOSH. She asked whether women were recruited to participate in the studies Dr. Whelan had mentioned, particularly women of reproductive age. Dr. Whelan said that it was largely dependent on the demographics of the worker population studied; however, women were not specifically excluded. Dr. Birnbaum asked Dr. Whelan if NIOSH is conducting any studies of nail salon workers. She replied that nail salon workers have been studied quite a bit over the years related to exposure to various chemicals. Dr. Whelan said that NIOSH probably needs to do a better job of communicating agency products, including determining more creative ways to make the products accessible. Dr. Peterson asked if the agency tweets. Dr. Whelan said that the agency has a Twitter account, and that it would be a good idea to use it more.

Dr. Stevens asked Dr. Whelan to comment on the recent discussion about the lack of occupational exposure data related to crumb rubber production. This would be a good opportunity to obtain information about high-exposure scenarios. Dr. Bucher said that California EPA is looking at occupational sites as well as playing fields in its exposure assessments.

X. NTP Monograph on Immunotoxicity Associated with Exposure to PFOA or PFOS

A. Presentation

Dr. Andrew Rooney from the NTP Office of Health Assessment and Translation (OHAT) briefed the board on the peer review of the draft NTP monograph on immunotoxicity associated with exposure to PFOA and PFOS. The monograph was the first OHAT evaluation to use the OHAT approach for systematic review and evidence integration to reach hazard conclusions. The peer review meeting took place at NIEHS on July 19, 2016, and was chaired by Dr. Weihsueh Chiu from Texas A&M University. Dr. Brandt-Rauf was the BSC liaison.

Dr. Rooney noted that the panel accepted the level of evidence ratings for the antibody response to PFOA as written. The draft conclusion was that PFOA suppressed the antibody response, with a high level of evidence in animal studies, a moderate level of evidence in human studies, and no change in conclusions after considering mechanistic data.

The panel recommended that the level of evidence for the animal hypersensitivity-related data was moderate, based on the limited number of studies and divergent response to PFOA. After downgrading the hypersensitivity data, the panel accepted the draft hazard conclusion for PFOA based on the antibody response data. The draft conclusion was that PFOA is presumed to be an immune hazard to humans.

The panel accepted the draft hazard conclusion for PFOS based on the antibody response data. Both PFOA and PFOS are presumed to be immune hazards to humans.

Following the peer review meeting, comments from the public and peer review panel were considered, and the NTP Monograph was finalized.

B. BSC Discussion

Dr. Brandt-Rolf, BSC liaison to the peer review meeting, said that the format of the meeting, with all of the reviewers attending remotely via WebEx, worked reasonably well. He said the reviewers did an excellent job, and that the scientific preparation for the meeting was quite well done. He noted that there was a robust discussion, and the technology did not present a barrier. He approved of the OHAT process, which made everything transparent and rigorous. He agreed with the conclusion reached by the panel.

Dr. Markowitz mentioned that one of the peer reviewers was from Dow Chemical, which is in the process of merging with DuPont, a producer of PFOA or PFOS. He wondered how conflict of interest was screened. Dr. Wolfe responded that at that time the companies had not merged. In addition, the panelists were screened for conflicts of interest and asked to declare any conflicts both before and during the meeting. No conflicts of interest were identified. Dr. Markowitz suggested taking a look at the timing of the various events.

He questioned the choice of the word “presumed” in the hazard conclusion, asserting that the word is softer than saying “it probably is.” Dr. Thayer agreed that there is no perfect phrase, but noted that the phrasing had been adopted from the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Dr. Wolfe added that NTP is using the category labels currently used by GHS. Dr. Wolfe described the current research to study the level of concern language, and noted there

will be study of how hazard calls are communicated. Dr. Bucher added that this is an active area of consideration, in order to communicate most clearly.

Dr. Barlow asked whether the availability of more studies would re-open consideration in areas where the conclusion had been that there was insufficient information. Dr. Rooney said that would be an ongoing issue, particularly with the focus on transparency in systematic reviews. The challenge, he said, would be determining when there are data that may change a conclusion. A formal process to accommodate such data does not exist; however, NTP is well-situated to be able to update as necessary. Dr. Wolfe added that the RoC has a process for reconsideration, if new information may affect a listing.

XI. NTP Scientific Publications: Fit for Purpose

A. Presentation

Dr. Wolfe briefed the BSC on the current status and new developments for NTP publications. The various NTP publications disseminate the outcomes of NTP's work in order to strengthen the science base in toxicology and provide information useful for decision-making by health research and regulatory agencies, medical and scientific communities, and/or the public.

She described the existing, traditional NTP scientific publications: report series, monograph series, and journal publications. Reports and monographs follow procedural standards. Some include policy decisions about hazard. Overall, they are a trusted source of information, within and outside the federal government. Literature analysis publications include *RoC Monographs* and the RoC itself, as well as *NTP Monographs*. Testing program publications include *Technical Reports*, *Toxicity Reports*, and *Genetically Modified Model Reports*.

Dr. Wolfe described new NTP publications. Based on its studies on reproduction, development, and the immune system, NTP is creating two new report series, the *Technical Reports on Developmental and Reproductive Toxicity* series and *Technical Reports on Immune System Toxicity*.

NTP also generates information that does not readily fit into existing report or monograph series, such as pilot studies. Thus, there is a need for a scientific publication to assimilate the information into a citable report and fill gaps in dissemination of NTP's work. That need led to the creation of a new report series called *Research Reports*, which is designed to disseminate results from NTP testing, research, and analysis activities not covered in existing series.

Dr. Wolfe described a need for periodic releases to communicate the findings of NTP studies related to emergency response. For the 2014 West Virginia Elk River chemical

spill, NTP launched a website to quickly disseminate its research plan and findings, and developed a new NTP scientific publication called the *NTP Updates*. *NTP Updates* provide short write-ups of studies, including the method, chemicals studied, findings, and next steps, if any. The web-based dissemination also allowed posting of the 2016 *NTP Report on Partial Findings from Cell Phone Radiofrequency Studies*, which received considerable public attention.

Dr. Wolfe showed the new web-based format for NTP scientific publications moving forward. Sections of the NTP publications will be in individual tabs. Hovering over an in-text reference will bring up the full reference. Appendices enable linking to tools and data for download.

Overall, NTP has a number of scientific publications to disseminate its work, each with a specific purpose. NTP has addressed needs to increase access to its work, including data, through additional report series and the use of web-based approaches.

B. BSC Questions and Discussion

Dr. Afshari asked about peer reviewers for the research reports in terms of conflicts of interest. Dr. Wolfe pointed out that in all NTP reports, peer reviewers are identified and undergo conflict of interest screening. Dr. Afshari asked if there is a strategy to ensure that the new types of publications will be valued similarly for the authors' careers to those appearing in journals. Dr. Walker said that as chair of the internal promotion committee, he sees to it that all publications are recognized, and that he encourages individuals to list all publications on their CVs. Dr. Birnbaum added that there is a movement to publish everything, with NIH encouraging publication of negative data, for example.

Mr. Kass, first discussant, said he appreciated the NTP's formal evaluation and literature analysis methods, with the quality of the products reflecting those efforts. He said NTP's documents specifically and NIH's more generally are without peer among U.S. government documents. He noted that there is currently a fundamental transformation in the way people seek and consume information. He felt that NTP still does not have a presence in the world of new media. He asked if that aspect was being considered going forward. Dr. Wolfe said that even in complex documents, a lay summary is included. She added that as the levels of concern categories are being addressed, ways to visually communicate that information would be explored. Ms. Robin Mackar, NTP liaison from the NIEHS Office of Communications and Public Liaison, described the NIEHS Twitter and Facebook presence. She cited fact sheets and the NTP and NIEHS websites as vehicles to communicate the science with the wider public. Dr. Wolfe cited the example of the *NTP Speaks About* website series as another example of communication with the lay public.

Mr. Kass asked if NTP regularly tracks use and consumption of its documents. Dr. Wolfe replied that NTP does not do so regularly, but does in certain cases like the cell phone report or the West Virginia chemical spill. She said study is ongoing to determine more effective methods to assess references to NTP on the web. She said NIEHS has instituted tools recently to analyze web trends. Mr. Kass said it would be interesting to see consumption information about the West Virginia chemical spill documents created by NTP.

Mr. Kass observed that other agencies are obviously one of the primary audiences for NTP publications and findings. He said it was clear that some of the findings have policy implications. He asked if NTP actively works with other agencies on the policy implications of its findings. Dr. Walker said there is a working group with the FDA, and there is a continuum of communication. He said that in certain areas, NTP is actively engaged with other agencies; however, these activities may not be visible. Mr. Kass noted that at least in public-facing documents, NTP does not make policy recommendations for other agencies. Dr. Birnbaum noted that one agency cannot tell another agency what to do; NIEHS can only inform other agencies. Dr. Wolfe said that there are several instances where other agencies are actively informed about NTP findings. Mr. Kass said that there is a vast reservoir of expertise in NIEHS and NTP about risk communication. Dr. Birnbaum said that risk communication is an evolving science, and NIEHS actually funds some work in that area.

Speaking to Mr. Kass's comments, Dr. Walker described the three-minute science talk competition that took place at the recent NIEHS Environmental Health Science Fest, and said that the younger scientists were enthusiastic about communicating in that medium.

XII. Adjournment

Concluding the meeting, Dr. Birnbaum said it had been one of the best two-day NTP Board meetings. She thanked the members and staff for their participation. Dr. Bucher thanked everyone for a great meeting, and said that NTP gets more from the BSC members than they may realize.

Dr. White also thanked the BSC members. Dr. Markowitz thanked Dr. White for her contributions on behalf of the BSC. Dr. Peterson thanked everyone for a productive meeting.

The meeting was adjourned at 3:30 pm, December 15, 2016.

[redacted]

Dr. Lisa Peterson

Chair, NTP Board of Scientific Counselors

Date: Feb 23, 2017