

National Toxicology Program
Board of Scientific Counselors
Summary Minutes
December 11, 2012
National Institute of Environmental Health Sciences
Research Triangle Park, NC

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I. Frequently Used Abbreviations and Acronyms

ADME	absorption, distribution, metabolism and elimination
BPA	bisphenol A
BSC	Board of Scientific Counselors
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HHS	Health and Human Services
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
PAH	polycyclic aromatic hydrocarbon
PCTC	Pavement Coatings Technology Council
PETA	People for the Ethical Treatment of Animals
RPF	relative potency factor
SAR	structure activity relationship
SR	systematic review
TK	toxicokinetic
WG	working group

II. Attendees

BSC Members in Attendance:

Robert Chapin, Pfizer
David Dorman, North Carolina State University
David Eastmond, University of California – Riverside (chair)
Miguel Fernández, University of Texas Health Science Center at San Antonio
Jack Harkema, Michigan State University
Dale Hattis, Clark University
Richard Miller, GlaxoSmithKline
Sonya Sobrian, Howard University
Judith Zelikoff, New York University School of Medicine

BSC Members not in Attendance:

Elaine Faustman, University of Washington
Dana Loomis, International Agency for Research on Cancer
Melissa McDiarmid, University of Maryland School of Medicine
Lisa Minor, *In Vitro* Strategies

NTP Federal Agency Liaisons:

Paul Howard, US Food and Drug Administration (FDA)
Gayle DeBord, National Institute for Occupational Safety and Health (NIOSH)

National Institute of Environmental Health Sciences (NIEHS) Staff:

Linda Birnbaum	Scott Masten	Kris Thayer
Abee Boyles	Barry McIntyre	Ray Tice
John Bucher	Aubrey Miller	Molly Vallant
Michael DeVito	Cynthia Rider	Suramya Waidyanatha
Paul Foster	Andrew Rooney	Nigel Walker
Dori Germolec	Kristen Ryan	Lori White
Michelle Hooth	Robert Sills	Mary Wolfe
Robin Mackar	Cynthia Smith	Rick Woychik
Aris Martone	Sheetal Thakur	

Public:

Nancy Bordelon, Battelle
Brian Burback, Battelle
James Bus, Styrene Information and Research Center (by telephone)
Robert Fensterheim, RegNet Environmental Services (by telephone)
Lynn Goldman, The George Washington University School of Public Health
Ernie Hood, Bridport Services
Anne LeHuray, Pavement Coatings Technology Council
Joseph Manuppello, People for the Ethical Treatment of Animals (PETA, by telephone))
Kimberly Wise, American Chemistry Council (ACC, by telephone)

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met December 11, 2012, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Dr. David Eastmond served as chair. He welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. He welcomed new BSC member Dr. Jack Harkema, and noted that the appointment of Dr. Miguel Fernández to the BSC was finalized. Dr. Lori White, BSC Designated Federal Officer, read the conflict of interest policy statement.

IV. Report of the NIEHS/NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, updated the BSC on NTP and NIEHS appropriations. She noted that the institute and NTP (which does not have a separate appropriation) had been funded under a Continuing Resolution for the first six months of the 2013 fiscal year, resulting in a basically flat appropriation. She said that if Congress did not act by January 2 regarding sequestration, many initiated programs would need to be halted. She said there had been a “soft freeze” on hiring within NTP and the NIEHS intramural program over the past two years due to federal budget uncertainties. If sequestration did not go into effect, key positions that have been on hold could be filled. However, if it does, it would result in an 8.2% retroactive budget cut, which would lead to loss of many extramural grants (35-40,000 jobs lost due to NIH grant cuts), but no layoffs within NIEHS. Although the current budget is flat, she said she had been told by members of the Appropriations Committee that “flat is the new success story.”

She reported on recent legislative activities, including Senate and House committee allocations, a bill to limit the use of funds for Title 42 positions, and the new restrictions on conference and travel support.

She briefly summarized several recent scientific advances involving NIEHS/DNTP personnel or NIEHS grantees, and reported on recent institute hiring, awards, and recognition. She updated the BSC on the status of the NIEHS Strategic Plan, which was published August 1. The institute's leadership staff, she noted, is currently heavily engaged in developing implementation plans to turn the goals of the plan into reality. She reviewed the new mission and vision statements and the 11 strategic goals that emerged during the process and were ultimately included in the strategic plan. Each NIEHS division has developed its own implementation strategy, and eight interdivisional implementation topics have been identified, each with co-leads. Plans from those teams are due January 31, and they are expected to be finalized in February or March.

Dr. Birnbaum thanked departing BSC members Drs. David Eastmond and Judith Zelikoff for their service to the BSC, presenting both of them with certificates of appreciation signed by HHS Secretary Sebelius. She also acknowledged and thanked other departing members for their service including Drs. Elaine Faustman, Dana Loomis, and Stephen Looney, who were not present.

V. NTP Research Concept: Polycyclic Aromatic Hydrocarbons (PAHs)

A. Introduction

Dr. Scott Masten, NIEHS/DNTP, briefed the BSC on the background behind the development of NTP research programs and why NTP is pursuing a research program focusing on PAHs.

He noted that for each research project, DNTP staff prepare a research concept, a brief document designed to outline the rationale, data gaps, key issues, and specific aims to be addressed by the proposed approach, as well as the significance and expected outcome of the proposed program. It is used to facilitate internal and external review of projects in the NTP research and testing program. The PAHs are a very large class of compounds that have received very little NTP testing to date; there is a need to expand the database for relative potency factor (RPF) development and cumulative risk assessment, particularly in light of new and old sources of exposure, including the Gulf Oil Spill. Sources of PAH exposure include crude oil, coal tar sealants, energy extraction, carbon nanofiber/nanotube manufacturing, and synthetic turf playing fields.

Dr. Masten said the proposed PAH research program is different than other programs the BSC has reviewed, and may serve as a model for future complex research program. The challenge, he pointed out, was to address the complexity involved, not reduce it. The scope and strategy chosen reflect a workable testing framework with flexibility built-in for periodic adjustments to add value to a heavily researched area while leveraging other ongoing efforts.

B. Public Comments

Mr. Joseph Manuppello, representing People for the Ethical Treatment of Animals (PETA), commented by telephone. He said PETA agrees that it is impractical to assess the toxicity of the 1500+ individual PAHs and the infinite number of mixtures containing PAHs using the two-year bioassay, PETA is encouraged that in the proposed research project, longer-term animal studies appear to be limited to targeted assessments, with the iterative testing approach promising to avoid unnecessary resource expenditure. However, PETA is concerned that a large number of PAHs and mixtures may be subject to a short-term testing panel that would include rodent studies with the oral gavage route of exposure. Instead of a mandatory testing panel, PETA recommends that the need for additional animal data be evaluated on an individual basis. He noted the existence of data from a large number of animal studies with PAHs, such as the more than 900 individual publications identified in the EPA's 2010 assessment, including dose-response data for 51 of the 74 PAHs. The International Agency for Research on Cancer assessed the potential carcinogenicity of 60 PAHs, with additional data on other outcomes included. Also, the Health Canada program may have archived tissue samples available that could be analyzed in place of new animal studies. He said the oral gavage route of exposure has "obvious animal welfare implications," and should not be selected over dietary exposure. He suggested a more thorough discussion of mechanisms of toxicity, identifying data gaps, a discussion that would also inform the selection of test articles. He cited the EPA's Science Advisory Board's discussion of the RPF approach to risk characterization, noting that the use of existing animal data mentioned should be considered by NTP as it would provide information about the RPF approach. He concluded by requesting that the public have another opportunity to review and comment on the proposed project once the initial test articles are selected.

Dr. Anne LeHuray of the Pavement Coatings Technology Council (PCTC) presented comments on behalf of her group, whose members manufacture or supply materials needed to manufacture pavement sealers and other pavement products. Her major comments were: (1) the primary goal of the PAH research program should be to study real world PAH mixtures, and (2) the BSC should defer consideration of the PAH research program pending public availability of the studies conducted by Health Canada, which seem to form the basis for the whole mixtures research design of the proposed PAH studies.

C. PAHs: Introduction, Toxicity and Human Health Risk Assessment

Dr. Cynthia Rider, NIEHS/DNTP, presented the details of the proposed research program on PAHs to the BSC. She provided background about the chemical composition of PAHs, noting that over 1500 distinct PAHs have been referenced in the literature. They occur naturally in petroleum and coal and are created and released into the environment through both natural and human activities. She described the properties of PAHs, including how they are metabolized. She detailed the known toxicities of PAHs including carcinogenicity, immunotoxicity, reproductive and developmental toxicity, and neurotoxicity. She noted that PAHs are ubiquitous in the environment, with several routes of human exposure. Estimating human health risk from exposures is challenging, with two distinct approaches available: the study of whole mixtures and the component-based approach, which includes the RPF or dose additivity method that was

used by the EPA in its PAH risk assessment guidance document. In reviewing the “Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures,” the EPA’s Scientific Advisory Board recommended that the agency seek support from the NTP to test a portfolio of 12-15 different complex mixtures in animal studies. Dr. Rider reported that there were several inherent challenges in that effort, including multiple issues in prioritization of PAH-containing mixtures, logistical challenges in acquiring and analyzing complex mixtures, and the fact that a large volume of material would be required for each 2-year cancer bioassay, resulting in a very resource-intensive effort. Also, once data are generated, significant work would be required to develop sufficient similarity methods. Thus, the component-based RPF approach, despite its shortcomings, has been chosen as the focus of the NTP research program with a goal of decreasing uncertainties associated with application of the RPF approach to PAHs.

The major knowledge gaps to be addressed include exposure (Do the 16 commonly monitored PAHs capture the class?), hazard characterization (the vast majority of PAHs have not been characterized, and there are additional toxicities beyond genotoxicity and carcinogenicity), and risk assessment (uncertainties in the application of the RPF approach; no currently identified path forward for developing a sufficient similarity approach to assess risk with complex PAH mixtures).

D. BSC Clarification Questions

Dr. David Dorman asked whether there is an overarching hypothesis driving the research program. Dr. Rider said that question had been considered during the development of the program, but the group decided to concentrate at this time on increasing the database for which RPFs can be developed, which includes several sub-hypotheses that she would discuss in more detail later in the presentation. Dr. Dorman noted that there was an overarching hypothesis that is not explicitly stated – that the RPF approach could be applied to mixtures. He asked at what point in the testing might that hypothesis be rejected, if it became clear that it would not be applicable in some instances. Dr. Rider said that such a thought process was what led the group to develop the proposed iterative design, beginning with testing some individual compounds followed by assessing the RPF approach as soon as possible. If it is found that the RPF approach proves to be very inaccurate in all outcomes, it would be a signal to move into developing a sufficient similarity of whole mixtures approach. Dr. Bucher added that the breadth of the structural classes of PAHs may allow the use of the RPF approach for a subset of compounds, without covering the entire class of PAHs. Dr. Birnbaum noted that given the complexity of the different compounds and the multiplicity of endpoints, it may be found that there are different mechanisms or modes of action involved in the various effects. Dr. Rider added that part of the process would be to find out when the RPF comes close enough and when it breaks down.

Dr. Harkema asked how many mixtures were in the literature that had been reviewed. Dr. Masten replied that there was a relatively small number of PAH-containing mixtures where a full database of long-term studies covering multiple endpoints was available. Dr. Rider added that only a handful have been studied due to the logistical difficulties of acquiring the samples and

the fear that co-contaminants would drive toxicity, with the challenge of teasing that apart. Dr. Harkema asked about the time frame involved in studying mixtures. Dr. Rider replied that the NTP would begin assessing mixtures early in the program, including a mixture(s) in the first round of testing. Dr. Eastmond commented that it should be recognized that there are many different classes of mixtures, many of which change over time due to factors such as weathering.

Dr. Dorman asked whether food safety was a major driver of the PAH program, or if it was more environmental non-food exposures. Dr. Masten replied that it was not the major driver, but that there were many drivers, which when added together, convinced NTP that a concerted effort to study PAHs was needed.

Dr. Fernández asked if there was a plan to look at food interplays and drug interplays with relation to PAHs exposures. Dr. Rider replied that there were no specific plans to do so at this time, with the current focus more on looking at the joint actions of chemicals within mixtures.

E. BSC Discussion: Charge Questions 1 & 2

Dr. Zelikoff, lead reviewer for question 1, noted that Dr. Rider's presentation had filled in many of the gaps she had originally perceived, pulling the concept together and addressing several of her concerns. She felt that the concept was quite good, but that it would be very difficult to build mixtures, constituting a very ambitious task given the challenges involved. She said the scope of the problem was well stated, and the proposed approach would fill in many of the knowledge gaps. She felt the iterative format was a good approach, but was concerned about whether some of the assays would be truly reflective of long-term outcomes. She expressed concern about the lack of neurotoxicological endpoints. Until the presentation, she said she had been unclear about the fact that the main focus initially would be individual components prior to moving into the mixtures. The plan for moving into mixtures was not well fleshed-out in terms of the thinking about how to get to that endpoint.

Dr. Dorman asked about wildlife, in that Dr. Rider had mentioned the issue but that it did not seem to be a major focus. Dr. Rider said studying the joint action of the PAHs would inform both human health and wildlife risk assessment processes. Dr. Dorman said in that case wildlife should not be even tangentially mentioned, since it raises the issue of ecotoxicity.

Dr. Dale Hattis, lead reviewer for question 2, said the goal of the program must be to provide practical, quantitative advice to risk assessors evaluating the risk of these mixtures "in the wild." He felt there should be as much comparison as possible between the RPF predictions and the observations of the actual effects of the mixtures. He noted that systematic error could be in both directions, either overstating or understating the toxicity of mixtures, and recommended that both systematic error and random error be measured and taken into account in risk predictions. Exploring the sources of error could be used to correct the models and increase the predictability of mixture effects. Correction and quantification of remaining uncertainty should also be included. His second major issue was that since different mechanisms and

different endpoints would be measured, it should be expected that there would be different sets of RPFs to capture those different actions.

Dr. Zelikoff noted there was a mention in the proposal of additivity or synergism or potential antagonism for the PAHs, and she felt that there should be more consideration of how those factors might complicate the matter. She said there were other non-PAH elements within some of the mixtures that could work to increase or decrease their overall potency.

Dr. Chapin felt that area was absolutely something NTP needed to be addressing aggressively. He said the value would come in learning how to predict the toxicity of a mixture based on its components.

Dr. Dorman said he had not seen the use of molecular modeling as a structure activity relationship (SAR) approach mentioned in the proposal, and recommended that it be considered, particularly with such a disparate group of compounds involved.

Dr. Eastmond noted that the metabolism issue had not been addressed directly, and that many of the components of the mixtures would likely be antagonists for carcinogens present in the mixtures. He said metabolism would be a key element in driving the outcome of the program's results and success. Dr. Birnbaum said antagonism would be very dose-dependent, and at very low exposure levels it would not be an issue, but might be seen at very high exposure levels. She added that extrahepatic metabolism would be where the main action would reside, mainly as a clearance function. Dr. Richard Miller wondered whether the existing *in vitro* assays might help with the metabolism and antagonism questions.

Dr. Harkema asked about how defining susceptible populations might fit into the issue of human risk. Dr. Rider said that would be hard to address at this time, but that more would be known as the project progressed. She said at this time, it is sufficient to focus on building the predictive mixture toxicity models, with consideration of susceptible populations coming downstream. Dr. Harkema suggested the health outcomes should be carefully defined from the outset, so that the question of susceptible populations would not be overlooked. Dr. Bucher said the NTP does have some parallel efforts underway to look at susceptibility.

F. PAHs: Background on Concept Development

Dr. Rider described the NIEHS Mixtures Workshop that took place in September 2011 as one galvanizing factor where many of the key issues addressed in the proposed research program were identified. She mentioned other recent mixtures-related activities, and noted that the issue of combined exposures is specified in Goal 4 of the new NIEHS Strategic Plan. She also described recent research activities by Health Canada, which have also helped form the basis for the current proposal.

Dr. Rider delineated the key research issues related to exposure, hazard, and risk characterization, including the key issues associated with the RPF approach and with the whole mixtures approach. The specific aims of the project are to:

1. Assess chemical, toxicokinetic (TK), and absorption, distribution, metabolism and elimination (ADME) properties of select, individual PAHs and mixtures to gain insight into exposure and dosimetry.
2. Characterize the toxicity of a broad range of individual PAHs, defined PAH mixtures and complex environmental mixtures containing PAHs using a short-term panel that incorporates *in vitro*, alternative animal, and *in vivo* models and captures a diverse array of endpoints/effects.
3. Compare predicted mixture toxicity results using component-based models that incorporate calculated RPFs or whole mixture approaches (e.g., complex mixture fractionation approaches, models based on sufficient similarity of whole mixtures) to observed toxicity.

The proposed NTP approach includes targeted selection of test articles; a flexible, iterative format; incorporation of a broad spectrum of endpoints; and cross-disciplinary and institutional collaborations. She described each of the proposed elements of the program in detail. It would start with Round 1 (examples of test articles that could be included in Round 1 are: PAHs with RPFs, alkylated PAHs, oxygenated PAHs, and simulated seafood extract, a complex environmental mixture), the results of which would be carefully evaluated, leading to Round 2 (examples of test articles that could be included in Round 2 are: a defined mixture, coal tar, a complex environment mixture, and targeted individual PAHs). Evaluation of Round 2 would lead to Round 3, the content of which would be determined based on results from the previous rounds. The program would further characterize the toxicity of PAHs and would strengthen the basis for assessing risk from PAH exposures, including understanding the role of PAHs in the toxicity of complex environmental mixtures. It is intended to provide an opportunity to address the significant knowledge gap regarding mixtures by building bridges between *in vitro* and *in vivo* approaches, employing a cross-disciplinary effort, using systems-based approaches, and establishing the need for both component-based and whole mixtures approaches, ultimately beginning to develop a path forward for comparing predictive-mixture modeling approaches.

G. BSC Clarification Questions

Dr. Miller asked about the diverse array of cell-based systems mentioned, as to whether they would be a mixture of rodent and human systems. He wondered if the idea was to link those to previous studies with individual PAHs or to guide the doses or endpoints in the *in vivo* studies, or a mixture of both. Dr. Rider replied that the goal of the use of the three diverse cell lines was to get the most biological diversity possible, to look for patterns across that diversity with individual PAHs and mixtures, particularly to see if they could be binned according to certain patterns.

Dr. Harkema asked if in the 28-day studies, the 28th day was the only endpoint. Dr. Rider said that for the immunotoxicity and the general toxicity, the 28th day is the endpoint, but that other time points could be built-in for the ADME/TK portion.

Dr. Chapin said he was heartened to hear that NTP would anchor its results to the research in the area going on elsewhere. He cautioned that recent research has shown that just 26-48% of

published studies are replicable, and that that could create discrepancies in later results. He also mentioned that one issue with the zebrafish model is that the tissue under the chorion is selective about what it lets into the fish; thus strengthening positive readings but compromising negative findings based on whether there is sufficient internal exposure. Dr. Rider said that this was one of the strengths of looking at the entire panel, in that there will be other endpoints that will provide information. Thus if there is an anomalous negative from the zebrafish, it may indicate that the model is not the best component of the testing paradigm.

Dr. Raymond Tice, NIEHS/DNTP, noted that in the experiments done by Dr. Robert Tanguay, the zebrafish are all dechorionated. Dr. Chapin said there were microscopic holes in the chorion, so that it provides no physical barrier to inputs. Dr. Tice said Dr. Tanguay has conducted experiments with and without chorions showing different results with certain classes of compounds. Dr. Chapin said that did not affect the concept that individual negative results would not factor in, but that a pattern of negatives in the zebrafish model might raise concerns about the validity of the model itself. Dr. Rider said there would be much evaluation, consultation, and judgment involved with the whole testing panel, so if there were suspect results, they would perhaps move into a mammalian test at that point. Dr. Nigel Walker noted that the concern was the difference in relative potencies in the different biological systems, but that the distributions among them could of themselves yield important information.

Dr. Fernández asked about the 28-day rat model being a gavage model, compared to real life where exposure is more likely to be dermal or inhalation. Dr. Rider replied that the bulk of the work on carcinogenicity has used the dermal route of administration, and that clearly more work is needed on the oral route, which is an important route of exposure. She said although bridges will be built to the other routes, looking at a large number of inhalation exposures might be prohibitively expensive. Thus, both biological and pragmatic factors went into the decision. Dr. Birnbaum added that for many PAHs, even those that are present in dust, the major pathway of exposure is ingestion. Dr. Howard appreciated the distinction Dr. Birnbaum made, noting that oral exposure is not necessarily synonymous with food. He also said any information that could shed light on predictivity of PAH mixtures that have been used to set guidelines would be very helpful. Dr. Walker noted that control of dose is very important when dealing with mixtures and another advantage offered by the oral gavage route. Dr. Fernández said that when considering the dermal route of exposure, the ambient environment must be considered as well.

Dr. Sonya Sobrian asked whether the route of exposure in the zebrafish would be dermal. She asked for some idea about the iterative scheme for Round 3, which had been left at “to be determined.” Dr. Rider said it would be very dependent on what was found in Rounds 1 and 2. Dr. Sobrian asked whether Round 2 findings might ever send them back to Round 1. Dr. Rider responded that that might take place on some occasions.

Dr. Harkema expressed concern that the outcomes being addressed were somewhat nebulous compared to the typical NTP cancer study outcomes, and perhaps should be more specific in terms of ultimate contribution to knowledge regarding health risks. Dr. Rider noted that the immunotoxicity assay is a defined, sensitive assay for suppression of the humoral immune response. She said the group had to balance the selection of endpoints to interrogate areas

that had been studied very little, such as the oxygenated PAHs, for which hazard characterization would be goal. Dr. Paul Foster, NIEHS/DNTP added that many of the proposed outcomes reflect standard subacute toxicity assessments. He noted that the zebrafish is a better model for early embryogenesis than it is for fetal development, and so mammalian tests may need to supplement them. Thus, there is a range in the NTP portfolio of other studies that could be used to look at specific disease and functional states. Dr. Birnbaum added that the outcomes to be studied to some extent reflect public concerns about PAH exposures affecting areas such as immune suppression, developmental and reproductive function, and developmental neurotoxicity, as well as cancer. Dr. Harkema said that should be clearly stated, with examples. Dr. Robert Sills, NIEHS/DNTP, added that there is a wide variety of studies available allowing a very focused approach in terms of pathology as well as toxicology and disease outcomes. Dr. Walker noted that NTP has criteria that apply to evaluation of immunotoxicity and reproduction and development studies.

Dr. Hattis suggested that one of the important endpoints in humans is fetal growth inhibition, as it is quite sensitive and perhaps could be effectively measured in shorter-term studies such as those proposed in the program.

H. BSC Discussion: Charge Questions 3-8

Dr. Chapin, lead reviewer for question 3, said that the draft concept did a good job of identifying the challenges and how the program plans to address them. He was also impressed by the NTP's outreach to other members of the PAH research community to learn from their experiences and discover where the pitfalls are in such a research endeavor.

Dr. Zelikoff suggested the addition of a section to the concept regarding what alternatives might be considered if the planned research approach does not work out. Dr. Howard asked Dr. Zelikoff to elaborate on what she meant by "not working out." She said that several things were being suggested for the iterative process as well as for the specific outcomes, and that it would be appropriate to have a "Plan B" in place should those approaches prove to not be adequately predictive or sensitive.

Dr. Sobrian felt that the challenges were well addressed, particularly some of the translational challenges associated with the 28-day testing approach. However, they only included the neurotoxicological endpoints, and she wondered if that section of the document might be expanded.

Dr. Hattis, lead reviewer for question 4, felt that the broad strategy delineated in the concept seemed quite reasonable. In efforts to reconstruct the observed mixture potency from the component potency, if systematic and random errors are identified, they should be quantified, which would provide information to risk assessors.

Dr. Dorman questioned how the chemical information in complex mixtures of interest would help inform the decision to select individual PAHs in Round 1. He said it could be a major disconnect in the process. Dr. Rider replied that environmental-exposure potential would also be

considered in individual PAH selection. She said it was likely that the alkylated PAHs selected would be environmentally relevant. She noted that more than one complex environmental mixture would be tested, and that they would be compared. Dr. Dorman recommended that the individual chemicals within mixtures of interest should be considered in selecting individual test articles.

Dr. Howard commented about the broad use of the term “environmental mixtures,” which he noted could mean anything from cigarette smoke components to food mutagens. He recommended that NTP focus on a particular subset of environmental mixtures, which would lend clarity to the program’s intentions.

Dr. Zelikoff suggested that NTP consider using the NIST standard as an initial complex mixture, since it has already been defined. Also, she wondered if persistence was part of the consideration when test articles were chosen, as it could be an important element of the rationale. She asked if any consideration had been given to studying benzo(e)pyrene, even using it as a control.

Dr. Zelikoff, lead reviewer for question 5, noted that the zebrafish is an excellent model for early development and teratogenesis. However, given the reproductive toxicity of PAHs, inclusion of more reproductive and developmental endpoints in the proposed program would have been desirable. She appreciated the explanation of why oral gavage was used, and approved of the approach as long as it is reflective of other exposures, such as food or water intake. She asked Dr. Rider to elaborate on Footnote 1 in the proposal, which stated, “Parallel histology on female reproductive tissue is not proposed at this time.” Dr. Rider said that endpoint had not been included because it would be too labor-intensive to deal with at present. Dr. Zelikoff agreed, but said she just wanted to make sure that nothing was being missed in terms of female outcomes. Dr. Walker added that clearly not every hazard for every PAH would be captured, but the intention is to interrogate a wide variety of endpoints to get a better evaluation of the fundamental framework of dose additivity and RPFs as it applies to mixtures. Pursuing every potential hazard would have generated a very different testing paradigm, he said, utilizing the full NTP workup with individual agents. Dr. Walker said the intent is to provide some hazard characterization, but not to address every potential health effect, as that would be impractical. He noted that that is a critical decision point, and that if the BSC feels it is the wrong direction, the NTP needs to hear that type of feedback before going forward.

Dr. Zelikoff asked how reflective the short-term assays are of long-term effects. Dr. Bucher replied that that is an important question, and has been a challenge in previous attempts to associate short-term outcomes with long-term impacts. Dr. Zelikoff suggested a birth parameter be added to the developmental element.

Dr. Dorman noted that it was not entirely clear how the 28-day assay would be informative for testicular effects. Regarding the tissue selection process, he was unclear as to whether the selection of lung tissue was based more on historical data from inhalation or as a representative target of gavage exposure. He also noted that the issue of developmental neurotoxicity with the zebrafish model is actually more one of structural neurotoxicity as opposed to behavioral

endpoints. He cautioned against trying to oversell some of the models for certain endpoints, and suggested a tighter focus.

Dr. Zelikoff suggested adding the thymus or a lymphoid organ to help reflect long-term outcomes for immunotoxicity.

Dr. Chapin, lead reviewer for question 6, said he liked the different levels of complexity involved with the iterative/evolving testing approach, as well as the use of several different cell lines chosen intentionally to represent different biological spaces. He said what he did not see was an intention to compare the toxicogenomic changes in the cell lines to the toxicogenomics in the *in vivo* tissues, and what would be done with that information. He asked for more explicit description of how that process would take place. He liked the multiple levels of biological complexity, but asked for more specific details, while recognizing that it may not be possible to fully articulate that information until the process has begun.

Dr. Miller felt the liver studies stood apart from the rest of the concept, as there was no other mention of hepatotoxicity. He asked how hepatic genomics data would be used. Dr. Walker said the liver is often seen as a sentinel organ, particularly for changes caused by oral gavage. Dr. Miller suggested the data could be linked to archival datasets. He noted that the liver would probably contain metabolites of mixture components, and suggested that samples could be frozen for later analysis.

Dr. Rider noted that some of the specific assays had been suggested by the prior work by Health Canada.

Dr. Birnbaum said that it would be important to acquire at least one readily accessible biological fluid to help extend findings to human risk assessment. Dr. Miller agreed, noting that hematology and general toxicology were mentioned in the proposal, but not clinical chemistry. Dr. Rider said clinical chemistry might take place if rats are included, but generally the design details would be finalized in consultation with the group.

Dr. Hattis cautioned that it would probably be tempting to try to develop measures of potency based upon the dose-response relationship for some of the short-term assays of genomic responses. He noted that it is not easy to correlate *in vivo* measures of toxicity with *in vivo* measures of fractional induction of different genomic receptors.

Dr. Fernández asked if any of the assays would look at electron transport in the cytochrome oxidase system. Dr. Bucher said there are some mitochondrial function assays in the Tox21 program, but there are no specific endpoints in that area in the proposed program.

Dr. Miller responded to the question about whether the NTP should continue to conduct deep hazard characterization on individual agents versus the proposed approach. He concurred with the NTP's proposed approach, particularly since there is already much data on many of the individual compounds, while mixtures remain elusive. He felt the proposed effort would be a contribution to mixture toxicology, in general, above and beyond the PAHs.

Dr. Chapin rated the project's importance as moderate or high for PAH work in general, but high for pushing forward a new approach to mixture science.

Dr. Hattis stressed that continuous variables have a better chance of providing information per unit of effort than quantal variables, and that endpoints such as inhibition of fetal growth have better chances of being directly predictive of human toxicity than even the best work with models such as zebrafish or some of the gene responses.

Dr. Walker asked for BSC members to comment on an issue that had arisen in several of the public comments NTP had received – how to report back on progress with the project. He said that in the past, NTP would provide the BSC with periodic updates, and that that is probably how it would go forward in this instance as well, but he asked for comments about a good communication plan that would be transparent. Dr. Miller said it was probably too early to answer the question, and that it might be more appropriate to comment once the project is in progress and appearing in the peer-reviewed literature. Dr. Chapin suggested that interested parties could sign up for an email distribution list for updates, alerting to new postings in a PAH section on the NTP website.

Dr. Sobrian asked if there was a time frame and mechanism for incorporating some of the suggestions made during the meeting. Dr. Zelikoff agreed, noting that there had been many comments and suggestions that would necessitate tweaking or re-thinking the proposal.

Dr. Eastmond summarized the BSC comments, stating that the BSC was quite supportive of the initiative, with several minor issues that may require some tweaking or re-focusing. In terms of understanding the PAHs in general, the priority would be moderately high, since it is an area where certain chemicals have been well studied already. The value would be in learning much more about the broader range of effects of the class of compounds, particularly in regions of the chemical space that are less familiar. The PAH program will be particularly valuable in moving forward mixture science, providing a solid basis for future work, particularly for those in regulatory agencies that have to deal with environmental pollutants or mixtures. As a long-term series of projects, it is an investment in the future. Dr. Eastmond said the project ought to be done, because the PAHs are a very important class of environmental chemicals with wide distribution.

VI. Report of the NTP Associate Director

A. Presentation

Dr. Bucher briefed the BSC on recent NTP activities. Meetings that took place since the June 2012 BSC meeting included an NTP Satellite Symposium associated with the Society of Pathology 31st Annual Meeting (June 24-26, Boston, MA), the NTP Working Group on Reaching Evidence Assessment Conclusions (August 28-29, Raleigh, NC), the annual Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting (September 5-6, RTP), an International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing (September 19-21, Ames IA), a peer review of the Draft NTP Monograph on Developmental

Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy (October 1-2, RTP), and an International Workshop on Alternatives to the Murine Histamine Sensitization for Acellular Pertussis Vaccines (November 28-29, Bethesda, MD). Upcoming meetings include peer review of the draft Report on Carcinogens monographs on 1-bromopropane and cumene (March 2013, RTP), web-based seminars hosted by the Office of the Report on Carcinogens on issues related to distinguishing potential cancer effects of pentachlorophenol from effects due to contaminants and occupational co-exposures in epidemiologic studies (late winter, 2013), a session at the Society of Toxicology meeting on Implementing Systematic Review (SR) at the NTP (March 12, 2013, San Antonio, TX), the next BSC meeting (June 25-26, 2013, RTP), and review of draft NTP Technical Reports (late summer, 2013, RTP).

Dr. Bucher reported on a 20th anniversary celebration of the FDA-NIEHS Interagency Agreement (IAG), which took place November 14, 2012, at FDA headquarters in Silver Spring, Maryland. The 1992 agreement was established to facilitate cooperation between the FDA and the National Center for Toxicological Research and NIEHS/NTP on compounds of interest to both institutions. The IAG has resulted in over 200 publications, including 15 NTP Technical Reports and 3 NTP Genetically Modified Models Technical Reports. The 20-year budget has been nearly \$200 million.

In senior staff changes, recent retirees include Jack Bishop and Beby Jayaram and upcoming retirements of Drs. Raj Chhabra, Michael Cunningham, Jef French, Williams Stokes (Public Health Service), and Cynthia Smith were noted. Dr. Stephanie Smith-Roe was hired recently.

VII. NTP Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments

A. Introduction

Dr. Mary Wolfe, NIEHS/DNTP, provided the BSC with background and perspective on the NTP systematic review (SR) and data integration ("NTP Approach") project. She said the project was not finished and at the meeting the BSC would hear about the status of the project and next steps. She introduced Drs. Kristina Thayer, Abee Boyles, and Andrew Rooney from the Office of Health Assessment and Translation (OHAT) that has taken the lead on the project. One of OHAT's activities is to conduct literature-based evaluations, often leading to an NTP monograph. Approximately two years ago, OHAT began to consider methods of improving its evaluation process, ultimately leading to development of the SR process being described at the meeting. OHAT outlined plans to incorporate systematic review into its literature-based assessments and presented new tools for information management and data display to the BSC at the June 2012 meeting. Plans included review of an initial draft approach for SR and evidence integration by a BSC Working Group (WG), which met August 28-29, 2012, in Raleigh. The draft approach was subsequently refined based on feedback from the BSC WG, detailed in the draft WG's report. At this meeting, Dr. Wolfe explained, OHAT would present the revised

draft approach, including how the WG's recommendations were incorporated. The BSC would vote whether to accept the WG's report and provide further feedback so that OHAT can work to finalize and ultimately implement the NTP approach. Dr. Wolfe also explained that Dr. Thayer would address next steps in the process of implementing the NTP Approach including release of the draft NTP Approach for public comment along with case studies to assess and refine methods.

B. Public Comments

Dr. Kimberly Wise, American Chemistry Council's Center for Advancing Risk Assessment Science and Policy, provided comments by telephone. She said she was pleased to see the revised draft approach document, but hoped that additional details about the framework would be forthcoming. She noted that there was little information in the current document about how stakeholders would be engaged in the process. She felt that there had not been adequate time for members of the public to review the revised draft approach, and encouraged opening the framework up to a 60-day public review period to allow for more extensive comments. She also called for a public-comment period on the protocol for case studies when it is made available, and looked forward to more details on the protocols within the framework, including considerations such as risk of bias. She offered to share some of the findings of her group's work on SR with NTP.

Dr. James Bus commented by telephone on behalf of the Styrene Information and Research Center. He said that the 7-step process for data evaluation and integration outlined in the NTP approach for systematic review is a promising beginning in honoring NTP's public commitment to development of evidence-based data assessment and has the potential to enable significant improvement in NTP hazard assessment. He said the current draft has not received sufficient input from the outside scientific community and the public. He felt it lacked detail and thought that it would be premature for the current draft to receive final BSC endorsement in this meeting. He noted that opportunity for public input in the iterative process was absent beyond the Step 1. He recommended that NTP: (1) initiate a 90-day public-comment period during which the larger scientific community could provide detailed input; (2) following that comment period and based on the input received, provide a revised proposal to the BSC that includes substantially more operational details; (3) prior to its formal adoption, initiate pilot studies with at least two different substances that actively engage interested scientists at each step of the process; and (4) bring the more detailed and more robustly, externally vetted approach back to the BSC for formal adoption. He said he was encouraged to hear Dr. Wolfe's reference to NTP plans to move forward with a series of case studies, in that such an approach would be consistent with his recommendations.

Dr. Bucher clarified that the single action item for this meeting was for the BSC to review the WG report and vote to accept or reject it. Dr. Eastmond added that the formulation of the approach is an ongoing process, and that this is the first step in a longer process, with additional opportunities to get feedback and make revisions as it progresses. Dr. Bucher noted that Dr. Thayer would outline some of the next steps in the process during her presentation.

Robert Fensterheim, RegNet Environmental Services, commented by telephone. He applauded the effort at transparency and step-wise process represented by the draft NTP SR approach. He said that his review of the material left it unclear to what extent NTP has considered the previous large body of experience in conducting chemical evaluations as part of its effort to develop its draft approach. He recommended that NTP adopt as a goal to describe the SR approach in a sufficiently clear and detailed manner for stakeholders and other risk assessors to replicate it, recognizing that the outcome may differ due to scientific judgment. He found the draft document to have been very well written, but only because the difficult issues were deferred to be addressed in the protocol to be prepared. He felt it did not adequately convey the complexities and difficulties that would be encountered in preparing the protocol. He outlined several examples of issues to be addressed in the protocol, which would be part of Step 1 of the process. He asked if the draft SR approach had ever been used for a chemical evaluation. He endorsed the idea of conducting pilot projects before receiving the final BSC “blessing.” He also agreed with the other commenters on the need for additional time to review the document, and that the opportunities for public comment throughout the process should be clarified.

C. Background on the Draft NTP Approach

Dr. Rooney, NIEHS/DNTP, briefed the BSC on the background of SR and the process employed to develop the NTP Approach. He discussed the issues OHAT had brought to the BSC WG. He defined SR, described its current uses (generally in assessment of healthcare interventions), and described what an SR does *not* do. He noted that existing SR methods do not provide guidance on how to integrate evidence across human, animal, and mechanistic studies or to reach hazard identification conclusions, both of which are necessary elements to apply SR methods to environmental health questions. Therefore, NTP had to extend existing methods to incorporate data relevant to environmental health questions.

He noted that the draft NTP Approach does not replace the existing OHAT evaluation process, but outlines a framework for developing NTP Monographs that fits within the overall OHAT evaluation process. He reviewed the process used to develop the draft NTP Approach, which included webinars, interagency communications, and input from the BSC. A variety of sources were considered, such as published SR methods and resources, technical expert consultations, and the establishment of the BSC WG to comment on the draft NTP Approach.

Dr. Rooney described the draft NTP Approach, which incorporates both SR and evidence integration in 7 distinct steps to develop hazard identification conclusions. He defined “evidence integration,” drawing a distinction with the “weight of evidence” approach. He illustrated the draft NTP Approach with a flow chart describing each of the 7 steps in more detail, and depicting the 4 specific aspects brought to the WG for comment – Steps 4-7. Going over each of those steps, he described the major issues under each step that were presented to the WG for comment.

D. NTP BSC Working Group Report on the Draft NTP Approach

Dr. Lynn Goldman, chair of the BSC WG, summarized the group's report on the draft NTP Approach. The WG had met August 28-29, 2012, and issued its report covering its discussions on each of the seven steps in the draft NTP Approach.

The WG report is available online at:

http://ntp.niehs.nih.gov/NTP/About_NTP/BSC/2012/December/DraftReport_LiteratureBasedEvi.pdf

For each step in the NTP Approach, there is a brief overview of the step, recommendations for which the WG had achieved consensus, and specific comments for consideration, which did not achieve full consensus as recommendations.

Dr. Goldman related the WG's conclusions:

- The WG commended the NTP for taking proactive steps to increase the transparency of hazard assessment.
- The WG enthusiastically supported the development of the NTP Approach.
- The WG encouraged the NTP to advance and evolve methodologies for hazard assessment.
- The WG thought the NTP's methodology is consistently moving forward the state-of-the-science for hazard assessment and is responsive to recent recommendations from authoritative scientific organizations (e.g., National Academies of Science)

E. BSC Discussion

Dr. Hattis, who was a member of the WG, extended some of Dr. Goldman's remarks to lend a sense of some of the specifics involved. Regarding "other mechanistic information," he cited the example of a plant hormone called ethylene that is known to be metabolized to ethylene oxide, which is known to be a human leukemogen. He said that a conclusion could be reached on the substance's carcinogenicity based on the mechanistic data available. He also discussed findings of a rare liver tumor in people who were scraping vinyl chloride at a PVC plant – case reports were important in identifying human carcinogenic activity.

Dr. Dorman, also a WG member, said that the group had spent much time discussing publications with fatal flaws, and when they should be culled. He noted that there could be fatal flaws, but that sometimes they might arise from factors such as a compound's instability or dosimetry issues. He said the WG thought that development of the protocol could be used *a priori* to exclude certain studies as opposed to carrying them all the way up to Step 4 or Step 5. He also mentioned that the issue of language and nomenclature would be a major challenge for NTP in this effort. He felt that some of the more contentious issues faced by the WG, where consensus could not be reached, were reflective of the inability of the subdisciplines to reach common ground. Dr. Goldman noted that in some instances that diversity was valuable in defining questions in the report, providing NTP valuable insight in how to word statements so they would work and be clearly understood by all concerned.

Dr. Sobrian noted that there were many more recommendations in the report itself than shown in Dr. Goldman's presentation, and wondered what would happen to them. Dr. Thayer said OHAT would look through the WG report again as it began to prepare the case studies, as many of the recommendations would apply to developing the protocols for the case studies.

Dr. Harkema asked Dr. Goldman to clarify the recommendations for Step 5. She said that a suggestion had been made that *a priori* a cohort study would be considered to be of higher quality than a nested case-control study, which would be considered to be of higher quality than a non-nested case-control study. Dr. Goldman described the differences between case-control studies and nested case-control studies. She said while in many cases the nested study could be considered to be of higher quality, they may also often be of roughly the same quality. Similarly, a well-conducted nested case-control study may be of similar value as a cohort study. An issue throughout was the representativeness of the controls, with the risk of bias involved. Dr. Thayer added that this was a great example of what the developers of the approach want to look at when using the case studies to refine the methodology. She noted that the dosing temporality issue could be folded into risk of bias. Dr. Goldman agreed that the temporality issue was important, illustrating the fact that rather than making the judgment just on the basis of how a study is classified, rather it should be done on the basis of how a measurement was actually done.

Dr. Birnbaum commented that the whole effort is an example of how toxicologists and epidemiologists need to talk to each other much more often, sharing data and terminology. It is critical to define the usage of terminology, and she hoped that as this effort moves forward, it will set the state of the art.

Dr. Eastmond noted that the action called for was the only formal vote required of the BSC during the meeting – whether to accept or reject the WG's report. By accepting the report, the NTP could then use it to move forward in further developing the Approach. It had been assumed that the BSC would approve the report; thus NTP had moved forward with further development of the Approach, as would be summarized in subsequent presentations. Dr. Chapin moved to accept the report, Dr. Miller seconded the motion, and the BSC voted unanimously (8 yes, 0 no, 0 abstain) in favor of the motion.

F. Initial NTP Response to the Working Group Report

Dr. Rooney presented the details of NTP's initial response to the WG report. He noted that NTP was present during the WG's discussions, and had received the WG's draft recommendations and begun preparations to incorporate them, but had not officially acted upon them pending BSC approval. He went through each of the seven steps in the draft NTP Approach, with consideration of the WG's comments in developing a revised draft NTP Approach. The WG had suggested that the 30-page description of the process that had been presented to them was too detailed, and asked for a framework presentation of the NTP Approach, with the details to be included in the protocols specific to each evaluation—that was the impetus for the revised draft NTP Approach.

Dr. Rooney emphasized that he was presenting the *initial* response to the WG report and that the methods were subject to further development within the revised draft NTP Approach. It has not yet been put into place within a full evaluation, and NTP particularly anticipates learning more within Steps 4, 5, and 7.

G. BSC Discussion

Dr. Hattis, first lead reviewer, said the chart (Step 5) showing upgrades and downgrades based on numerical scores gave him the impression that NTP is still doing a numerical adjustment based on categorical analysis. He felt that it would be better to use expert advisers to give an overall judgment of what the final results should be, without necessarily having a numerical process, because it distracts from the main goal of reaching an overall conclusion. Dr. Thayer said that some of the initial protocols will use the “minus one and two” framework, but a more narrative format may work better.

Dr. Dorman, second lead reviewer, noted that NTP had largely implemented most of the major recommendations contained in the WG report. He felt more clarity is needed on when the protocol could be changed, as it was a major issue for the WG. He reported that it had taken much work for the WG to agree that there should be any changes at all in the protocol, and that the next revision of the NTP Approach document should capture when the protocol becomes immutable. He noted that the framework was largely adapted from human clinical therapeutic intervention types of studies, and he recommended that NTP try to separate the idea of toxicological risk assessment versus the more traditional approaches. He felt much of the content of the public comments was based on the initial frameworks, raising concerns about whether the approach could even be used for health-hazard risk assessments for environmental exposures. Mixing of the domains could be a cause for confusion, in other words. He did not have a specific solution to offer, but suggested NTP pay attention to the issue. Dr. Rooney asked if Dr. Dorman felt it required further communication efforts, or if it would become clear as the protocol is put into practice how the approach applies to the animal studies. Dr. Dorman replied that both efforts would likely be needed.

Dr. Eastmond said he clearly saw this as an ongoing process in an early stage. He said it was valuable that NTP had heard and taken into full consideration the comments of the WG. He recommended making the plan available for public comment at various stages with sufficient time for review, and seriously considering those comments for future incorporation. He felt that the overall outcome would be improved by doing so.

Dr. Eastmond departed the meeting at that point; Dr. Zelikoff took over as chair for the duration of the meeting. Dr. Bucher thanked Dr. Eastmond for chairing the meeting and Dr. Goldman for serving as chair of the WG and for sharing the group’s report with the BSC at this meeting.

H. Implementation of the NTP Approach in Office of Hazard Assessment and Translation (OHAT) Evaluation

Dr. Thayer briefed the BSC on how OHAT planned to implement the NTP Approach in its evaluations, putting it into the larger context of the OHAT evaluation process. She described that process, which is comprised of three major steps: a plan for evaluation, conducting the evaluation, and peer review and publishing of the NTP monograph. She noted there are many opportunities for public comment throughout the process, and that there is much attention to methods in the early documents. Also early in the process, there is a draft concept topic prepared along with a protocol, which would describe the methods to be employed in Steps 1-7 of the SR. Thus, external scientific input will be pulled in earlier in the process than it has been previously. When conducting the evaluation itself, the protocol is implemented – Steps 2-7 of the NTP Approach. She reviewed the elements of the protocol including how upgrade and downgrade factors would be assessed. She noted that the protocols are typically long documents.

Dr. Thayer described the next steps in the process of implementing the NTP Approach. She said the current presentation represented a working draft, providing enough of a framework to move forward with case studies, with the expectation that it would be revised further. The revised guidance will be released for public comment, and then case studies will be undertaken to assess and refine methods. They will be shared with other agencies to solicit their input, and protocols will be released for public comment. Ultimately, once the case studies have been worked through, a finalized guidance document will be released for public comment. Still, the NTP expects that the guidance will be updated periodically as new methodologies are developed.

I. BSC Discussion

Dr. Dorman noted that each of the case studies under consideration are prospective, and asked if there had been any consideration of developing a retrospective case study on a recent NTP monograph, to show how that monograph might have been developed differently. Dr. Thayer said it had been considered, perhaps not taking on an entire monograph, but instead working on a specific health outcome, for example, from the low-level lead evaluation.

Returning to Dr. Thayer's depiction of the OHAT process, Dr. Howard asked if participation in external scientific review in the evaluation would exclude scientists from being on the peer-review panel. Dr. Wolfe replied that it would; an individual could not be involved in multiple parts of the process.

Dr. Birnbaum pointed out that there were at least six opportunities for public comment within the OHAT process. Dr. Wolfe added that there could be other methods of engaging the public, such as listening sessions. Dr. Birnbaum noted that there could be opportunities to engage stakeholders during workshops.

Dr. Hattis said that case studies are clearly the appropriate method to clarify the guidance.

Dr. Chapin, first lead reviewer, commented on NTP's proposed plans for implementation of the NTP Approach. He approved of the early public-comment period. He was amazed at the confidence the NTP had to be able to prospectively prepare a protocol for complex exposures and complex situations without conducting a "dry run." He did not see how such a protocol could be written to exclude poor studies at the outset of the process. He approved of transparency and clarity provided by an explicit protocol that includes all of the details. He recommended conducting two or three case studies, but not re-evaluating previously conducted studies. He guessed that it would be a continuously iterative process at least for the next five case studies. Generally, he commended the NTP for tackling a tremendously complicated topic.

Dr. Fernandez, second lead reviewer, agreed that it was important to include case studies. He noted that the use of the term "Bradford-Hill criteria" is inaccurate since they are really considerations and not criteria.

Dr. Hattis suggested that the NTP start with the first one or two case studies as ones that could be anticipated to be relatively simple, with a limited database.

Dr. Zelikoff summarized the BSC's comments. She said there was overall agreement that the members liked the implementation plan, particularly in that there is early scientific discussion and room for public comment throughout the process. There was a sense that there should be a limit on flexibility in that there should be a defined time when the protocols become immutable. There was also agreement that members were pleased by the inclusion of case studies.

VIII. NTP Update: BPA Studies and a Cooperative (U01) BPA Research Consortium

A. Presentation

Dr. Bucher briefed the BSC on a large research program with a new approach to carrying out interactive research with an academic consortium and federal funding devoted to guideline studies. He related the relevant history, noting several instances of FDA involvement with BPA, including its August 2009 assessment of the literature supporting effects on brain and behavior, prostate, mammary gland and age at which females attain puberty, several of which reflected endpoints in the draft NTP conclusions.

Dr. Bucher cited a variety of BPA studies underway and completed, including the 2009 creation of the BPA Grantee Consortium by NIEHS, funded by a U01 grant mechanism. He described several chronic and sub-chronic studies being jointly conducted by NTP and NCTR, and listed the members of the BPA Grantee Consortium and their areas of study. He noted that the chronic Good Laboratory Practices study would comprise a very comprehensive, unprecedented data set when completed, linking outcomes seen in shorter-term academic studies with the longer-term chronic studies. Almost all of the diseases reported in the literature to be associated with BPA exposures were included in the BPA Guidelines Study, and they should be able to link the information generated through the funding of a large number of grants

and publications with the BPA Guidelines Study outcomes. He acknowledged the contributions of FDA and NCTR in such an enormous undertaking.

B. BSC Discussion

Dr. Zelikoff applauded the effort as a venue for increasing integration and access to resources that would not be available to independent investigators.

Dr. Birnbaum said that the BPA study is a novel approach and going forward there would be more such opportunities in areas where there are major issues with considerable controversy. This will allow the NTP to play a role in helping resolve those controversies by having academic and other collaborators work with NTP and NIEHS intramural scientists to address the key issues.

IX. Adjournment

Dr. Birnbaum and Dr. Bucher thanked the BSC and NTP staff for their excellent contributions and hard work during the meeting. Dr. Zelikoff adjourned the meeting at 4:35 pm.