Summary Minutes

NTP Board of Scientific Counselors

June 16, 2015

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I. Frequently Used Abbreviations and Acronyms

ACC	American Chemistry Council
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BPA	bisphenol A
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
CHEAR	Children's Health Exposure Analysis Resource
DIR	Division of Intramural Research
DMCHDC	Dimethyl 1,4-cyclohexanedicarboxylate
DNTP	Division of the NTP
DWAL	Drinking water advisory level
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HAWC	Health Assessment Workplace Collaborative
HHS	Health and Human Services
HTS	high throughput screening
IARC	International Agency for Research on Cancer
ILS	Integrated Laboratory Services, Inc.
LoC	level of concern
MCHM	4-methylcyclohexanemethanol
MeSH	Medical Subject Headings
NCATS	National Center for Advancing Translational Sciences
NCS	National Children's Study
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NLM	National Library of Medicine
NOEL	no observed effect level
NTP	National Toxicology Program
NTPL	NTP Laboratories
ODS	Office of Dietary Supplements
OHAT	Office of Health Assessment and Translation
OMB	Office of Management and Budget
PCACS	People Concerned About Chemical Safety
PECO/PICO	population, intervention or exposure, control or comparator, and outcomes of interest
PPH	propylene glycol phenyl ether
SAR	structure-activity relationship
SSS	Social and Scientific Systems, Inc.
SWIFT	Sciome Workbench for Interactive Computer-Facilitated Text Mining

UL	tolerable upper intake level
WHO	World Health Organization
WVBPH	West Virginia Bureau for Public Health
WVDEP	West Virginia Department of Environmental Protection

II. Attendees

Members in Attendance:
Robert Chapin, Pfizer
George Corcoran, Wayne State University
David Dorman, North Carolina State University
Dale Hattis, Clark University
Steven Markowitz, City University of New York (by telephone)
Lisa Peterson, University of Minnesota (chair)
Sonya Sobrian, Howard University
Iris Udasin, Rutgers University, Robert Wood Johnson Medical School

***Ad Hoc* Members:**
Aaron Michael Cohen, Oregon Health & Science University (by telephone)
Daniel Kass, New York City Department of Health & Mental Hygiene (pending BSC member)

Members not in Attendance:
Milton Brown, Georgetown University Medical Center
Mary Beth Genter, University of Cincinnati
Jack Harkema, Michigan State University

Other Federal Agency Staff:
Paul Howard, U.S. Food and Drug Administration (FDA), BSC Liaison
Elizabeth Whelan, National Institute for Occupational Safety and Health (NIOSH), BSC Liaison (by telephone)

National Institute of Environmental Health Sciences (NIEHS) Staff:

Scott Auerbach	Darlene Dixon	Kelly Lenox	Veronica Robinson
Mamta Behl	Susan Elmore	Yin Li	Andrew Rooney
Linda Birnbaum	Paul Foster	Ruth Lunn	Andy Shapiro
Chad Blystone	Jean Harry	Robin Mackar	Vicki Sutherland
Windy Boyd	Stephanie Holmgren	Dave Malarkey	Kristina Thayer
Abee Boyles	Michelle Hooth	Alex Merrick	Velvet Torain
John Bucher	Brian Howard	Dan Morgan	Molly Vallant
Natasha Catlin	Kembra Howdeshell	Esra Mutlu	Nigel Walker
Bradley Collins	Grace Kissling	Rick Paules	Vickie Walker
Gwen Collman	Erin Knight	Katherine Pelch	Porscha Walton
Helen Cunny		Cynthia Rider	Lori White
Michael DeVito		Georgia Roberts	

Kristine Witt Mary Wolfe

Public:
Christopher Bartlett
David Budescu, Fordham University (by telephone)
Rich Cohn, Social and Scientific Systems, Inc. (SSS)
Michael Easterling, SSS
Reshan Fernando, RTI International
Sanford Garner, Integrated Laboratory Services, Inc. (ILS)
Ernie Hood, Bridport Services
Beth Warren Koncicki
Maya Nye, People Concerned About Chemical Safety (PCACS)
Ivan Rusyn, Texas A&M University
Pam Schwingl, ILS
Ruchir Shah, Sciome
Mayo Smith, SSS
Thomas Wallsten, University of Maryland (by telephone)

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened June 16, 2015, at 8:30 a.m. in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Dr. Lisa Peterson served as chair. She welcomed everyone to the meeting, asked BSC members and other attendees to introduce themselves, and noted that the meeting was being webcast. 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, updated the BSC on developments at NTP and NIEHS since the last BSC meeting in December 2014.

In her legislative report, she described recent congressional hearings on the NIH budget and the budget resolution for FY 2016 passed by the House and Senate. She reported on recent briefings to congressional staff people and currently relevant legislation, including the 21st Century Cures Act, which would provide an extra $10 billion in funding to NIH over the next five years. Later in the morning, she shared an announcement that the full House Appropriations Committee had just released its FY 2016 Labor, Health and Human Services funding bill, which included funding recommendations for NIH. The bill provides a total of $31.2 billion for NIH, $1.1 billion above the FY 2015 appropriation and $100 million above the President's budget request.

Dr. Birnbaum recognized NIEHS congressional liaison Mary Gant, who would retire at the end of July, for her 27 years of service.

Dr. Birnbaum related a number of science advances by NIEHS and NTP scientists and grantees in recent months. She recognized the recent release of the *OHAT Handbook for Conducting a Literature-Based Health Assessment Using the OHAT Approach for Systematic Review and Evidence Integration*. She noted that NIEHS is now recruiting participants for two new clinical studies, one on black cohosh consumption, the other looking at the pharmacokinetics of dermal bisphenol A (BPA) exposure.

She described several meetings and events that took place earlier in 2015, including a public meeting at Toms River, New Jersey and the annual Society of Toxicology meeting. She looked ahead to upcoming workshops, including meetings on alternative approaches to identifying acute systemic toxicity and challenges in the assessment of botanical dietary supplement safety.

She mentioned several recent awards and recognitions of Division of NTP (DNTP) personnel and took note of the recent death of former BSC member Dr. Edward Carney.

V. Contract Concepts: Introduction

Ms. Velvet Torain, NIEHS Contracting Officer, briefed the BSC on contract concepts, and the BSC's charge with regard to the concepts being presented during the meeting.

VI. Contract Concept: Statistical Support

A. Presentation

Dr. Grace Kissling, NIEHS Biostatistics and Computational Biology Branch, briefed the BSC on the proposed contract for statistical support. The purpose of the contract is to provide statistical and mathematical support for DNTP and Division of Intramural Research (DIR) studies, 67% and 33% of effort, respectively. For the DNTP, analytical support is provided for its rodent bioassays, which include traditional 14-day, 90-day, and 2-year studies assays, in addition to multigenerational and modified one-generation studies. Dr. Kissling provided estimates of bioassay analyses per year and recent examples of statistical and mathematical support for DNTP and DIR programs. She noted that proposed changes to the current contract include a request for 1 base year and 9 option years, totaling 10 years, and removing bioinformatics support, which is expected to be covered by other contracts. BSC members were asked to review the concept for overall value and scientific relevance, as well as for fulfilling the program's goal of protecting public health.

B. BSC Questions and Discussion

Dr. David Dorman said much of what Dr. Kissling had described was not what he would consider as classical statistical support, but more as computational support. He asked whether NTP had considered if the contract should be geared more broadly to include computational methods. Dr. Kissling said the contract is designed to include both statistical and mathematical modeling support.

Mr. Daniel Kass asked what the expected value of the contract might be on an annual basis, whether there would be a single contractor or multiple contractors, and whether the work is contracted out because NIEHS does not have the appropriate resources internally. Dr. Kissling said that in the past, including bioinformatics support, the contract had been approximately $2.5 million and that there had been one contractor and a sub-contractor, with no restriction on a future contract. Dr. Kissling confirmed that NIEHS does not have the appropriate resources internally to complete the work.

Dr. Dale Hattis, lead BSC discussant, said it was a good idea to have the proposed capability. He noted that it would be important to include Bayesian analyses in the contract to allow combination of data from different sources. He said it would also be important to carry forward the idea of quantifying interindividual variability.

Dr. Peterson called for a motion and vote on the contract concept. Dr. Hattis moved to approve the proposed contract mechanism and Dr. George Corcoran seconded the motion. The BSC voted unanimously (7 yes, 0 no, 0 abstentions) to approve using this contract mechanism for support of these activities.

VII. Contract Concept: Conduct of Studies to Evaluate the Toxicologic Potential of Selected Test Agents for the NTP

A. Presentation

Ms. Molly Vallant, DNTP Program Operations Branch, briefed the BSC on a proposed contract to support toxicity and carcinogenicity studies in laboratory animals as part of NTP's work to characterize the toxicity of agents of public health concern. She described existing contract activities, which consist mainly of *in vivo* toxicology studies. She explained the evolving NTP testing paradigm and new hazard evaluation strategies. The purpose of the contract will be to conduct *in vitro* and *in vivo* studies with special emphasis on novel approaches and methodologies, along with alternative animal models, to facilitate NTP's efforts to characterize the potential adverse effects of test agents. She provided details regarding the anticipated *in vitro* assays and alternative animal models such as *Caenorhabditis elegans* and zebrafish, as well as descriptions of the anticipated biochemical and molecular endpoints to be addressed through use of biochemical assays and several "omics" platforms. Several functional assessments are also included, e.g., neurotoxicity, reproductive, developmental, cardiac, and pulmonary assessments. The proposed changes to the current statement of work would expand capabilities with an emphasis on *in vitro* studies, use of alternative animal models, developmental exposures, and evaluations of functional and molecular endpoints using current and advanced technologies. BSC members were asked to review the concept for overall value and scientific relevance, as well as for fulfilling the program's goal of protecting public health.

B. BSC Questions and Discussion

Dr. Robert Chapin asked about the overlap between the scope of the studies done under the contract under discussion and those of the NTP Laboratories (NTPL). Dr. John Bucher said there is overlap, with a considerable difference in the capacity to perform studies. He noted that

NTPL is focused on providing quick responses related to integrating high throughput screening (HTS) and traditional data, allowing NTP to generate more information through non-traditional models. A variety of different contractors have been used in those efforts; this contract would provide another way to do so.

Dr. Corcoran asked the dollar value of the current contract. Ms. Vallant said there is a base contract for $6 million annually, with options. Dr. Corcoran asked if that was with one contractor with a capability to subcontract, or with multiple contractors Ms. Vallant said in the past many of the studies used the same contractor, but if some other capability or expertise were needed, it could be subcontracted. Dr. Corcoran asked why portions of the guideline document for NTP specifications referenced in the concept were in bold type. Ms. Vallant said there were two sets of specifications involved; one for the toxicity and carcinogenicity studies, the other for reproductive and developmental studies. Dr. Bucher explained that the bolding might indicate sections of the guidelines that have been updated to bring them to the attention of the laboratories using the guidelines.

Dr. Dorman asked about the inclusion of alternative animal models in the written document. Ms. Vallant said the plan is to include the alternative animal models; omission in the written document is an oversight. Dr. Dorman recommended updating the written document with that information. He also asked how often dogs are used in NTP studies. Ms. Vallant said NTP had used dogs just once, at the request of the FDA, in a study of QT prolongation. Dr. Bucher added that the study had been a specific request to evaluate single vs. dual electrode leads in a standard model; NTP has not used dogs in other studies and does not anticipate doing so in the future.

Dr. Corcoran, lead BSC discussant, said some flexibility appears to be built into the contract, which would include the use of alternative animal models. He said it is abundantly clear why the NTP is the gold standard for highly detailed, deeply considered, and well-executed studies. He felt the need for the contract is apparent and well justified, and fully supported its renewal.

Dr. Peterson called for a motion and vote on the contract concept. Dr. Corcoran moved to approve the proposed contract mechanism and Dr. Chapin seconded the motion. The BSC voted unanimously (7 yes, 0 no, 0 abstentions) to approve using this contract mechanism for support of these activities.

VIII. Report of the NTP Associate Director

A. Presentation

Dr. John Bucher, NTP Associate Director, updated the BSC on NTP developments since the last BSC meeting. He mentioned three upcoming advisory committee meetings, including two peer-review meetings (on the NTP Technical Report on the Toxicology Studies of A Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)] and the Draft Report on Carcinogens Monograph on Cobalt and Certain Cobalt Compounds) and the annual meeting of the Scientific Advisory Committee on Alternative Toxicological Methods.

He reported that NTP had successfully applied for NIH funding made available following cancellation of the National Children's Study (NCS) in December 2014. The $4 million received by NTP (with another $4 million going to National Center for Advancing Translational Sciences [NCATS], the program's collaborator) will be used to expand the Tox21 Developmental Toxicity Program, to study the influence of environment on *in utero* development with the goal of identifying the "seeds" of future diseases and conditions, and the Tox21 Developmental Biology Program.

Dr. Bucher announced that Dr. Kristina Thayer has been named Deputy DNTP Director for Analysis. She will oversee both the Office of Health Assessment (OHAT) and the Office of the Report on Carcinogens.

Dr. Birnbaum provided additional information regarding NCS funding distribution. She said of the $130-135 million distributed, NIEHS received a total of $57 million. This comprised several programs, including the exposure biology program titled Children's Health Exposure Analysis Resource (CHEAR). She noted that the Tox21 programs, mentioned by Dr. Bucher, were the only intramural initiatives funded, probably because the tools to be developed by NTP and NCATS would be used by multiple groups.

B. BSC Discussion

Dr. Hattis said he had not seen success yet in terms of Tox21 providing quantitative predictions of *in vivo* mammalian toxicity. He felt it is important to show that the Tox21 assays are allowing quantitative *in vivo* predictions. Dr. Bucher noted that there are programs underway, including within the NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods, looking specifically at assays for the estrogen receptor-mediated pathways and associating those outcomes with high-quality uterotrophic assays, with very good success. He said there must be high-quality, *in vivo* assays to go along with a number of different, high-quality, *in vitro* assays. In many cases, it would not be possible to attain the correlation between *in vitro* and *in vivo* results due to the fact that the level of organizational complexity of an *in vivo* assay is not mimicked by any particular receptor-mediated assay. Such comparisons will require acceptance by the scientific community of the importance of mechanistic information from the *in vitro* studies, and acknowledgment that combining a number of different *in vitro* assay outputs may be required to allow even an attempt to correlate with an *in vivo* response. Regarding quantitative assessments, he noted that Dr. Michael DeVito, NTPL Branch Chief, is working to develop capabilities for *in vitro* to *in vivo* extrapolation through pharmacokinetic modeling. He acknowledged that much work remains to address quantitative predictions.

Dr. Steven Markowitz asked about the fate of the epidemiologic studies that were part of the NCS funding, and whether the NIEHS funded activities would be related to human health effects. Dr. Birnbaum said all of the extramural studies would be based on epidemiological samples and cohorts. Along with $48 million for the CHEAR program, an additional $5 million will fund the conduct of additional analysis in some of the existing children's cohort, for analytes that were not previously measured. She noted that most of the FY 2015 dollars, which have been redirected from the original NCS vanguard studies, are directed to human studies, both

epidemiological and clinical. She noted a program at the National Institute of Child Health and Human Development focusing on placental development, as an example.

IX. Report on NTP Response to the Elk River Chemical Spill

A. Presentation

Dr. Scott Auerbach, DNTP Biomolecular Screening Branch, briefed the BSC on results of NTP research program on the Elk River, West Virginia chemical spill, which occurred January 9, 2014.

He first provided background information about the spill of a liquid from a tank leaking into the river. The liquid, which was used to wash coal, contained primarily 4-methylcyclohexanemethanol (MCHM), along other minor constituents from crude MCHM and stripped propylene glycol phenyl ether (PPH). The Centers for Disease Control and Prevention (CDC) issued an initial drinking water advisory level (DWAL) of 1 ppm for MCHM. In July 2014, the CDC requested NTP undertake research to address lingering uncertainties regarding the point of departure, or starting point for reevaluation of the DWAL, and safety factors used to set DWALs.

Structure-activity relationship (SAR) studies designed to rapidly identify potential toxicological hazards found that the MCHM class of chemicals, a major component of the spill, had positive predictions of moderate to high confidence for developmental toxicity and irritancy. The PPH class had no positive SAR predictions. None of the chemicals subjected to Tox21 HTS showed activity in the assays. All were also inactive in nematode screening studies. In zebrafish, the chemicals were inactive, with the exception of dimethyl 1,4-cyclohexanedicarboxylate (DMCHDC), a minor spill component, which was toxic to developing fish at a dose of 67.3 µM and above. Bacterial mutagenesis studies conducted to date were negative.

Dr. Auerbach described the toxicogenomics study to identify the lowest dose level (benchmark dose, BMD) that produced an integrated biological response as measured by the response of genes in molecular biological process groups. For MCHM, crude MCHM, and PPH, minimum biological effect BMDs were 107 and 63 and 0.6 mg/kg/day, respectively. MCHM was a mild irritant, but not a sensitizer, and crude MCHM was a mild irritant and weak sensitizer. At doses well in excess of the DWAL, MCHM was toxic to developing rats. Toxicity in the developing rats was observed at dose levels where there was no maternal toxicity. The most sensitive effect in the rat developmental toxicity study of MCHM was decreased fetal weight.

In the context of the NTP study goals, results from the rat developmental toxicity studies and 5-day toxicogenomics studies confirmed a no observed effect level (NOEL) of approximately 100 mg/kg/day for MCHM, which was consistent with the 28-day study that had been used to develop the DWAL. Starting at approximately 1 mg/kg/day (approximately 30 ppm in drinking water), PPH produced changes in biological activity. The toxicological implications of those findings require further investigation, but many guideline studies available for PPH support the point of departure used by the CDC. NTP studies confirmed the lack of genotoxic potential of the spilled chemicals, reducing concerns related to long-term effects such as carcinogenicity. In

terms of life-stage-specific hazards, in rats, it was observed that the fetus is more sensitive to toxicity from MCHM than the adult, although toxicity was observed only at doses well in excess of the DWAL derived by CDC. There were minimal differences in potency or toxicity among most of the minor constituent chemicals and MCHM, and there were minimal differences in potency or toxicity between MCHM and crude MCHM.

Dr. Auerbach concluded by saying the data produced by NTP to date support a focus on MCHM in determining the health risks associated with the spill, and also support the selection of 100 mg/kg/day as a point of departure upon which to base a DWAL.

B. BSC Questions

Dr. Iris Udasin asked if anyone in the area of the spill is still symptomatic. Dr. Auerbach said he did not believe anyone is. She asked about the mechanism behind increased triglycerides and elevated liver function tests in the rat 5-day studies and if the effects would be reversible. Dr. Auerbach said MCHM is an alcohol, which could be metabolized to an aldehyde. He said alterations in liver function could be due to the large amounts of chemical entering the liver, and reversibility of these effects has not been studied. Dr. Udasin speculated that the material might be a sensitizer, and asked if anyone had studied respiratory effects, such as asthma. Dr. Auerbach said there is some degree of relationship between dermal sensitization and respiratory sensitization, so it is plausible. He said despite the odor of the chemical being detected at extremely low levels, because of the low water concentration and low vapor pressure, it would be difficult to achieve an air concentration sufficient to produce toxicological effects. Dr. Udasin noted that anytime an odor is detected, there is a health effect, ranging from an annoying smell to an acutely irritating effect. Dr. Auerbach agreed, and noted that it is a very difficult message to communicate, in that simply smelling the material could produce psychological stress.

Dr. Hattis asked for clarification regarding the reference to a fit being a p-value >0.5 for the 5-day rat toxicogenomics data. Dr. Auerbach explained that it is the opposite of an intuitive conclusion, in that it is a chi-square test that evaluates the fit of the curve to the data. The better the fit to the data, the higher the chi- square or p-value, he added. The protocol had been implemented extensively in the software used to develop BMD values from data, as an accepted standard. Dr. Hattis questioned the use of default factors of 10 for incorporating uncertainty into guidance values and said the system should be replaced by a probabilistic one based on real data. Dr. Auerbach agreed that a probabilistic model would be preferable, and said there are groups working on that issue; CDC used currently accepted guidelines to derive the DWAL.

Dr. Dorman asked about pharmacokinetic analysis examining the differences between gavage and drinking water and dose rate in terms of how it might impact toxicity. Dr. Auerbach said that currently there are no plans for toxicokinetic studies.

Dr. Corcoran said the rapid response to the Elk River spill was new ground for NTP, and asked if there were plans to extrapolate this experience to other expected emergencies, particularly in the case of on-land oil spills or other chemical releases, such as the 2010 Enbridge oil spill in

Michigan. Dr. Birnbaum said NIEHS has been actively involved in disaster response research, both toxicological and epidemiological, working closely with the National Library of Medicine (NLM). She said the NLM website has a list of pre-approved protocols facilitating rapid disaster response research efforts. She cited several other examples of related NIEHS and NTP programs and said whenever an emergency arises NIH's cross-institute group discusses their involvement. The Elk River spill presented missing toxicological information that was worth pursuing, but it was already too late to assess population effects when the agency was contacted. Dr. Corcoran asked about NTP's involvement in oil spills. Dr. Birnbaum said NIEHS had learned a great deal from the toxicology and epidemiology work related to the Gulf oil spill. Dr. Bucher noted that an oil spill presents different challenges than an event such as the Elk River chemical spill, and as NTP moves more toward being a problem-solving organization, the characteristics of the situation need to be taken into account. For rapid response research, the level of desired confidence in the outcomes being reported should be matched to the particular incident being studied.

Dr. Dorman asked about the DMCHDC that had tested positive in zebrafish for developmental effects, and whether NTP had considered running it through the prenatal developmental toxicity testing, to complete the database and see how predictive the zebrafish toxicity assay might be for mammalian response. Dr. Auerbach said it would be possible, and would need to go through the NTP nomination process; currently such a study is not seen as a priority. Dr. Dorman questioned the value of the zebrafish as a screening model if its results can't be benchmarked against mammalian endpoints; he considered this is a general dilemma with alternative animal models. Dr. Auerbach said the same issue is also true for the rodent, in that specific findings are not necessarily translatable to humans. He added that there is also the question of whether such findings need to be validated against humans. Dr. Bucher said Dr. Dorman had raised questions NTP deals with regularly, and that if the BSC feels it to be an important issue, a recommendation could be made to NTP.

Dr. Chapin raised the same issue. His recollection was that MCHM was positive in the rodent developmental toxicity assay, and not positive in the zebrafish assay. Dr. Auerbach said this is the main reason he would like to see a pharmacokinetic study, specifically to compare the internal doses of MCHM received by the zebrafish and the pregnant rats, because there is suspicion that the rats received a higher internal dose.

Dr. Chapin supported the use of more than three dose levels in the rat studies. He felt that a set of standard protocols to be used in a rapid response would be valuable. He also felt that NTP's efforts demonstrated that NTP can produce useful information in a disaster situation in a very short period of time after a specific event.

C. Public Comment

Ms. Maya Nye, President and Executive Director of People Concerned About Chemical Safety, addressed the BSC, summarizing the written comments she had submitted.

Ms. Nye expressed her thanks to the people present who had been working on investigating the spill. She noted that approximately 300,000 residents of the area had experienced the event,

with at least one-third having been documented with symptoms of exposure. She said one important consequence had been development of adult-onset asthma in vulnerable populations with pre-existing respiratory illnesses. She expressed particular interest in discovering more about the volatility of the chemical, and how its toxicity might vary at different temperatures. She noted that many people had avoided ingesting the chemical, but were unable to escape inhalation in the shower or when flushing pipes. Ms. Nye emphasized the need for inhalation studies, noting that air samples had not been taken, despite the fact that inhalation was one of the main pathways of exposure.

D. BSC Discussion

Dr. Markowitz, lead BSC discussant, expressed his admiration for the project. He noted the effective planning, execution, achievement of consensus, and arrival at final results within one year. He also praised the sophistication of the project, given the crudity of the overall system for screening and monitoring largely untested chemicals and their uses. He felt the online reports and Dr. Auerbach's presentation were exceptionally clear. He said risk communication is a major challenge in these studies, and that NTP is doing very well with communications. He asked about the plan for further communication with the local community. Dr. Bucher said this was the first public presentation of the scientific information, and that he would be conducting interviews with local news reporters later in the day. Additionally, NTP would prepare an overall report that would be made available publically. There were no official plans for press conferences or similar events, but he said he would be open to interactions that would further distribution of the information to interested people. Dr. Auerbach noted that any communication with local residents would be coordinated with the CDC and West Virginia officials.

Dr. Markowitz asked whether there are plans for additional studies and if anything was learned regarding internal doses as they might model inhalation exposures. Dr. Auerbach said the biggest concern had been to evaluate the point of departure, and so further studies might not add significant value. Dr. Bucher said it is important to have a target when designing a series of studies addressing a public health issue, and in this case the goal was to see if the study findings supported the DWAL. He added that it would have been preferable to have inhalation measurements at the times of exposure. Since those data were lacking, the focus on the point of departure was critical.

Dr. Howard asked about CDC's involvement in the project. Dr. Auerbach said all of the updates had been communicated to the stakeholders for their review prior to release and there were ongoing communication with CDC. Dr. Howard asked why pharmacokinetics studies had not been done. Dr. Auerbach cited resource capabilities as a main reason. He said additional information would be interesting, but would be unlikely to change the main conclusions.

Dr. Chapin asked if there might be any value in working toward a list of genomic markers in different tissues such as gonads, thymus, and bone marrow, to look more in depth at dosed mammals rather than a limited number of surrogate tissues. Dr. Nigel Walker, Deputy DNTP Director for Science, said the issue of studying only liver and kidney had been discussed. He said there would be an after-action discussion and evaluation of the whole process. Dr. Chapin

noted that public response to the rapid response report would be useful for gauging public concerns going forward. Dr. Walker said that was another reason for the focus on the liver and kidney, in that there was already much information available about signaling pathways in those tissues, which provided needed context to the generated information. Dr. Chapin agreed that it was a wise approach. Regarding communications, he said, there would likely be questions and concerns from the local community, which would make it important to communicate appropriately and clearly. Dr. Bucher said that a lay-level version of Dr. Auerbach's talk with text would be provided on the website. Dr. Birnbaum said the materials are developed in close consultation with institute's communications experts to ensure that the appropriate messages are conveyed.

Dr. Hattis said he would not expect to make a human health risk assessment on the basis of *C. elegans* or zebrafish toxicity information, because the predictive databases between those systems and *in vivo* mammalian toxicity do not exist; those databases must be built if such information is to be useful. Dr. Auerbach noted that that is part of what is being done with the NCS funding. In addition, the project on the S1500 gene set will allow evaluation of a subset of genes representative of the whole genome, based on next generation sequencing.

Dr. Peterson said that the general feeling of the BSC is that NTP should be strongly commended for its rapid response to the Elk River chemical spill, using the available science and exposure information to arrive at reasonable and solid, scientifically rational decisions that are useful moving forward.

X. Office of Health Assessment and Translation (OHAT) Update

A. Introduction

Dr. Kristina Thayer, Deputy DNTP Director for Analysis, introduced the session devoted to OHAT projects and the new tools under development.

She provided background information about OHAT, which conducts literature-based evaluations and has developed systematic review and evidence integration tools. She described several recent OHAT activities, including the *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration,* released in January and the expert panel meeting in May, *Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid*. She also discussed several OHAT activities currently in progress, including three peer reviews expected in early 2016, and several systematic reviews and research projects being conducted. Introducing the NTP tools session, she showed a graph that illustrated the concept that topics under consideration for systematic review are often complex, with many studies. Thus, text mining and machine learning tools are being developed to automate part of the process, including production of "scoping reports" to evaluate new nominations or facilitate problem formulation. New data warehousing and display tools are also in development to facilitate structured data extraction and allow interactive, web-based reports with many options for visual display.

B. Clearing New Ground with New Tools: Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid

Dr. Abee Boyles, OHAT, described the folic acid project. She said it was one of the first OHAT projects that used some of the recently developed tools, and also identified where there is still a need for additional tools.

She discussed the background of the project, which began in 2011. The concept for the project was presented to the BSC in April 2011. It was the first OHAT project that used a comprehensive literature search, a systematic screening approach, database data extraction and display, and an online resource for experts and the public. She described some challenges with the project that included the contentiousness of the topic, despite evidence that folic acid fortification is the most effective birth defects prevention method. Other OHAT projects have been built on the lessons learned from the folic acid project. OHAT partnered with the Office of Dietary Supplements (ODS) on this project.

First, the literature was assembled by broad literature screen, based on population, intervention or exposure, control or comparator, and outcomes of interest [PICO/PECO] criteria. OHAT then completed a detailed tagging of human studies, outcome prioritization, and data extraction. Eventually OHAT produced a monograph, which served as the foundation for expert panel discussions.

The expert panel was held May 11-12, 2015, at NIH in Bethesda, Maryland. The panel was charged to evaluate the state of the science in four general health effect categories to identify areas for further research: cancer, cognition and vitamin B_{12}, hypersensitivity-related effects, and thyroid and diabetes-related effects. Dr. Boyles then presented some highlights of the expert panel recommendations.

The project reaped several benefits to both the folic acid research community and OHAT, including the fact that it saw the successful implementation of systematic review methods, and identified areas where new approaches and new tools are needed.

C. BSC Discussion

Dr. Udasin asked how the folic acid dose that caused cancer in the adenoma patients compares to the usual dose in a prenatal vitamin. Dr. Boyles said the standard dose in a multivitamin is 400 µg; the dose in prenatal vitamins ranges from 600-1000 µg. The doses used in the adenoma trials ranged from 1 mg to 5 mg. Dr. Udasin asked if, based on that information, pregnant women perhaps do not need the large doses that are close to the UL. Dr. Boyles replied that people should consult their physicians, and that the project was not designed to make any health recommendations.

Dr. Dorman asked whether the group had considered the possibility, when scanning the literature, that there might be a different spectrum of teratogenic responses with high dose folate. Dr. Boyles said the literature search identified a few high dose studies that reported

multiple congenital anomalies; however, the effects were considered beyond the scope of the monograph.

Dr. Sonya Sobrian, lead BSC discussant, was the BSC liaison to the expert panel meeting. She said it was an excellent and very interesting meeting. She attended the sub-panels and each had a good mix of experts from relevant disciplines. She noted that Dr. Boyles and her team had provided an excellent review of the literature and would be a valuable resource.

XI. NTP Tools and Approaches for Enhancing Evaluation and Communication of Analysis Activities

Dr. Peterson announced the participation of Dr. Aaron Cohen (by telephone), from Oregon Health and Science University, as an *ad hoc* reviewer for the NTP Tools topic.

A. Systematically Searching the Literature

Ms. Stephanie Holmgren, NIEHS Office of Scientific Information Management, reported on the steps involved in conducting a literature search for a systematic review. The literature search is one of the first steps in the systematic review process, and the quality of a completed systematic review is partly a function of the underlying literature search. The goal of a search is to be comprehensive, retrieving as much of the relevant literature as possible. The key metrics involved are precision, i.e., how much of what is retrieved is actually relevant, and recall, i.e., what percentage of the relevant literature is actually retrieved. There is typically a tradeoff between the two measures. A search strategy favoring high recall includes two types of search terms: controlled vocabulary and text words, each of which has advantages and disadvantages.

Ms. Holmgren then reviewed the seven steps involved in the conduct of a literature search: (1) define key concepts; (2) select resources; (3) identify terminology; (4) tailor the search strategy; (5) compile a test set; (6) run, analyze, revise, and finalize search; and (7) document the process. She said a methodical and thorough literature search generates an unbiased and comprehensive literature base for evaluation. The nature of the topic under review, i.e., the subject matter and the complexity, influences how each step in the literature search process is conducted. Comprehensiveness is achieved through searching multiple databases appropriate to the topic, identifying all pertinent terminology, tailoring the search strategy to leverage each database, and repeatedly testing and refining the search strategy.

B. SWIFT: A Text-mining Workbench for Systematic Review

Dr. Ruchir Shah, Sciome LLC (a contractor to NTP), reviewed the Sciome Workbench for Interactive Computer-Facilitated Text Mining (SWIFT) systematic review software. Faced with large bodies of literature, reviewers must determine what are the major topics being discussed and how to facilitate manual screening to make it more efficient. SWIFT was developed to address those questions and remove bottlenecks to make literature screening more efficient. Dr. Shah's group has implemented concepts from text mining, information retrieval, and machine learning to statistically analyze large collections of documents, providing a user-friendly, interactive workbench.

In SWIFT, documents are automatically assigned relevant annotations in a process called "tagging," which is used to organize, explore, and filter documents according to specific tags. The system also can define a subset of literature by identifying over-represented concepts, terms, and phrases via "fingerprints." SWIFT also employs the powerful Lucene data indexing engine, providing another form of built-in search functionality. "Topic modeling" is also included, to help understand the topics contained in a large document set when no prior knowledge is available. The system uses machine learning to rank documents, based on a small "seed" set provided by a reviewer, which helps determine "included" or "excluded" documents. Other features of SWIFT are under development.

C. BSC Questions

Dr. Cohen asked if SWIFT works with databases beyond PubMed, if it is capable of de-duplicating articles that are present in multiple databases, and if SWIFT will be available free of charge. Dr. Shah said SWIFT can utilize data from any other database and can de-duplicate articles. He confirmed that the current base version of SWIFT will be available free of charge. Dr. Cohen encouraged Dr. Shah to provide more detailed information about SWIFT in the website devoted to the tool. Dr. Shah noted that his group is working on two publications that will document SWIFT methods in more detail. He agreed that reproducibility and transparency would be important features. Dr. Cohen asked if SWIFT would be capable of providing expanded searches beyond the original efforts. Dr. Shah said the possibility of automating some of the functions has been discussed; at this point SWIFT functionalities can be used to identify over-represented concepts and then iteratively use that information to refine a search. He added that given how many databases exist and that they are not readily integrated it may still be more practical to incorporate them manually than in a semi-automated fashion. His group has developed some modules that may help speed up that process. Dr. Cohen asked about the training set or seed set, and how big it should be. Dr. Shah said that for the results shown in his presentation, the seed set was about 30 articles; however, there is no set answer as the size of the seed set needs to correctly represent the diversity of the body of literature. In some cases, the seed set may need to be re-visited upon testing in an initial model. Dr. Cohen asked if they were specifically using an active learning process. Dr. Shah said they are currently using that method.

Mr. Kass asked whether SWIFT looks only at abstracts, or at full texts. Dr. Shah said that in the materials he had presented, it was only abstracts. He said the results do not use full text, although the software and the methods are designed to use full text. Mr. Kass asked how the software knows when it identifies a health outcome (an example depicted by Dr. Shah) and not some other health-related term. Dr. Shah replied that SWIFT compares the words and phrases in a document to textual fingerprints derived from a previous analysis of a large number of independently annotated documents. Mr. Kass asked about the potential sustainability of SWIFT in terms of funding support, given that it will have a wide audience. Dr. Shah said he hopes his tool will be well received, used, and supported. Dr. Bucher added that NTP believes SWIFT will be supported.

D. Environmental Influences on the Epigenome: Using SWIFT Text Mining

Tool to Explore the State of the Science

Dr. Katherine Pelch, OHAT, described how OHAT used SWIFT to generate a scoping report on environmental influences on the epigenome. The topic had been identified as a primary goal in the 2012-2017 NIEHS Strategic Plan. OHAT was asked to investigate the topic by a cross-divisional implementation planning group and formed an evaluation design team to work out the best approach for moving forward. The largest of the preliminary literature searches resulted in 107,000 records.

OHAT recognized that the focus of the research question needed to be narrowed. At the same time, it was decided that this would be a good project to test SWIFT to help generate a new type of report – a "scoping report," which differs from a systematic review in that it provides a high-level overview of the literature, not a detailed evaluation.

The research question was focused on DNA methylation, and only studies in which genome-wide analysis had been employed were included. A concept-based search of the PubMed database yielded more than 35,000 records, of which just over 21,000 were deemed "in scope." Topic modeling and similarity ranking were then applied, and OHAT decided to just look at records that ranked in the top 25% of the list – more than 5,000. A word cloud was used to illustrate the frequency of words in the search as a way to assess the effectiveness of the enrichment. Using SWIFT machine learning, the remaining 5,000+ records were visually displayed as categorized by health outcome, exposure, and model system. Just 1,130 of the records were associated with an exposure and within SWIFT, it was possible to explore the intersections between exposure and health outcome. Dr. Pelch showed as an example of how an evaluation tagged as pesticide exposure yielded just 26 records.

Dr. Pelch said scoping reports are useful for large, complex, or emerging literatures, to help get a sense of the literature and the variety in the field, and to help identify future projects. This was the first project where text mining and machine learning tools were used. She said this approach holds promise for improving workflow efficiency and the problem scoping and formulation steps in a systematic review.

E. BSC Questions

Dr. Dorman said he was confused by the word cloud illustration Dr. Pelch presented, in that the MeSH term "DNA methylation" had been a search term, but it was not prominent in the word cloud. Dr. Holmgren noted that MeSH terms comprised only about one-quarter of the terms in that search strategy.

Dr. Sobrian asked for the rationale behind the choice of using the top 25% of the records. Dr. Pelch said it was based on predicted performance of the ranking, seeking both high recall and high precision. It was predicted that within that 25%, there would be at least 80% recall.

Dr. Howard asked how long the project took. Dr. Pelch said the project started in 2013, but that the time frame was not truly reflective of how long the process would normally take, due to the

training and methods development involved. She noted that Dr. Thayer cited one example of a similar project that took two weeks, and said that once the literature search has been conducted, it should typically be a matter of weeks, not months, depending on the desired level of detail. Dr. Birnbaum said this project highlights a cross-institutional activity, as the evaluation design team was part of the cross-institute epigenetics faculty.

Mr. Kass asked for more information regarding the cutoff between precision and recall. He wondered if there was any effort to think about whether there might be any bias in the outcomes at the margins. Dr. Thayer replied that right now the effort is to "stress test" to find out the boundaries, without being locked into a 25% cutoff. Dr. Shah said SWIFT features for release in the near future would address that question.

Mr. Kass noted that publication bias could be another problem and asked how that was dealt with. Dr. Shah said there is currently no approach to address publication bias. Dr. Thayer added that there is a confidence framework for the body of evidence, which could be downgraded if publication bias is suspected.

Dr. Corcoran noted that all publications are not created equal, with some highly cited and others never cited; some publications appear in highly regarded journals and others in obscure ones. He asked if the weight of the quality of the publication, through some bibliometric measure, is taken into consideration in constructing the algorithm. Dr. Shah replied that so far, SWIFT models do not use citation numbers as a modeling feature, although it would be very easy to include it if the scientific community decided it would be a useful feature. Dr. Corcoran said it might be useful to convene an expert panel to identify the most impactful papers to assist in developing a training set. Dr. Pelch noted that a similar approach was taken with the evaluation design team assisting with the literature search. She observed that just because a paper is impactful does not necessarily mean it is relevant to the research question being asked. Dr. Hattis felt that the 25% cutoff was much more than should be included.

F. Health Assessment Workplace Collaborative (HAWC)

Mr. Andy Shapiro, NTP Program Operations Branch, described his project, the Health Assessment Workspace Collaborative (HAWC). HAWC was originally his master's thesis project, and is now an open-source development project. The project has a steering committee and support from multiple organizations, including NIEHS/NTP, the World Health Organization (WHO)/ International Agency for Research on Cancer (IARC) Monographs Program, and EPA's National Center for Computational Toxicology.

He said the goal of HAWC software is to develop a web-based content management system to create, store, share, and display data and results in order to conduct human health assessments. He described the HAWC project requirements: team collaboration, a standardized process for building an assessment, automated report generation, modular architecture, integration with existing tools and information, stakeholder involvement, a transparent process, and an open source platform that is free to use and easy to collaborate with.

Mr. Shapiro described the HAWC database schema, with 102 tables in 9 modules. The modular design is intended for extensibility. He provided several examples and live demonstrations of HAWC in use: literature-review in the WHO/IARC monograph 112 on parathion, animal bioassay data extraction and visualization in the NTP/OHAT fluoride assessment, epidemiological data extraction and visualization in the NTP/OHAT folic acid assessments, and *in vitro* data extraction in the NTP/OHAT BPA analogues study. He demonstrated features allowing data exporting to Microsoft Excel and Word, and gave examples of some of the web-based interactive reports that HAWC can generate. He delineated features of HAWC under development or contemplated for the future: (1) continued development of visualizations and tables for summarizing data findings, (2) pair review and conflict resolution for literature review and risk of bias, (3) creation of assessment-specific data extraction fields, (4) improved QA/QC tracking, and (5) future integrations with SWIFT or other tools for literature review and automated data extraction.

G. BSC Discussion

Dr. Cohen said the text mining tools are definitely state-of-the-art and that he was really excited to see them being applied in the real world of systematic reviews. He felt determination of an appropriate precision/recall tradeoff would be a critical question to be decided based on the approach being taken and the project's aims. He noted that no one would recall 100% of anything, and other factors enter into the equation, such as publication bias and language issues. He felt there are always issues of bias in systematic reviews, whether or not machine learning has been used. Dr. Thayer said when an evaluation is conducted, over and above the machine learning tools use, there is a reference list of included studies, documents are posted for public comment, and the reference list of reviews is noted, so there are other ways to enhance what the machine learning provides. Dr. Cohen agreed that the machine learning approach is just a component of the larger process and larger context, with the additional elements mentioned by Dr. Thayer serving as error-checking methods.

Dr. Peterson summarized the discussion, stating that the BSC had a lot of enthusiasm for the tools being developed.

XII. Updating Level of Concern Categories

A. Presentation

Dr. Mary Wolfe, Deputy DNTP Director for Policy, briefed the BSC on an initiative to update the level of concern (LoC) categories used to provide an opinion regarding whether an environmental substance might be of concern for causing adverse effects on human health, given what is known about its toxicity and current human exposure. LoC conclusions have been utilized since 1998 by NTP as the outcomes of in-depth, scientific assessments. The LoC conclusions are qualitative in nature, being more than a traditional hazard evaluation, but not a risk assessment.

The current LoC conclusions follow a 5-level scale: 1) *SERIOUS Concern,* 2) *CONCERN,* 3) *SOME Concern*, 4) *MINIMAL Concern,* and 5) *NEGLIGIBLE Concern*, with an additional

category of *INSUFFICIENT DATA*. This scale expresses evidence of toxicity and extent of human exposure and other factors for a given substance. Each category includes narrative labels, and a vertical orientation and color gradient (red to green) is applied, along with arrows and short narrative statements to describe potential health concerns for affected populations

Dr. Wolfe said there are several issues associated with the current LoC framework, including the fact that the selection of the 5-level scale of concern was arbitrary, confusion over the meaning of different category labels, whether the multiple modalities for communicating LoC conclusions are appropriate, and the new process for reaching hazard conclusions and new categories being employed by OHAT as part of its approach for systematic review.

The LoC Framework Project is designed to develop an improved LoC framework. Its specific aims are: (1) determine optimal number of LoC categories, (2) test the revised X-level LoC categories and determine suitable category labels, (3) identify visual and/or other technologies (e.g., interactive web-based strategies) to enhance the communicability of LoC conclusions, and (4) obtain stakeholder feedback on the revised LoC framework as a transparent communication tool, and refine if needed.

Dr. Wolfe said the initial focus is on the first specific aim, engaging in a three-stage study to include approximately 160 experts in toxicology, epidemiology, and risk assessment to sort "LoC cards" into LoC categories. Experts will be recruited from academia, industry, non-government organizations, the federal government, and state agencies. A web-based tool will be used for LoC card-sorting exercises and four trials are planned for the exercises to identify and test the updated LoC category scale.

Currently, the set of LoC cards is being designed, and preparations are underway for submission to the Office of Management and Budget (OMB) for its review and approval. A pilot will be conducted, and the full project will launch once OMB approval is secured.

B. BSC Questions

Dr. Dorman asked Dr. Wolfe to clarify the 1-5 category scale that would be used in the card sorting. She said that it would be clear that "1" is the lowest LoC category, with higher numbers progressively above the low category. Dr. Dorman asked whether the cards would be agnostic as to chemicals; Dr. Wolfe confirmed that they would be. Dr. Dorman asked about the use of duplicate information within the cards, to see if the choices would align during the trials. Dr. Thayer replied that that had not been considered and probably would not be, in order to cover a wide span of scenarios in the cards and minimize the time burden involved in the sorting exercises.

Mr. Kass said the project would likely yield some very interesting and surprising results. He asked about the definition of "concern," given relative risks to public health. He said he understood that in this case it is being limited to a toxicologic evaluation, but he was unsure that people would understand it that way. Dr. Wolfe said it is one goal of the focus groups to have different stakeholder groups consider scenarios and what the conclusions derived might mean

to them. She said that is the goal for not only putting the new framework together, but also testing it to see how different stakeholder groups will react to it.

Dr. Markowitz asked whether it was a goal to see how much inter-operator/intra-operator variability may exist in the LoC designations, regardless of the number of levels. Dr. Kissling said that reliability of responses would be assessed.

Dr. Udasin noted that the term "consistent enough suggestion" had been used during the earlier presentation on folic acid, and wondered what category that might fit into under the old categories, making the need for new categories evident. Dr. Thayer said the old categories never had definitions, and as an expert panel-driven process, there could be variations across different panels according to their interpretations of the categories.

C. Public Comment

Dr. Nancy Beck, representing the American Chemistry Council (ACC), provided comments by telephone. She said the ACC had closely followed OHAT developments on systematic review, and appreciated the leadership that NTP is providing in that area. She said the ACC is also very supportive of NTP efforts to update LoC categories, and is pleased to see that NTP is working with risk communication experts to accomplish the task. She emphasized the need to understand the audiences, which are very different, and their understanding of the LoC categories will be different. The tools and categories must be easily understandable by the general public. Changing the categories should not be taken lightly and NTP should make sure that the scientific information does not get lost in the categorizations. Dr. Beck felt the current OHAT language is confusing, and that this effort could be an opportunity to clarify it. She added that NTP should be looking at an approach that considers the confidence in the judgments that are made. She recommended conducting the testing among many stakeholders, including the general public, and not restricting it to the experts alone. She asked for further descriptions of the sources of information to be used to characterize and measure exposure. She suggested that NTP solicit public comments on the proposed categories.

D. BSC Discussion

Dr. Dorman, lead BSC discussant, said he was very supportive of the process, which would help to provide information about reliability of categorization from experts. He was concerned about the audience; he could envision experts suggesting 8-10 categories, which the general public might not be able to understand. He suggested moving solicitation of stakeholder input and feedback earlier in the process. He also brought up the question of what LoC means on a population basis, as well as an individual basis.

Dr. Udasin, lead BSC discussant, said she agreed that as a public health professional, she would likely derive different meanings from some terms compared to what a toxicologist, or member of the general public, would. She asked if NTP had considered using numbers, such as a Likert-like scale, instead of using terms such as "some," "minimal," and "negligible."

Dr. Peterson said there appeared to be enthusiastic support from the BSC for the LoC project.

XIII. Adjournment

Closing the meeting, Drs. Birnbaum and Bucher thanked the BSC members and NTP staff for their participation in the meeting. Dr. White added her thanks and noted that the next BSC meeting will be on December 1-3, 2015. Dr. Peterson adjourned the BSC meeting at 5:00 p.m.

Dr. Lisa Peterson

Chair, NTP Board of Scientific Counselors

[Redacted]

Date: 8/24/15