Summary Minutes

NTP Board of Scientific Counselors

December 1 - 2, 2015

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I. Frequently Used Abbreviations and Acronyms

AAPHD	American Association of Public Health Dentistry
BSC	Board of Scientific Counselors
CDI	Cobalt Development Institute
CERHR	Center for the Evaluations of Risks to Human Reproduction
CHEAR	Children's Health Exposure Analysis Resource
DIR	Division of Intramural Research
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
EPL	Experimental Pathology Laboratories
FDA	U.S. Food and Drug Administration
HHS	Health and Human Services
HTS	high throughput screening
IARC	International Agency for Research on Cancer
ILS	Integrated Laboratory Services, Inc.
MTR	mountaintop removal mining
NC DHHS	North Carolina Department of Health and Human Services
NCS	National Children's Study
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NRC	National Research Council
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
ORoC	Office of the Report on Carcinogens
PD	Parkinson's disease
PECO/PICO	population, intervention or exposure, control or comparator, and outcomes of interest
RoC	Report on Carcinogens
SES	socioeconomic status
USGS	United States Geological Survey

II. Attendees

Members in Attendance:

Norman Barlow, Johnson & Johnson
Robert Chapin, Pfizer
George Corcoran, Wayne State University
David Dorman, North Carolina State University
Mary Beth Genter, University of Cincinnati
Jack Harkema, Michigan State University
Dale Hattis, Clark University
Steven Markowitz, City University of New York
Lisa Peterson, University of Minnesota (chair)
Sonya Sobrian, Howard University
Iris Udasin, Rutgers, University of Medicine and Dentistry of New Jersey

Other Federal Agency Staff:
Barry Delclos, US Food and Drug Administration (FDA), BSC Liaison
Elizabeth Whelan, National Institute for Occupational Safety and Health, BSC Liaison (by telephone)

National Institute of Environmental Health Sciences Staff:

Steven Akiyama	Gordon Flake	Robin Mackar	Kelly Shipkowski
Mamta Behl	Julie Foley	Dave Malarkey	Robert Sills
Linda Birnbaum	Paul Foster	Scott Masten	Nisha Sipes
Chad Blystone	Jean Harry	Barry McIntyre	Jennifer Smith
Windy Boyd	Ronald Herbert	Christopher	Diane Spencer
Abee Boyles	Stephanie Holmgren	McPherson	Greg Tavlos
John Bucher	Michelle Hooth	Alex Merrick	Kris Thayer
Vivian Chen	Kembra Howdeshell	Thomas Michal	Thai Ton
Raveena Chhabria	Heather Jensen	Eli Ney	Molly Vallant
Sheba Churchill	Debra King	Arun Pandiri	Nigel Walker
Helen Cunny	Angela King-Herbert	Katherine Pelch	Lori White
Mike DeVito	Grace Kissling	Erin Quist	Mary Wolfe
Darlene Dixon	Kelly Lenox	Cynthia Rider	
June Dunnick	Chris Long	Georgia Roberts	
Susan Elmore	Ruth Lunn	Andrew Rooney	

NIEHS Contractors:
Amy Brix, Experimental Pathology Laboratories (EPL)
Neal Cariello, GlaxoSmithKline
Carolyn Favaro, Vistronix
Sanford Garner, Integrated Laboratory Services, Inc. (ILS)
Ernie Hood, Bridport Services
Marcus Jackson, Vistronix
Kyathanahalli Janardhan, ILS
Amy Johnson, Charles River
Ramesh Kovi, EPL
Rachel McIntosh-Kastrinsky, Kelly Services
Isabel Lea, Vistronix
Cynthia Willson, ILS

Public:
Rebecca Boyles, RTI International
Ruth Danzeisen, The Cobalt Development Institute (CDI, by telephone)
Anna Fernandez, Booz Allen Hamilton
Daniel Kass, New York City Department of Health & Mental Hygiene (by telephone)
Michael Keller, Booz Allen Hamilton
Beth Warren Koncicki
Carol Kwiatkowski, TEDX
Nancy Love, Antech Imaging Services
Howard Pollick, University of California School of Dentistry
Jennifer Romaszewski, North Carolina Department of Health and Human Services (NC DHHS)
Anthony Scialli, Scialli Consulting LLC
Rhonda Stephens, NC DHHS

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened in public session December 2, 2015 in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. The first day of the meeting (December 1) and the morning of December 2 were sessions closed to the public in accordance with provisions set forth in section 552(c)(6), Title 5 U.S.C., as amended, to review Drs. Robert Sills and David Malarkey and the Cellular and Molecular Pathology Branch. Dr. Lisa Peterson served as chair and opened the meeting on December 2 at 10:00 am. She welcomed everyone to the meeting and 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 June 2015.

In her legislative report, she noted that there is still not a completed budget, and the federal government is funded until December 12. The House bill contained a $1.1 billion increase in NIH funding. This would represent an approximately 1.2% increase for NIEHS, which would still not restore FY2012 funding levels. The Senate bill proposed a $2 billion increase for NIH, which is roughly a 4.2% increase for NIEHS. Superfund appropriation remains flat.

Dr. Birnbaum mentioned that local Representative David Price (D-NC) would visit NIEHS on December 14, with Connecticut congresswoman Rosa DeLauro (D-CN), for a tour and town hall meeting.

Dr. Birnbaum summarized the current status of several pieces of legislation relevant to NIEHS and NTP, most prominently the 21st Century Cures Act, which was passed by the House, with a similar bill under development in the Senate. It would add $1.75 billion per year to the NIH appropriation for five years. She described the three bills aimed at Toxic Substances Control Act reform, none of which appear likely to pass in the near future.

She discussed the Children's Health Exposure Analysis Resource (CHEAR), which represents redirection of the funds for the discontinued National Children's Study (NCS). The funds have been used to establish six extramural exposure centers for four years, focusing on inclusion of environmental exposures in children's health research. FY2016 may see creation of a successor program called Environmental Children's Health Outcomes, which would focus on specific health outcomes including respiratory disease, neurodevelopmental disorders, obesity, and peri-/post-natal effects.

Dr. Birnbaum spoke about several scientific advances by NIEHS/NTP scientists and grantees in recent months. Tox21 researchers published a study on the results of high throughput screening for aromatase inhibitors in the Tox21 10K library. Another group reported results of experiments in rodents with chronic inhalation exposure to cobalt metal. She discussed several other studies

of note, including a screening for bisphenol compounds in the blood and urine of cashiers, which was conducted at the NIEHS Clinical Unit. She also mentioned a special issue of the journal *Reproductive Toxicology* from July 2015 that focused on environmental impacts on breast development and disease. Dr. Suzanne Fenton, NTP Laboratory, was the guest editor and contributed to three papers. Drs. Birnbaum and Gwen Collman and members of the Interagency Breast Cancer and the Environment Coordinating Committee wrote the overview titled *Environmental exposures, breast development and cancer risk: Through the looking glass of breast cancer prevention*.

Dr. Birnbaum described several recent meetings and events. They included meetings co-sponsored with the Environmental Defense Fund and the U.S Environmental Protection Agency (EPA). NIEHS/NTP held two peer-review meetings, on the *Draft NTP Technical Report on Pentabromodiphenyl Ether Mixture (DE71 [Technical Grade])* and on the *Draft Report on Carcinogens (RoC) Monograph on Cobalt and Certain Cobalt Compounds*. In September the Scientific Advisory Committee on Alternative Toxicological Methods met and a workshop was held on *Alternative Approaches for Identifying Acute Systemic Toxicity: Moving from Research to Regulatory Testing*. She also previewed several upcoming meetings, including a workshop scheduled for April on *Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety*.

She thanked and presented certificates of appreciation to retiring BSC members Robert Chapin, David Dorman, Jack Harkema, Dale Hattis, and Sonya Sobrian.

V. Contract Concept: Bioinformatics Support for DNTP and DIR

A. Presentation

NIEHS Contracting Officer Jennifer Smith briefed the BSC on contract concepts, and the BSC's charge with regard to the concept being presented. Dr. Alex Merrick, DNTP Biomolecular Screening Branch, presented the contract concept titled *Bioinformatics Support for DNTP and DIR* to the BSC. He defined bioinformatics, and outlined the need for bioinformatics support by NIEHS and NTP. He described the general and specific requirements included in the contract concept, as well as the bioinformatics needs of investigators. They include NextGen sequencing (RNASeq); Tox21 and chemoinformatics; high throughput transcriptomics for Tox21 and toxicity screening projects; informatics for systematic literature review; and informatics for impact research. A Request for Information for the project was issued in August 2015, which resulted in 15 respondents.

B. BSC Discussion

Dr. Dale Hattis, first BSC discussant, said an informatics capability is very much needed by DNTP and DIR, but expressed concern about a tendency to use new technologies in ways that do not lend themselves to review and that may not allow a critical review of results. He said there needs to be careful exposition of the basic assumptions that go into the analyses, so that they can be used in the next round of decision-making. He felt the high throughput systems

have overwhelmed the lower throughput regulatory system, with much information generated and without much serious consideration of regulatory opportunities to inform public risk. He recommended using a benchmark dose framework as an intermediate step to more descriptive dose/response modeling. Dr. Hattis noted that he was very impressed by one the abstracts referred to in the concept regarding the usefulness of formalin-fixed tissues.

Dr. Merrick said data reduction techniques are always a challenge, which is why more than one method is used, with raw data provided as supplementary information. Dr. John Bucher noted that the bioinformatics contract represents one component of three (statistics, toxicology, and bioinformatics) that all work together. He added that the bioinformatics platform would be a tool used very carefully with respect to all aspects of interpreting data.

Dr. David Dorman, second BSC discussant, felt a pressing case had been made for the scientific, technical, and program significance of the proposed activity. He was surprised about the absence of the text mining requirements in the concept that was provided to the BSC. He was unsure that the contract requirements would fulfill NTP's needs for chemoinformatics support, including the evolving world of predictive toxicology using physico-chemical properties, quantitative structure-activity relationships, and development and validation of different models. He recommended that NTP consider obtaining support for chemoinformatic needs under a separate contract. He fully supported the practical, clinical, and scientific uses under the concept.

Dr. Peterson called for a motion and vote on the concept. Dr. Hattis moved to approve the proposed contract mechanism and Dr. Chapin seconded the motion. The BSC voted unanimously (10 yes, 0 no, 0 abstain) to approve using this contract mechanism to provide bioinformatics support for DNTP and DIR.

VI. Report of the NTP Associate Director

A. Presentation

Dr. Bucher, NTP Associate Director, reported to the BSC on NTP's activities associated with the redirect of funding for the NCS, which was discontinued by the NIH Director in 2014. Under the FY2015 appropriation, $165 million was directed for the NCS. NIH was directed by Congress to redirect the funds while maintaining the mission and goals of the NCS. NIH identified three initiatives for the redirect: (1) develop tools that would enhance studies of environmental influences on pediatric diseases, (2) study the influence of environment on *in utero* development with the goal of identifying the "seeds" of future diseases and conditions, and (3) expand examination of environmental influences on later child development by leveraging extant programs.

NTP will use some of the funding redirect to expand the Tox21 program to include a specific focus on developmental toxicology, by conducting transcriptomic studies to map patterns of gene expression during development. The NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods will establish a database of approximately 100 developmental

toxicants. The NTP Laboratory will develop metabolically competent models for high throughput and mid throughput screening, to aid *in vitro* to *in vivo* extrapolation. The Biomolecular Screening Branch will work on development of a high throughput screening transcriptomics platform to conduct targeted transcriptomic interrogation of human, mouse, rat, and zebrafish cellular lysates. A systematic evaluation of the use of zebrafish in toxicological screening of chemicals will be conducted to assess the use of zebrafish in the screening of chemicals to which humans are exposed during development. Also, DNTP will work on enhanced data streams and informatics support.

B. BSC Questions and Discussion

Dr. Dorman asked to what extent dosimetry extrapolation issues would be addressed in the zebrafish evaluation effort. Dr. Bucher said issues regarding the permeability of zebrafish chorion were being assessed in terms of how much chemical transfers into the embryo. Dr. Nigel Walker noted the challenge of extrapolating between water concentration and *in vitro* concentration. Dr. Dorman said it might be an opportunity for compartmental modeling and dosimetry modeling. He noted that the issue is a challenge with zebrafish screening and that there might be an opportunity for broader scientific impact by NTP partnering with ecological toxicology researchers. Dr. Bucher said that was an excellent idea.

Dr. Robert Chapin said Pfizer has been unable to create a structure-activity relationship to help understand permeability of compounds into zebrafish. The only way to understand and fully interpret a chemical's effect on a fertilized zebrafish embryo is to directly measure it; presence of the chorion does not matter. Water solubility of compounds is also a major issue. He said interpretable data could be acquired only by measuring compound concentrations directly. Dr. Walker noted that part of the project is a significant investment in chemistry. Dr. Hattis said additional tools, such as identifying adducts as biomarkers of exposure, could be useful.

VII. NTP Technical Report Peer-Review Panel Meeting on Pentabromodiphenyl Ether Mixture (DE-71 [Technical Grade])

A. Presentation

Dr. Chad Blystone, DNTP Toxicology Branch, briefed the BSC on the June 25, 2015 peer review of the draft NTP Technical Report on the flame retardant pentabromodiphenyl ether mixture (DE-71 [Technical Grade]). The peer-review panel was charged with reviewing and evaluating the scientific and technical elements of the study and its presentation, and determining whether the study's experimental design, conduct, and results supported the NTP's conclusions regarding the carcinogenic activity and toxicity of the substance. The panel recommended accepting the report's level of evidence conclusions of *clear evidence* by a vote of 4 yes, 2 no, 0 abstentions, with a recommendation that thyroid cell adenomas alone, not adenomas or carcinomas combined, were related to exposure. The NTP reviewed and agreed with the panel's recommendation.

Dr. Blystone also described the inclusion of perinatal exposure in the two-year bioassay, and noted that the peer-review meeting was the first conducted remotely. He also alluded to several NTP Toxicity Reports in preparation; six have been reviewed or are in the review process. Also, he noted that the first reports of the NTP Developmental and Reproductive Toxicity Series would be peer reviewed in 2016.

B. BSC Questions and Discussion

Dr. Mary Beth Genter was the BSC liaison to the peer-review meeting. She reported that the meeting went well and that the presentations were clear. She described considerable discussion about the issues raised and felt overall that it was a very successful peer-review meeting.

Dr. Norman Barlow asked about nominations of chemicals for the toxicity reports and how some chemicals are subsequently studied in the two-year bioassays. Dr. Blystone said the selection of chemicals that go forward to a two-year bioassay depends on a variety of factors. The chemicals published in toxicity reports are generally ones that do not go on to a two-year bioassay since the nomination was for a short-term study. Usually the results of a short-term study that go on to a two-year study are published together in a NTP technical report. In some cases, short-term studies are published in toxicity reports for chemicals that have gone on to a two-year bioassay in order to get the data more quickly to various stakeholders. Dr. Bucher added that some of the chemicals are simply nominated for toxicology characterization, without intent to go to a two-year study.

VIII. Office of Health Assessment and Translation (OHAT) Draft Concept: Literature-Based Analysis of Mountaintop Removal Mining: Impacts on Health in the Surrounding Community

A. Presentation

Dr. Abee Boyles, OHAT, briefed the BSC on OHAT's proposal to conduct a systematic review of the literature on mountaintop removal (MTR) mining and community health effects. The review is in response to public and government interest, including a request from the West Virginia Department of Health and Human Services for federal expert input. The nomination is to explore whether there is evidence in the published literature for health effects of MTR mining on people living in the nearby communities. The overall objective of the review will be to understand the human health effects of MTR mining by conducting a systematic review of published studies of MTR mining and community health, occupational studies of MTR mining, and any available animal and *in vitro* experimental studies of exposures to MTR mining-related mixtures.

Dr. Boyles provided background information about MTR mining, which is the predominant form of coal mining in Central Appalachia. She noted that existing epidemiological studies are limited, with most studies comparing the prevalence between populations living close to the mining with more distant populations. There has been little accounting for confounding factors such as socioeconomic status (SES), smoking, reduced access to health care, and limited mobility.

Occupational studies will be used to provide context to effects seen in community-based studies. The exposure mixture is understood to be quite complex.

Dr. Boyles described the 8-step process for the proposed literature-based analysis and noted a protocol will be developed based on the OHAT approach and handbook (*http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf*). She provided details regarding the project's population, exposure, comparators, outcomes (PECO) statement and the proposed literature search strategy.

B. BSC Questions and Discussion

Dr. Steven Markowitz asked for clarification of the term "excluded" in the inclusion/exclusion criteria. Dr. Boyles said an excluded study would be one that did not meet the PECO criteria, such as an exposure-only study without exploration of health outcomes.

Regarding the comparators referred to in the PECO statement, Dr. Dorman asked what the surrogate for exposures might be for comparative groups, given the complex mixtures and stressors involved. Dr. Boyles said the guidelines are to help consider what studies would be included, without looking at primary data to create groups. Dr. Dorman asked what the comparator might be that would allow determination of whether a control group is actually exposed less. Dr. Thayer said that in the observational studies, the control group would be people living farther away from MTR mining. Dr. Dorman observed that the surrogate has nothing to do with exposure *per se*, but just distance. He was concerned about the ability to make comparisons between groups. Dr. Boyles said it assumes the control group had less exposure, which could be difficult to compare quantitatively.

Dr. Hattis suggested that in addition to distance, some weighting according to the size of the operation might be appropriate.

Dr. Iris Udasin suggested that fish and wildlife studies would be relevant and should be included along with exposure studies, at least in the narrative reports. Dr. Boyles said those studies would probably be included due to the characterization of exposure (such as metal content in local fish populations), although she cautioned that tying those data back to MTR mining could be tenuous.

Dr. Birnbaum noted that there should be caution about characterizing MTR mining as lower risk than underground mining, because there is evidence of black lung in MTR miners as well.

Dr. Markowitz, first BSC discussant, was supportive of the review, and said an enormous range of health outcomes and exposures associated with MTR mining has already been documented. He suspected that the review would not reach a firm conclusion or a high level of confidence in the evidence, but the value would be to point out the direction of the research. He noted that studies in the literature seem to pay more attention to confounders than to exposures. He said some attention should be paid to sample size and the power to evaluate certain issues, noting that they are not mentioned in the proposal. He suggested getting a better understanding of the population at risk, the time trend in MTR mining activities, and its impact on chronic disease. For

some of the communities, MTR mining is related to income, which is related to health, and so there may be a beneficial impact of MTR mining that is perhaps not felt uniformly among the communities. He asked why the proposal includes reference to other forms of surface mining. He also mentioned that MTR mining might lead to other outcomes aside from health effects, such as social disruption, community changes, and more, which would in turn have impact on health. He felt that those factors should be included in the review to the extent that such studies might be available. He recommended a high priority for project.

Dr. Boyles noted that a description of the population would be included in the protocol and the methods would be clearly stated in the report. She explained that the inclusion of other surface mining methods stemmed from the West Virginia request. Dr. Boyles added that the psychological effects were included in the literature search and was expanded beyond just PubMed.

Dr. Udasin, second BSC discussant, understood that OHAT was asked to undertake the project to help identify potential health effects from MTR mining. Because the duration of exposure is so short (the practice dating from the mid-1990s), there may not be many chronic health issues, but there could be birth defects. She said the evaluation should be done to help inform low SES communities. She recommended a high priority for the evaluation and said the potential of extracting coal in a safer way could improve the health in affected communities. Dr. Birnbaum noted that the regions in Pennsylvania where MTR mining is practiced is also where fracking is widespread currently, and cautioned that in those areas fracking could be a confounding factor. Dr. Boyles agreed that it should be listed as a possible co-exposure.

Dr. Dorman noted that compounds, such as selenium, found in MTR mining complex mixtures exposures, might be used as surrogate markers of exposure. Dr. Boyles said NTP would not measure field exposures; studies with data presented on levels of specific compounds in mixtures will be considered.

Dr. Peterson felt the BSC had a high level of support for the project.

IX. NTP Evaluation of Fluoride Exposure and Potential for Developmental Neurobehavioral Effects

A. Presentation

Dr. Thayer, OHAT, briefed the BSC on a new program of activities to evaluate fluoride exposure and potential developmental and neurobehavioral effects. The program would involve both systematic literature analysis and new research.

She provided background about sources and extent of fluoride exposure and described prior literature reviews of human and animal evidence for neurological effects. Regarding animal evidence, it is clear that there are a number of important research needs including some that could be addressed by the NTP Laboratories (NTPL). The proposed systematic review would integrate human, animal, and mechanistic data, and be timed to incorporate the new NTP research.

Dr. Thayer described the landmark 2006 National Research Council (NRC) report, *Fluoride in Drinking Water*, which is a scientific review of the EPA's maximal contaminant level goal. That systematic review includes evaluation of the available neurological literature. She also discussed a 2015 systematic review conducted for the Republic of Ireland's Department of Health, which contains information about potential neurological effects. She noted NTP has a draft systematic review of animal studies, conducted in collaboration with the Australian National Health and Medical Research Council. This review is currently undergoing external peer review and is expected to be finalized and published in 2016. The review considered exposure during development or adulthood and identified studies on a broad range of neurobehavioral outcomes.

Dr. Thayer provided details about the proposed NTPL animal studies, which would be led by Dr. Jean Harry, group leader of the NTPL Neurotoxicology Group. The studies, which are still in the early planning stages, would focus on assessing learning and memory in rats following developmental exposure.

The proposed systematic review, which is in response to a nomination by private individuals in June 2015, will evaluate the human, animal, and mechanistic studies to develop hazard identification conclusions about whether fluoride is a developmental neurobehavioral toxicant.

Dr. Thayer presented the PECO statement for the project, as well as the 9-step approach to be used for the systematic review. She said the protocol would be posted on the OHAT website during Spring 2016. The draft systematic review is anticipated to be available for public comment and peer review in 2018.

B. BSC Questions

Dr. Chapin asked whether the existing animal studies that were already reviewed are being used to design the new animal studies. Dr. Thayer said Dr. Harry participated directly in the review of the animal literature and has read the existing studies. NTP is currently communicating with EPA about the studies, as the agency is evaluating its maximum exposure limits.

Dr. Sobrian asked about the PECO statement in terms of whether there is a plan to expand beyond learning and memory-related outcomes to include important outcomes such as emotional, motor, or psychomotor. Dr. Thayer said those outcomes are in the report already completed and any behavioral response would be part of this review. Dr. Sobrian asked which compounds are most likely to be found in water. Dr. Thayer said sodium fluoride would be the most common form.

Dr. Genter asked whether the studies evaluated would be limited to oral exposure and whether oral would be the proposed route of exposure in the animal studies to be conducted. Dr. Thayer said there would be no exclusion of studies based on route of administration for the systematic review. Dr. Bucher clarified that the route of administration in the new animal studies would be oral.

Dr. Sobrian asked if the systematic review would provide a real understanding of what the safe levels of fluoride exposure are, and whether the U.S. Public Health Service recommendation of 0.7 mg/L is useful. Dr. Thayer said it is unlikely that the systematic review would yield that type of conclusion, but the experimental animal studies would add to the body of knowledge in that area. Dr. Sobrian asked how doses would be extrapolated from the epidemiological studies to the animal studies. Dr. Thayer said the drinking water concentration used in prior animal studies would be used. Dr. Bucher added that the dose issue is complicated; it was difficult in past animal studies to replicate high human bone levels of fluoride in high endemic fluoride areas. Past studies have shown dose response at higher levels, but results at lower dosages were less conclusive. Part of the intent of the planned studies is to better define the curve. Dr. Birnbaum noted the difficulty of extrapolating between human levels and animal doses, which would appear to require higher concentrations. To achieve equivalent internal dose, which is the appropriate metric, higher administered doses must often be used in animals.

Dr. Dorman recommended carefully choosing the diet for the experimental animals because standard diets are often over-supplemented with trace minerals. Due to electrolyte-mineral interactions in gut or other tissue, it may be difficult to get a skeletal concentration of fluoride in rodents that one would expect that is comparable to levels in humans.

Dr. Harkema asked whether there are data about mouse strains used in fluoride studies, and whether another mouse strain might be closer to human. Dr. Bucher said most studies used a Chinese/Swiss mouse strain. Dr. Birnbaum said Dr. Harkema's idea is interesting and perhaps differential variability and susceptibility among strains should be incorporated into planning for the animal studies.

C. Public Comments

Dr. Anthony Scialli provided oral comments on behalf of the Consumer Healthcare Products Association. He noted that consumer products are minor sources of fluoride exposure, with the majority of exposure coming from drinking water. He expressed concern that the NTP evaluation could have adverse effects on public health, as has already occurred in some communities that have declined to provide fluoridated drinking water to the public. He reviewed several of the evaluations over the past ten years, none of which concluded that there is a health risk in fluoridated community drinking water. He said those studies excluded some of the studies involving high exposure levels as not being informative to U.S. applications. He said the additional research on the effects of fluoride on intelligence called for in the NRC 2006 review has already been conducted and published. He reviewed results of some of those subsequent publications.

He expressed concern that there could be unintended consequences, not from the overall evaluation of fluoride in the context of exposure, but from hazard identification resulting in "naked hazard calls." He cited the US EPA Guidelines for Developmental Toxicity Risk Assessment (1991) as an approach avoiding those issues. He also cited NTP Center for the Evaluation of Risks to Human Reproduction guidelines, which state that conclusions about adverse reproductive and/or developmental effects may occur only under the exposure

circumstances specified. He said the problem with the naked hazard calls is that they might be interpreted by third parties, without regard to exposure level, perhaps leading to labeling of fluoridated dental products as hazardous.

He suggested that fluoride exposure, as it occurs in the U.S., has been demonstrated to be safe, and that additional NTP activity is not needed. He said that if NTP goes forward, care should be taken that hazard calls are expressed only in the context of specific exposure scenarios.

Mr. Daniel Kass, New York City Department of Health and Mental Hygiene, provided oral comments, noting that he is a regulator of the fluoride content of the New York City drinking water supply. He said that although he has not previously heard the term “naked hazard call,” it seems to capture his concerns about the project. He said in his role in public health, he is aware that the final product of scientific activities can be oblivious to the consequences of interpreting hazard assessment. He felt that part of that term refers to the absence of any effort to evaluate comparative harm and benefit. Mr. Kass said fluoride is a rare compound intentionally added to people’s exposure profiles around the country, and NTP should be mindful of the need to fully evaluate the comparative harm question, including the absence of fluoride.

Dr. Howard Pollick, University of California School of Dentistry, provided oral comments on behalf of the American Association of Public Health Dentistry (AAPHD). He said AAPHD agrees with the NTP summary statement that the existing literature is limited in its ability to evaluate potential neurocognitive effects of fluoride in people associated with the current U.S. Public Health Service drinking water guidance (0.7mg/L). He noted that the best available science-based evidence does not establish a causal relationship between lowered intelligence (or IQ) in children, behavioral disorders, or central nervous system disorders with consumption of water fluoridated at recommended levels and use of fluoride dental products. He said AAPHD understands the rationale for the NTP evaluation and that NTP should commit resources appropriate to the level of existing knowledge of fluoride. Because knowledge indicates a lack of concern as well as significant benefit from the use of community water fluoridation and fluoride dental products AAPHD will continue to promote those strategies. He cited the well-recognized public health benefits of fluoride and described the limitations of some of the previous studies linking high levels of fluoride and low IQ scores. He noted that the New Zealand study from 2015 indicated that exposure to fluoride had no effect on neurological development or IQ. He reviewed the scientific issues important for prioritizing and assessing adverse health outcomes as described in the NTP review proposal. He said AAPHD would be following the results of the NTP experimental studies in rats and added that it would be important to consider the issue of potential skeletal fluorosis when dosing rats or mice at very high levels.

D. BSC Discussion

Dr. Sobrian, first BSC discussant, said she was unclear about what the BSC was to comment on regarding the three different components of the project that were presented. She noted that there are mixed findings from the human data, with the same data being used by both proponents and opponents of the concept. She felt that the epidemiological data are

methodologically flawed, with many confounders and said that determining the levels of fluoride to which the U.S. population is exposed would be the biggest problem. Fluoride is in a wide range of foods, pharmaceuticals, and water so it may be impossible to determine the exposure level to any degree of accuracy. She concurred with the approach and proposed scope for the systematic review, and recommended adding other outcomes beyond learning and memory. She hoped the information from the systematic review of the animal literature would inform the larger effort. She was in favor of NTP proceeding with both the systematic review and the animal study.

Dr. Chapin, second BSC discussant, said the clarity and validity of the draft OHAT concept were fine, as was the summary of literature gaps. He felt that the proposed evaluation is something that NTP does well. He approved of the proposed approach and scope of the project. He said the focus on neurodevelopment is warranted, but is not without risks given the challenges of extrapolating rodent behavior to humans. He recommended focusing on behavioral domains. He gave the proposed evaluation a high priority ranking. He concurred with Dr. Scialli's remarks regarding potential unintended consequences and trusted that NTP would be able to present its findings in the appropriate context.

Dr. Barlow, third BSC discussant, agreed that the concept was clearly stated and the proposal is valid and in line with NTP's mission. The project would strengthen the science base of toxicology and ultimately contribute to translation of that information regarding fluoride to humans. He found the proposed approach and project scope acceptable, although he questioned whether the proposed review should await the results of the review currently being peer reviewed. He suggested adding some endocrine endpoints to the animal studies. He recommended giving the project a medium priority, given discrepancies and flaws in the data and the concerns about unintended consequences. He was also sensitive to budgets and resources, which affected his thinking regarding the potential priority to be assigned to the project.

With respect to the timing of the evaluation in relation to the draft report under review, Dr. Thayer said there is a clear lack of data on neurodevelopmental outcomes at low concentrations and this would not change as a result of the ongoing peer review. She said the issue regarding the potential consequences of hazard identification of fluoride had been considered and the systematic review would include consideration of the hazard conclusions in the context of human exposure levels.

Dr. Birnbaum noted that Dr. Bucher and she had both served on the Department of Health and Human Services panel for the revised fluoride exposure safety recommendations. She said nothing is known about differential susceptibility or variability within a population, which was part of the justification for reducing the level recommended for public health protection.

Dr. Peterson said the priority for the project ranged from medium to high.

X. Office of the Report on Carcinogens (ORoC) Report on Peer Review of the Draft RoC Monograph on Cobalt and Certain Cobalt Compounds

A. Presentation

Dr. Ruth Lunn, ORoC, briefed the BSC on the peer review of the Draft RoC Monograph on Cobalt and Certain Cobalt Compounds, which was held on July 22, 2015.

She provided background information about the congressionally mandated RoC and the current status of the review in the NTP RoC process. She described cobalt and cobalt compounds evaluated in the review and sources of significant exposure from both occupational and non-occupational uses. She described the development and review of the draft monograph, including opportunities for scientific input and public comments.

Dr. Lunn summarized the charge and actions of the peer-review meeting, as well as the revisions made to the monograph based on peer-review panel comments. The panel, she noted, agreed with the draft NTP conclusions and listing recommendation of *reasonably anticipated to be a human carcinogen*. The panel's recommended the definition of "certain cobalt compounds" as "cobalt compounds that release cobalt ions *in vivo*" in the listing rather than the word "certain." She reviewed the rationale for listing cobalt as a class, including the fact that cobalt metal and compounds cause similar biological effects associated with carcinogenicity.

Dr. Lunn reported that the panel voted to recommend that NTP review the literature on human cancer associated with cobalt-containing joint implants, with the instruction that another peer review be convened if that review yielded relevant data that might change the evaluation. The NTP's assessment of implant studies concluded that joint implant studies are not informative for evaluating effects of cobalt *per se*.

Just before the peer-review meeting, the Cobalt Development Institute (CDI) provided NTP new research, which at that time had just been accepted for publication. The publication (Kirkland *et al.* 2015) consisted of more than 40 genotoxicity studies. NTP concluded that the new studies are unlikely to change NTP's conclusions, as the findings of the individual studies are largely consistent with NTP's conclusions concerning specific genotoxic endpoints.

B. BSC Questions

Dr. Markowitz asked why the substances had been ranked as *reasonably anticipated to be a human carcinogen* when others with similar levels of evidence are listed as *known to be a human carcinogen*. Dr. Lunn said the mechanistic evidence was not compelling and there would need to be more mechanistic data in humans for the call to be elevated to *known to be a human carcinogen*.

C. Public Comment

Dr. Ruth Danzeisen provided oral comments on behalf of the CDI. She described three areas of CDI's concern: (1) the relevance of the "Trojan Horse"-type toxicity, as not being a reflection of

in vivo bioavailability, (2) table 7-1 in the draft monograph misrepresents the *in vivo* bioavailability of the poorly soluble cobalt compounds and groups two very different cobalt oxides (CoO and Co_3O_4) in one group, and (3) CDI was unable to locate the historic database to which the systemic tumor incidence was compared. She suggested the database could be explained better in the revised monograph.

D. BSC Discussion

Dr. Corcoran served as BSC liaison to the RoC peer-review meeting. He said he assessed the integrity of the process and noted that the peer-review panel was very strong with a high level of expertise and experience. He said the panel reviewed all of the important areas and observed that the presentations by ORoC staff and contractors were clear and that there was very active participation by every panel member in the peer review. He described the panel's decision to question the exclusion of literature on medical implants and its request for NTP to re-examine the question with the potential for reconvening a panel if there was sufficient need. He said NTP had added two pieces of information to the monograph regarding concentrations of cobalt in hip implants. He noted that the public provided both oral and written comments. He commended the NTP on the thoroughness of the review process for the monograph.

XI. Adjournment

Closing the meeting, Dr. Birnbaum thanked the BSC members for their hard work and constructive suggestions. Dr. Bucher also thanked the BSC members for their service. Dr. White added her thanks and noted that the next BSC meeting would be held June 15-16, 2016.

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Dr. Lisa Peterson

Chair, NTP Board of Scientific Counselors

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Date 2/12/2016