Summary Minutes
NTP Board of Scientific Counselors Meeting
April 17-18, 2014

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I. Frequently Used Abbreviations and Acronyms

BSC	Board of Scientific Counselors
CDC	Center for Disease Control and Prevention
DNTP	Division of the NTP
EBV	Epstein-Barr virus
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HEI	Health Effects Institute
HIV-1	human immunodeficiency virus type 1
HHS	Department of Health and Human Services
HTLV-1	human T-cell lymphotrophic virus type 1
IARC	International Agency for Research on Cancer
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ILS	Integrated Laboratory Services, Inc.
KSHV	Kaposi sarcoma-associated herpes virus
PCP	pentachlorophenol
IRIS	Integrated Risk Information System
MCV	Merkel cell polyoma virus
NAS	National Academy of Sciences
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NICEATM	NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
ORoC	Office of the Report on Carcinogens
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
TR	Technical Report

II. Attendees

Members in Attendance:
Milton Brown, Georgetown University Medical Center
Robert Chapin, Pfizer
George Corcoran, Wayne State University
David Dorman, North Carolina State University
Mary Beth Genter, University of Cincinnati
Dale Hattis, Clark University
Steven Markowitz, City University of New York
Lisa Peterson, University of Minnesota (chair)
Sonya Sobrian, Howard University
Iris Udasin, University of Medicine and Dentistry of New Jersey

***Ad Hoc* Member:**
Richard Miller, GlaxoSmithKline

Member not in Attendance:
Jack Harkema, Michigan State University

Other Federal Agency Staff:
Paul Howard, U.S. Food and Drug Administration (FDA)
Gayle DeBord, National Institute for Occupational Safety and Health (NIOSH)

National Institute of Environmental Health Sciences (NIEHS) Staff:

Mamta Behl	Gloria Jahnke	Raymond Tice
Linda Birnbaum	Grace Kissling	Molly Vallant
Chad Blystone	Kelly Lenox	Nigel Walker
Abee Boyles	Ruth Lunn	Lori White
John Bucher	Robin Mackar	Mary Wolfe
Warren Casey	Dave Malarkey	Rick Woychik
Vesna Chappell	Barry McIntyre	Yun Xie
Mike Devito	Rick Paules	
Paul Foster	Katie Pelch	
Rachel Frawley	Wei Qu	
Dori Germolec	Cynthia Rider	
William Gwinn	Robert Sills	
Stephanie Holmgren	Diane Spencer	
Michelle Hooth	Vicki Sutherland	
Kembra Howdeshell	Kris Thayer	

Public:
Stan Atwood, Integrated Laboratory Services, Inc. (ILS)
Chris Bartlett, SciMetrika
Julie Bishop, ILS
Ella Darden, ILS
Andy Evans, ILS
Sanford Garner, ILS
Ernie Hood, Bridport Services
Erin Mullaney, ILS
Julie Panko, Cardno ChemRisk
Alton Peters, ILS
Pam Schwingl, SSS

Webcast Participants:
Joseph Algaier, MRI Global
Brad Collins, NIEHS/NTP
Sylvia, NETE WDDMS
Pat Kablach Casano, General Electric Company
Susan Felter, Procter & Gamble
Christine Flowers, NIEHS
Robbin Guy, NIEHS/NTP
Kristina Hatlelid, US Consumer Product Safety Commission

Anna Jones, Social & Scientific Systems, Inc.
Cynthia Rider, NIEHS/NTP

III. Information Regarding the Meeting

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met April 16 - 18, 2014 in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. The meeting was originally scheduled for December 18 - 19, 2013, but was postponed due to the October 2013 Federal government shutdown. The first part of the meeting (April 16 and until 2 PM on April 17) had sessions closed to the public in accordance with the provisions set forth in section 552(c)(6), Title 5 U.S.C., as amended, to review Dr. Michael Waalkes and the NTP Laboratory.

April 17, 2014

IV. Introductions and Welcome

Dr. Peterson, BSC chair, opened the general BSC meeting at 2 PM on April 17, 2014. She welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. Dr. Lori White, BSC Designated Federal Official, read the conflict of interest policy statement. NTP Associate Director Dr. John Bucher welcomed the BSC members to the meeting.

V. 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 2013. She reported on recent efforts at NIH regarding reproducibility of research, big data and scientific computing, increased workforce diversity, and training. She described the priority activities associated with the eight cross-divisional implementation teams for the NIEHS Strategic Plan.

Regarding appropriations, Dr. Birnbaum noted that the NIEHS appropriation for FY2014 is essentially flat. Although sequestration cuts have been partially restored, funding is still below where it was in FY2012, both for NIEHS and NIH as a whole.

Dr. Birnbaum briefly summarized recent scientific advances and publications involving Division of the NTP (DNTP) scientists or NIEHS grantees, including a study of disposition of OTNE ([1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethylnaphthalene-2yl]ethan-1-one), a fragrance ingredient, in male Fisher rats, and a study of polyfluoroalkyl chemicals and menopause among women 20-65 years of age.

Dr. Birnbaum summarized several of the ongoing “One NIEHS initiatives,” including Disaster Response Research (DR2), Partnerships for Environmental Public Health, the Exploring the Exposome project, the recently released NTP Nonneoplastic Lesion Atlas, and the establishment of NIEHS as a World Health Organization Collaborating Center. She described recent accomplishments in data management and technology, including enhancements to the

Comparative Toxicogenomics Database, the release of new chemical screening data by the interagency Tox21 collaboration, the November 2013 announcement of the winners of the DREAM Toxicogenetics Challenge, and the March 2014 Institute of Medicine Roundtable Workshop on Data Sharing for Environmental Health.

VI. Office of the Report on Carcinogens (ORoC) Peer-Review Meeting on o-Toluidine and Pentachlorophenol (PCP) and By-products of its Synthesis

A. Presentation

Dr. Ruth Lunn, Director of the ORoC, reported to the BSC on the peer-review meeting on the draft RoC monographs for *ortho*-toluidine and PCP and by-products of its synthesis, held December 12 - 13, 2013 at NIEHS. The meeting was originally scheduled for October 7 – 8, 2013, but was rescheduled due to the October 2013 Federal government shutdown.

She provided background information about the two candidate substances under review for the RoC, and reviewed the steps in the review process. She described the draft RoC monographs and listing recommendations. She reported the preliminary NTP listing recommendations for the RoC, their bases, and the panel's actions related to each candidate substance. Regarding the *ortho*-toluidine conclusions, the panel agreed with the NTP's preliminary listing recommendation of *known to be a human* carcinogen based on studies showing it causes urinary bladder cancer in humans along with studies in experimental animals. Regarding the PCP conclusions, the panel agreed with the NTP that there was sufficient evidence of carcinogenicity from studies in experimental animals, but recommended a conclusion of limited evidence from studies in humans. The panel recommended that there was sufficient evidence for PCP by itself in experimental animals; however, the NTP did not concur that the body of evidence is sufficient to make a conclusion on PCP alone. The NTP agreed with the panel's recommendation that PCP and by-products of its synthesis should be listed in the RoC as *reasonably anticipated to be a human carcinogen*.

Dr. Lunn said ORoC would finalize the monographs, post them on its website, and submit the substance profiles to the Secretary of the Department of Health and Human Services (HHS) for review and approval for the next edition of the RoC.

B. BSC Discussion

Dr. Chapin chaired the meeting during this topic and Dr. Peterson, who served as the BSC liaison to the peer-review meeting, led the discussion. She said it had been a well-run meeting, with effective, thorough scientific presentations presenting background information and justifying the levels of evidence and listing recommendations. She reported that there had been an open, constructive, animated debate during the meeting, and that the decisions reached had been through careful review of the data and discussion.

Dr. Mary Beth Genter, second discussant, thought the peer-review report and response were very logical and constructive, and that the documents were extremely well prepared and complete.

Dr. Chapin summarized the discussion, stating that the BSC supported and had admiration for the RoC process and the strong scientific bases for the evaluations.

VII. Report on Carcinogens (RoC) Concepts - Introduction

Dr. Lunn reviewed the background of the RoC and the process for its preparation, as context for the concepts to be presented. She described the rolling process for selecting nominations for NTP review. After interagency review and public comments, the ORoC develops draft concept documents for substances proposed for evaluation. The draft concept document is designed to provide the rationale for reviewing the proposed candidate substance and presents the proposed approach for conducting the cancer evaluation; it is not a review or assessment of the data. She described the variety of mechanisms the ORoC might use to obtain scientific and public input, including consultation with technical advisors, the establishment of an information group, and public web-based symposiums. ORoC establishes a website for each candidate substance, which is another forum for public input. After the BSC meeting, NTP would consider the comments on the draft concepts, and the NTP Director would make the final selection decisions on the proposed candidate substances. The concept documents are finalized based on comments from the BSC and the public. ORoC then initiates the scientific evaluation of the candidate substances leading to development of the draft RoC monographs.

VIII. Draft RoC Concept: Selected Viruses

A. Presentation

Dr. Gloria Jahnke briefed the BSC on the draft RoC concept on several viruses selected for review, including Epstein-Barr virus (EBV), human immunodeficiency virus type 1 (HIV-1), human T-cell lymphotrophic virus type 1(HTLV-1), Kaposi sarcoma-associated herpes virus (KSHV), and Merkel cell polyoma virus (MCV). She reported that all five viruses are present in the U.S. and they constitute a public health concern. A significant number of people in the U.S. are infected with four of the five viruses; HTLV-1 has a lower prevalence of infection, but has a higher prevalence in endemic areas in the U.S. There is a large cancer database on the viruses, and there have recently been authoritative reviews by the International Agency for Research on Cancer (IARC). She said all five viruses would all be evaluated independently, but in a similar fashion, and a monograph would be prepared for each virus.

Dr. Jahnke described the transmission, populations at risk for cancer, exposure information, and scope and extent of the human cancer database for each of the viruses. As IARC has conducted authoritative evaluations on the viruses, the ORoC plans to use the information provided in the IARC monographs to conduct its own cancer assessment. The plan is to establish an ORoC monograph planning team, consisting of external expert technical advisors, NTP staff, ORoC staff, and contractor staff. The team will assist in protocol development, identification of key studies, and cancer assessments. Protocol development will employ a literature search strategy for evaluating the quality of studies published since the IARC reviews. Public input will be requested throughout the review process, and the RoC will establish a webpage for each of the viruses under review, including a mechanism for public input.

The intent is to provide information about the physical characteristics, exposure, transmission, human cancer studies, and potential cancer mechanisms of the viruses, to inform the public about transmission and increase awareness of the viruses as potential carcinogens.

B. BSC Discussion

Dr. Hattis asked the source of the quantitative estimates of worldwide and U.S. prevalence of cancers attributable to viruses. Dr. Jahnke replied that the figures had come from IARC studies (IARC 100B (2012). Biological Agents. International Agency for Research on Cancer. Lyon, France).

Dr. Dorman pointed out that part of the diagnostic criteria for Kaposi sarcoma is positive HIV status. Although it is not the sole diagnostic test, it has been part of the diagnosis for that disease. He questioned the purpose and use of resources for listing viruses in the RoC. Dr. Bucher explained that there is a requirement to list all known carcinogenic substances, including biological agents. He noted that the purpose for this project, which would be conducted in a circumscribed manner compared to some of the other evaluations, is to get the information on transmission in the public domain, allowing people to exercise appropriate cautions and allowing drug companies to identify potential vaccines or therapeutic targets. Dr. Lunn added that the absence in the RoC of substances strongly suspected of being carcinogenic could take away from the RoC's overall credibility. Utilizing the IARC monographs, fewer NTP resources would be needed for the evaluation. Dr. Dorman noted that other authoritative bodies such as the National Cancer Institute (NCI) have evaluated the viruses, and asked whether NTP has a mechanism to simply accept the findings of such organizations. Dr. Mary Wolfe said NTP has no recognized, authoritative bodies whose information can automatically be put into the RoC, although the RoC serves as an authoritative body for other groups.

Dr. Howard clarified that the five viruses, if listed, would be added to the virus listings already in the RoC, e.g., hepatitis B and hepatitis C; the viruses currently listed would not be updated at this time. Dr. Jahnke added that the letter nominating the five viruses had inquired about their absence from the report; that inquiry had provided impetus for NTP to consider them.

Dr. Markowitz commented that although HTLV-1 has a low seroprevalence, he agreed with its inclusion, because certain subpopulations have a much higher exposure. Dr. Udasin agreed, noting that the low levels of seroprevalence are likely due to HIV-positive people, if aware of their HIV status, being unlikely to attempt to donate blood. Thus, the cited statistic is likely to be an underestimate of prevalence.

Dr. Udasin, first discussant, said the high degree of prevalence of EBV in the U.S. supports its inclusion, especially since the level of immunocompromise required to develop cancer is probably much less than for a virus like HIV. It has the highest priority in terms of public health significance. Regarding HIV, she noted that a significant population in the U.S. is infected, and supports the scientific evaluation of its carcinogenicity. Regarding KSHV, the estimated seroprevalence of 3.5% among blood donors is extremely high, so people with such a known risk factor would probably not be donating blood. Dr. Udasin said MCV is known to be prevalent

among healthy people, and the scientific evidence supports future studies, including reaching out to the blood bank community to raise their awareness of the issue.

Dr. Markowitz, second discussant, concurred with Dr. Udasin.

Dr. Peterson summarized the BSC discussion, stating that there was agreement by the BSC that a RoC evaluation of the five viruses should be a high priority.

IX. Draft RoC Concept: Goldenseal Root Powder

A. Presentation

Diane Spencer briefed the BSC on the draft RoC concept for goldenseal root powder, which currently has widespread exposure in the U.S. due to its use as an herbal remedy. Goldenseal was studied previously and reported in an NTP Technical Report (TR), and an IARC review classified goldenseal root powder as *possibly carcinogenic to humans*. There has been little investigation of goldenseal itself, but there are several studies in the literature on berberine, a topoisomerase II inhibitor and one of goldenseal's main active ingredients. Key scientific questions and issues include the level of evidence for carcinogenicity from studies in animals, potential mechanisms, and characterization of the active components.

Scientific input would be gained from a monograph planning team consisting of NTP staff and technical experts with relevant expertise in chemistry, metabolism, human exposure, and uses of herbals or their metabolites. The protocol would include a literature search strategy with an approach for evaluating the quality of experimental animal studies. Public input would be solicited throughout the review process, and the ORoC would establish a webpage for the documents related to the review, including a mechanism for public input.

B. BSC Discussion

Dr. Milton Brown, first discussant, considered the doses used in the NTP study quite high, showing little evidence of tumors until very high doses were used. He was concerned that a large clinical trial of goldenseal as a potential cancer therapeutic agent, by the National Center for Complementary and Alternative Medicine (NCCAM), was not mentioned. He also expressed concern about the presence of flavonoids in goldenseal, with potential risk to pregnant or pediatric populations, and noted that this concern had not been addressed in the report. Ms. Spencer agreed that the dosing in the NTP study appears high, but was roughly equivalent to plasma concentrations in humans who have been exposed. She said ORoC was aware of the NCCAM trial and would consider obtaining technical advisors from that group. She noted that goldenseal preparations sold in stores include a caution directed at pregnant women, and that the flavonoids issue would be included in the literature search.

Dr. Genter, second discussant, stated that the doses used in the chronic bioassay were equivalent to about 10 grams/kilogram/day in humans. She noted that another population using goldenseal root is cancer patients, who are using it as a homeopathic medicine, often as an alternative to conventional chemotherapeutics. She said both NCCAM and the American

Cancer Society caution that the science is not adequate to make it a viable replacement for more conventional cancer chemotherapies. The literature she reviewed reported characterization of no more than 20% of the components of goldenseal root powder, leaving 80% unknown, and making it challenging to perform consistent analyses. Ms. Spencer agreed and said there seems to be consensus that the berberine is the most active component.

Dr. Genter noted that although the NTP had not found genotoxicity in its assays, berberine is known to be a topoisomerase II inhibitor. Dr. Hattis said that issue should be emphasized in the evaluation, as the potential for DNA damage is a cause for concern. He recommended inclusion of information about some of the other topoisomerase II inhibitors. Dr. Brown noted that many compounds are topoisomerase II inhibitors, but in *in vitro* assays, at high doses, it may not be that significant. Dr. Hattis concurred, saying what matters is that a compound inhibits topoisomerase *in vivo.*

Dr. Genter noted a study suggesting that goldenseal may have a protective effect against liver tumors in mice, and this should be considered in the evaluation. She questioned NTP's policy regarding moving forward on the evaluation of chemicals that seem to have a high-dose threshold mechanism, noting that the tumors were only present at the highest doses.

Dr. Bucher replied that many of the issues that had been raised would be examined in the course of an evaluation for potential listing in the RoC. He said these are important elements that may ultimately lead to a decision that the substance should not be listed, but the purpose of the concept is to review the approach proposed by ORoC to conduct the review – whether the outside advice being solicited from experts is adequate, and whether there is an adequate database to carry out the review. However, if the BSC feels the likelihood of listing is very low, they can recommend a low priority for the evaluation.

Dr. Brown thought the available data supported the conclusion that there is little risk at this point. Dr. Nigel Walker cautioned against prematurely assessing the carcinogenicity before the assessment is done. He said the issue of dose response is complicated, and emphasized that the RoC is a hazard assessment document. Dr. Howard agreed and also stressed that goldenseal root powder should be referred to as a dietary supplement, not a drug. The compound is a moving target in terms of the plant species and what is on the market; it is not a single chemical entity, but a complex mixture. He added that the issue of polypharmacy must be considered, particularly in the case of cancer patients who may be using the substance as an adjunct to other therapies.

Dr. Walker noted that the question of co-exposure to known carcinogens is often an issue in literature regarding botanicals.

Dr. Peterson summarized the discussion, noting that there was some concern among BSC members about dose levels in the animal data, and the fact that the compound is a botanical and therefore a mixture. She felt there was modest support for moving forward with the evaluation.

X. Draft RoC Concept: Cobalt

A. Presentation

Ms. Spencer briefed the BSC on the draft RoC concept for cobalt, noting the previous authoritative reviews and listings. Exposure in the U.S. occurs in occupational settings and in the general population through diet and environmental contamination. A new cobalt mine-and-mill complex has been proposed in Idaho. There is an adequate database to draw upon, including the NTP cancer bioassay on cobalt metal and mechanistic studies on several other cobalt compounds. The first step in the review would be to define the candidate for evaluation–some cobalt alloys or radioactive cobalt may not be included due to confounding issues.

Ms. Spencer provided information on cancer studies in humans and experimental animals, and described potential mechanisms for cobalt carcinogenesis, including reactive oxygen species and inhibition of DNA repair. Key scientific issues include level of evidence in humans and experimental animals and biological plausibility. Scientific input would be gained from a monograph planning team consisting of NTP staff and technical experts as well as technical advisors such as chemists, metal experts, and others with relevant expertise on human exposure and uses of cobalt. The team would develop a written protocol to clearly define the candidate substance(s) and the rationale for the review. Public input would be solicited throughout the review process, and the RoC would establish a webpage for the RoC documents related to the review, including a mechanism for public input.

B. BSC Discussion

Dr. Dorman asked whether the concept included any form of cobalt and about the rationale for evaluating certain alloys and not others. He felt the scope should be narrowed, so the BSC would have a better idea of what cobalt compounds would be addressed. Dr. Lunn replied that the initial focus was the NTP cobalt bioassay, but it is recognized that there are other compounds with similar mechanisms, although a limited database. The first task would be to provide information about the mechanisms to see whether there are enough data available to list cobalt as a class. Every single cobalt compound would not be evaluated. Dr. Dorman asked what the scope would be, given so many cobalt-containing compounds, both dietary and non-dietary. He suggested that cobalt might be evaluated in an iterative fashion. Dr. Lunn noted that originally alloys were not going to be considered due to confounding. Dr. Bucher said, from a historical perspective, the original thinking on the cobalt nominations was that cobalt metal might be carcinogenic with inhalation exposure. The cobalt sulfate studies were positive and the cobalt metal studies indicated even more potent carcinogenicity. Thus, the driving force behind cobalt carcinogenicity is still unknown, and in the current concept, the mechanistic information would be evaluated to better understand cobalt's carcinogenicity.

Dr. Bucher said one of the functions of the RoC is to elaborate what distinguishes different potencies within a class of compounds. He recalled that there had been instances where within a class some compounds were described as carcinogenic, while others were seen to be non-carcinogenic. He said that approach would be part of the communication aspect of the RoC if something as broad as a class listing is undertaken. The class would not be characterized in

blanket fashion; the evaluation would be more nuanced. Dr. Dorman asked whether there might be information about valence to characterize sub-classes of cobalt compounds. Dr. Bucher said there are clearly redox-active compounds, but he did not have enough information to answer the question.

Dr. Dorman, first discussant, noted that exposure to cobalt is widespread, with dietary intake, exposure to naturally occurring forms of cobalt, and potential occupational exposure. The scientific database appears to limited, but is likely to be sufficient to support a RoC evaluation, including the results of the 2-year NTP rodent bioassay. He reiterated his question about the forms of cobalt to be investigated. He suggested that if a broad approach is taken, the metal-on-metal alloys should be included, and the decision to exclude them should be revisited. He said the plan for public and scientific input is adequate and rated the impact to be "somewhat moderate," but could be higher if medical uses were considered as well.

Dr. Hattis, second discussant, said he supported the project going forward, with increasing exposure in the U.S. due to the new mine. New uses of cobalt are being identified and there is considerable documentation of dietary exposure. He was encouraged by the availability of good mechanistic information, particularly in the substitution of cobalt for zinc in zinc finger DNA repair enzymes. He said he would also rate the concept as "moderate" in significance.

Dr. Peterson summarized the discussion by noting moderate support by the BSC for moving forward with the evaluation.

The public meeting adjourned for the day.

April 18, 2014

Dr. Peterson welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. Dr. White read the conflict of interest policy statement.

XI. Report of the NTP Associate Director

Dr. Bucher, NTP Associate Director, briefed the BSC on recent and upcoming meetings and events, staff changes, and other NTP-related developments since the last BSC meeting in June 2013.

Recent meetings included the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM, September 2013), peer reviews of draft NTP TRs (October 2013) and RoC monographs (December 2013), an ORoC webinar on trichloroethylene (March 2014), and NTP staff participation in an IARC advisory group (April 2014). Upcoming workshops and events include the *Collaborative Workshop on Aquatic Models and 21st Century Toxicology* (May 5-6, 2014), the NTP satellite symposium at the Society of Toxicologic Pathology 33rd Annual Symposium (June 21, 2014), and a NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods (NICEATM) and Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) workshop *Adverse Outcome Pathways: From Research to Regulation*" (September 3-5, 2014). Upcoming advisory activities include the

Division of NTP Intramural Research Program Review, peer review of NTP draft TRs (May 22, 2014), BSC meetings in June and December, and a SACATM meeting in September.

Dr. Bucher noted the awards presented to NTP staff at the Society of Toxicology 53rd Annual Meeting, held in March 2014 in Phoenix, Arizona. He detailed several NTP staff changes, and discussed the new Transdisciplinary Environmental Health Fellowship program. He mentioned recent publications from the Tox21 program and described the NICEATM/ICCVAM project on skin sensitization. He updated the BSC on Office of Health Assessment and Translation (OHAT) efforts related to systematic review, including the publication of a systematic-review-framework paper in *Environmental Health Perspectives* in April.

XII. NTP Technical Reports Peer Review

Dr. Chad Blystone, NIEHS/DNTP/Program Operations Branch, briefed the BSC on the NTP TR peer-review meeting that was held on October 29, 2013. He reviewed the TR program, in which NTP conducts rodent toxicity and cancer studies on agents of public health concern to identify potential hazards for human health. Peer reviews of draft TRs on cobalt metal dust, vinylidene chloride, tetrabromobisphenol-A, and glycidamide were conducted by a panel of eight experts, chaired by Dr. John Cullen of North Carolina State University. The panel was charged to review and evaluate the scientific and technical elements of the study and its presentation and to determine whether the study's experimental design, conduct, and results support the NTP's conclusions regarding the carcinogenic activity and toxicity of the substance tested. The panel voted to accept as written the NTP recommendations for each substance. The panel was also updated on the transition of rat stocks in the NTP testing program, the extended pathology evaluation of the uterus, and new molecular analysis of tumors.

Dr. Richard Miller, GlaxoSmithKline and recent BSC member, served as BSC liaison to the peer-review meeting. He said it had been an extremely well run peer review. He reported there had been some debates resulting in non-unanimous votes, but felt that it was a demonstration of the robustness of the process. He noted that much of the discussion had centered on the use of molecular pathology endpoints in decision-making.

Dr. Bucher said there was an ongoing discussion within NTP about whether tumor incidences information on molecular mechanisms, which distinguish background tumors from chemically induced tumors, should drive the level of carcinogenic activity call for a substance. He noted the issue might be brought to the BSC in the future.

Dr. Dorman asked whether urine or serum samples are archived for potential later proteomics use. Dr. Bucher said those samples are not stored.

Dr. Hattis said he was glad the molecular mutagenic spectra analysis is being conducted, in that it could detect a genetic mode of action in tumors.

Dr. Peterson summarized the discussion, saying the BSC felt the TR review process was thorough and well done. The BSC recommends that the NTP continue to explore the use of

molecular analyses to determine their role in helping to evaluate the studies' findings and investigate what changes in genetic signatures mean in terms of mechanism of tumor induction.

XIII. Office of Health Assessment and Translation (OHAT) Concepts

A. Introduction

Dr. Thayer provided the BSC background information on the OHAT evaluation process, including some of the tools used, and where the draft concept documents are within that process. The draft concepts are intended to provide a high-level overview of a project and its proposed focus, without many of the details on how the evaluation itself would be conducted. The BSC, in their review of the concept documents, is asked to take that perspective. The next step in the process is formulation of the protocol. After the meeting to gain BSC and public comments, OHAT would develop the detailed protocol. Dr. Sobrian asked about the emerging issues that OHAT might evaluate. Dr. Thayer gave as examples transgenerational inheritance of health effects and epigenetics related to environmental exposures. She noted that some of the evaluations on emerging issues may not culminate in hazard identification conclusions.

Regarding the text mining tools, Dr. Hattis urged caution about eliminating the use of manual searching of studies.

XIV. Draft OHAT Concept: Adverse Health Effects Associated with Occupational Exposure to Cancer Chemotherapy Agents

A. Presentation

Dr. Kembra Howdeshell briefed the BSC on the draft OHAT concept, Adverse Health Effects Associated with Occupational Exposure to Cancer Chemotherapy Agents, noting that the data need was identified during the 2012 peer-review meeting on the draft NTP Monograph on Cancer Chemotherapy Use During Pregnancy. Occupational exposure to cancer chemotherapy agents occurs in many professions, with exposure potentially occurring over a long period of time and involving many chemotherapeutic agents.

She described recent systematic reviews, dating from 2005 and 2010, and a NIOSH study currently under editorial review. The preliminary literature search for the OHAT evaluation covered chemotherapy, health staff, occupational exposure, and health outcomes/genotoxicity. More than 4,000 references were initially identified, and 233 were ultimately considered eligible for data extraction and risk-of-bias assessment. The key question is what is the confidence in the body of evidence for an association between occupational exposure to cancer chemotherapy agents and adverse health effects, based on the results of observational studies in humans. The aim of the evaluation is to develop hazard identification conclusions, or if insufficient data exist, to write a state-of-the-science paper. The approach would include working with technical advisors and an evaluation design team, and then conducting the evaluation using the OHAT Approach to Systematic Review and Evidence Integration (the Approach).

B. BSC Discussion

Dr. Dorman asked whether individuals handling radioactive materials such as iodine would be excluded. Dr. Howdeshell said radiation exposure would be excluded. Dr. Dorman noted that, at least in veterinary oncology, personnel would be handling radioactive iodine as well as other chemotherapeutic agents. He asked whether secondary tumor rates in patient populations who are administered chemotherapy would be used as evidence for whether there is an increased risk of exposure and associated hazard. Dr. Howdeshell said that question had been raised in discussions with technical advisors.

Dr. Hattis asked about the inclusion of fetal growth inhibition or birth weight among the reproductive indices. Dr. Howdeshell said literature on fetal growth would be included.

Dr. Brown asked whether the occupational hazard to those who make chemotherapeutics had been considered. Dr. Howdeshell replied that any literature addressing manufacturing would be included, although the exposures experienced by those workers may be very different from those in the medical profession.

Dr. Udasin, first discussant, noted that some chemotherapy agents are now administered via viruses, which may affect reactivity. She said in many institutions, animal handlers are at risk of exposure to cancer chemotherapy agents. Drugs used to treat cancer and immunologic diseases can cause cancer in other people; the more pertinent questions are about the routes of exposure and how exposure can be prevented. There is a need to identify earlier biomarkers of exposure to the agents prior to any organ damage occurring. She noted that many chemotherapeutic agents are used in homes, prisons, hospices, nursing homes, and a variety of other settings, making the study important. She rated the project a very high priority. She felt the estimate of 5.5 million people exposed in 2006 was extremely conservative, and encouraged further research, consistent with the missions of NIEHS, NIOSH, NTP, and state occupational health and safety groups.

Dr. Chapin, second discussant, approved of the general concept and proposed approach. He noted that as baby boomers age, the information will become more important as there will be more exposures. Also, as the next generation of cancer chemotherapeutics becomes available, the compounds may be much more potent. Thus, there may be greater potential risk associated with surface contamination. He recommended a high priority for the project.

Dr. Markowitz asked whether the OHAT team would review unpublished reports from pharmaceutical companies. Dr. Howdeshell said the evaluation would include only published literature. Dr. Thayer added that unpublished data could be considered, if the owners of the data are willing to make it publicly available; the NTP would have the data peer reviewed the before inclusion in the evaluation. Dr. Howdeshell noted that the NTP is working closely with NIOSH to ensure that efforts are not duplicative, and is closely following the recent NIOSH review on reproductive effects due to occupational exposure. Thus, the focus of the proposed evaluation may shift to non-reproductive effects if that is the logical course. Dr. Gayle DeBord agreed that review of patient literature might be helpful, as well as looking at other health effects

of chemotherapy drug exposures. Dr. Markowitz thought the literature on second cancers from chemotherapeutic agents would be large.

Dr. Udasin asked about the literature on how agents are metabolized, particularly after vivarium airborne exposures. Dr. DeBord said the studies typically do not assess airborne exposures, because the agents are in such low concentrations that the analytical methods are not sensitive enough to detect or measure them. Most of the exposures occur dermally in nurses, technicians, and janitorial staff. Dr. Bucher noted that the NTP always uses the appropriate protective equipment in its animal care facilities. Dr. Birnbaum added that dermal exposure also includes ingestion.

Dr. Peterson summarized the discussion, stating that the BSC strongly supports going forward with the evaluation, giving it a very high priority.

XV. Draft OHAT Concept: Pregnancy Outcomes Associated with Traffic-Related Air Pollution

A. Presentation

Dr. Howdeshell briefed the BSC on the draft OHAT concept, Pregnancy Outcomes Associated with Traffic-Related Air Pollution. She said the proposed evaluation is the result of an external nomination to evaluate emerging children's health issues associated with ambient air pollution. The concept was developed following consultation with federal experts on research efforts and the need for a synthesis of the literature on ambient air pollution. She discussed recent reviews of health effects of ambient air pollution, including a 2010 review by the Health Effects Institute (HEI) and recent EPA and Center for Disease Control and Prevention (CDC) reviews. Of more than 28,000 identified references, 2,204 were deemed eligible for data extraction and risk-of-bias assessment – 300 on pregnancy outcomes, 1,904 on other health effects.

She said the focus of the proposed OHAT evaluation is to conduct a systematic review of the literature to evaluate the association between pregnancy outcomes and traffic-related air pollution. Key issues include (1) multiple exposure surrogates are used to measure traffic-related air pollution, (2) composition of the traffic-related pollution changes over time, (3) many of the exposure surrogates also generated by sources other than traffic, and (4) synthesis of the international literature is complicated by differences in the composition of the vehicle fleet.

The specific aims of the project would be to develop hazard identification conclusion(s) for the association between traffic-related air pollution and pregnancy outcomes, and if insufficient data exist, to write a state-of-the-science paper on the topic.

The pregnancy outcomes to be included would be pregnancy complications, congenital malformations, fetal growth, preterm birth, perinatal mortality, and postnatal (infant) mortality. The OHAT team would work with technical advisors and an evaluation design team to refine the exposures included in the evaluation and consider statistical approaches to compare the effects of the various exposure metrics. The evaluation would be conducted using the OHAT Approach.

B. BSC Discussion

Dr. Birnbaum asked whether the evaluation would be restricted to vehicles and not include rail or ship traffic. Dr. Howdeshell clarified that the evaluation did not include rail or ship traffic. Dr. Birnbaum asked whether some of the data emerging from personal monitors would be included, since there are currently a fair number of studies, particularly from NIEHS Children's Centers. Dr. Howdeshell said that any study with such data would be included as long as the data were associated with a health outcome.

Dr. Dorman asked for more information on what CDC is doing regarding the topic. Dr. Howdeshell described the recent CDC publication on childhood cancers and air pollution, as well as the CDC pregnancy outcome review. Dr. Dorman questioned the rationale for putting considerable NTP effort into activities overlapping with the CDC pregnancy outcomes review. He said the suite of pregnancy outcomes proposed for evaluation by NTP may be broader, but that may or may not be worthwhile. Dr. Howdeshell said the exposure paradigm being proposed is different from the CDC's.

Dr. Dorman asked what the analytic metric would be for the effects of exposure surrogates. Dr. Howdeshell said the evaluation would be focused on looking at correlations, but its development has not gotten to the point of having specific plans for analysis metrics or data interpretation. Dr. Dorman asked how "traffic-related air pollution" would be defined. Dr. Howdeshell explained the reasoning for using that term, but acknowledged that it may be useful to adjust the title of the project to "ambient air pollution," instead of "traffic." Dr. Birnbaum noted that there is a distinction between the two terms in the literature and that the concept's title has no reference to children's health, but rather pregnancy outcomes. Dr. Howdeshell said "adverse pregnancy outcomes" was identified in the nomination.

Dr. Peterson asked about the role of tobacco smoke exposures. Dr. Howdeshell said that all such confounders would be identified and acknowledged.

Dr. Sobrian felt the OHAT group had taken on a daunting subject and expressed concern regarding the analysis plans. She asked about the literature on sound stress and sound pollution, noting that noise pollution was not listed as a possible confounder. She said the draft concept included a large number of independent and dependent variables, and a wide range of confounders, and asked how all of these factors would be handled. Dr. Howdeshell said those are broad questions, which have not been worked through by the evaluation team, and all potential confounders would be identified. She said a sub-analysis of the data might be conducted.

Dr. Thayer described how the OHAT Approach works with confounders to evaluate an overall body of evidence. She said one factor to be considered would be unexplained inconsistency, which would require more careful analysis of the data to identify factors that might account for it. The data extraction process is comprehensive in terms of characterizing confounders.

Dr. Sobrian noted that the exposures described in the HEI study were from a decade prior to its publication and asked how that issue would be addressed. Dr. Howdeshell said the literature

review could be broken down by time period. Dr. Sobrian said that with a maximum of 300 papers, she would start worrying about the numbers when so many confounders must be incorporated into the analysis.

Dr. Dorman asked about the main hypotheses being proposed, and specifically the "other health effects" mentioned in the concept document. He questioned whether neurological effects would be considered. He described drug-induced effects in asthmatic children from their inhaled medications as a potential co-exposure. Dr. Howdeshell replied that if the decision were made to pursue neurological outcomes, it would be brought to the BSC as a separate concept. She said the HEI study did not include human studies of neurological outcomes, but did discuss the toxicological literature.

Dr. Birnbaum noted that there is currently public health concern about various adverse health effects associated with exposure to traffic-related air pollution. She asked whether OHAT would evaluate pregnancy-related outcomes first, and then potentially move into some of the other areas of concern, such as developmental neurotoxicology, asthma, and/or obesity and diabetes. Dr. Howdeshell confirmed that as the current OHAT plan.

Dr. Dorman asked whether the NTP would still perform the evaluation if the CDC study evaluating pregnancy outcomes had been available and had not detected a very strong signal. He suggested waiting for the CDC report's release, and then proceeding accordingly. If this path is followed and the CDC evaluation does not identify a strong signal for pregnancy outcomes, Dr. Thayer said the BSC would be asked to consider whether NTP should continue with the proposed evaluation or perhaps have a different focus.

Dr. Sobrian said the potential for the CDC study to inform NTP's direction is one of the reasons she assessed the concept as being of low or medium priority at this time. She reiterated that waiting might provide a better outlook about what other endpoints to address. Dr. Chapin mentioned that he was not familiar with the CDC's review process, but that he had not seen any as comprehensive or balanced as OHAT's. Thus, he felt that regardless of CDC's findings, the OHAT evaluation would likely uncover additional considerations, or do a good job of identifying and weighing confounders. Even if the end product is only a state-of-the-science paper, he said, it would still move the field forward and be valuable.

Dr. Dorman, first discussant, described the wide range of pollutants being considered, said he did not understand the rationale for the choices, and asked for more explanation. He felt that the pregnancy outcomes being considered were also not well defined. More clarification in both of those areas would be necessary to evaluate how responsive the NTP is to the initial nomination. He felt the proposed evaluation is relevant to the overarching goals of the NTP, and that it would be a good use of the OHAT Approach. He was unclear on how the effort is coordinated with other DHHS and/or governmental entities such as EPA and CDC. He found it problematic that OHAT would depart from inclusion/exclusion criteria used by other agencies, which might lead to confusion, and called for clear identification of what constitutes "traffic-related air pollution." Regarding the scope of the proposed evaluation, he noted that the concept identifies several specific aims that could be pursued through the systematic review

process, and identified numerous technical areas to address. He reiterated that he was struggling with what the analytical approach would be to delineate the different surrogates. He was concerned about historical changes in traffic-related air pollution in the U.S. and worldwide. He was unsure how developmental toxicology studies would be used, as most are single-agent studies versus the complex mixtures in air pollution. He gave the study "moderate" priority, being unsure about how it would further existing knowledge beyond HEI and CDC efforts. He said his support would be higher if the issue of exposure surrogates were better addressed. There are many other stressors that should be taken into account as potential confounders.

Dr. Sobrian, second discussant, rated her priority for the project as "moderate, at best."

Dr. Thayer asked whether the priority would change if the focus were a different health outcome. Dr. Sobrian said it would not. Dr. Dorman said that his enthusiasm might rise in that case, but a more focused question would be needed. He added that a more defined approach would even potentially raise his support for the current proposal.

Dr. Markowitz said he did not understand Dr. Dorman's points about defining the exposure better, narrowing the focus, and excluding other types of exposure up front. Dr. Dorman said the plan was not to simply look at traffic measures, but a number of other metrics as well. Dr. Howdeshell said OHAT was planning to review the literature on several types of exposures. Dr. Dorman said how OHAT defines traffic-related air pollution is not clear. He was fine with including the other exposures, but in that case it should not be called "traffic-related air pollution." He said the scope needs to be more clearly defined.

Dr. Bucher said the current discussion had been very helpful and the issues raised by the BSC would be communicated to the nominator, which was originally a pediatric environmental health group.

Dr. Peterson summarized the discussion, saying that in its current form, the BSC felt the priority was low-to-moderate, due to insufficient clarity about the exposures and how the overall review would be focused.

Dr. Birnbaum said the discussion reflected the issue of complex mixtures and the challenges they represent to environmental health science. She added that despite potential differences in the composition of air pollution in different geographic regions, identifying consistencies across regions could be informative.

Dr. Birnbaum thanked the BSC for its constructive comments, and noted that it can be difficult to evaluate a draft concept. Dr. Dorman said part of the problem might lie with the charge questions, which take the reviewers farther into the process than what may be applicable at the concept stage. He suggested instead asking the BSC for input on the technical issues to be considered, and for help defining the next steps in the process, i.e., a more iterative approach. Dr. Walker noted that the current approach for BSC review of concepts stems from the testing program; there was internal debate about when to involve the BSC, but stressed the importance of the BSC's feedback. Dr. Bucher added that it was at this stage when the most public

comments would be expected. The NTP would work toward determining the best timing for BSC involvement.

Dr. Udasin, citing the HEI report, said she would support a higher priority if the focus of the project were narrowed.

Dr. Peterson said that given the BSC's comments it would be valuable for OHAT staff to consider what kind of feedback they want. She noted that many questions remain about the project.

XVI. Adjournment

Dr. Bucher thanked the BSC and the NTP staff for their excellent contributions and hard work during the meeting. Dr. Peterson adjourned the meeting at 11:30 AM on April 18, 2014.