National Toxicology Program

Board of Scientific Counselors

Summary Minutes

June 21-22, 2012

National Institute of Environmental Health Sciences

Research Triangle Park, NC

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I. Frequently Used Abbreviations and Acronyms

AZT	zidovudine
BPA	bisphenol A
BSC	Board of Scientific Counselors
CDC	Center for Disease Control and Prevention
CERHR	Center for the Evaluation of Risks to Human Reproduction
CEBS	Chemical Effects in Biological Systems Database
DIR	Division of Intramural Research
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HHS	Health and Human Services
HPV	high production volume
IARC	International Agency for Research on Cancer
ILS	Integrated Laboratory Systems
IRIS	Integrated Risk Information System
MSDS	material safety data sheet
NAS	National Academy of Sciences
NHL	non-Hodgkin's lymphoma
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
ORoC	Office of the Report on Carcinogens
OSHA	Occupational Safety and Health Administration
PCP	pentachlorophenol
PETA	People for the Ethical Treatment of Animals
POP	persistent organic pollutant
PPARα	peroxisome proliferator-activated receptor alpha
RCT	randomized clinical trials
RoC	Report on Carcinogens
RFA	Request for Application
SR	systematic review
TCE	trichloroethylene
TRI	Toxic Release Inventory
TR	Technical Reports

II. Attendees

BSC Members in Attendance:

Robert Chapin, Pfizer
David Dorman, North Carolina State
David Eastmond, University of California – Riverside (Chair)
Dale Hattis, Clark University
Dana Loomis, University of Nebraska Medical Center (by telephone for RoC concepts only)
Melissa McDiarmid, University of Maryland School of Medicine
Richard Miller, GlaxoSmithKline
Lisa Minor, *In Vitro* Strategies
Sonya Sobrian, Howard University
Judith Zelikoff, New York University School of Medicine

BSC Members not in Attendance:

Elaine Faustman, University of Washington
Stephen Looney, Georgia Health Sciences University

Other Federal Agency Staff:

Paul Howard, U.S. Food and Drug Administration (FDA)
Gayle DeBord, National Institute for Occupational Safety and Health (NIOSH)
Beth Whalen, NIOSH

National Institute of Environmental Health Sciences (NIEHS) Staff:

Scott Auerbach	Kembra Howdeshell	Andrew Rooney	Michael Waalkes
Linda Birnbaum	Gloria Jahnke	Robert Sills	Nigel Walker
Jack Bishop	Angela King-Herbert	Diane Spencer	Lori White
John Bucher	Ruth Lunn	William Stokes	Kristine Witt
Raj Chhabra	Robin Mackar	Kristina Thayer	Mary Wolfe
Michael Devito	Scott Masten	Ray Tice	Rick Woychik
Paul Foster	Deborah McCarley	Velvet Torain	
Michelle Hooth	Barry McIntyre	Molly Vallant	

Public:

David Allen, Integrated Laboratory Systems (ILS)
Nancy Bordelon, Battelle
Alka Chandna, People for the Ethical Treatment of Animals (PETA, by telephone)
Milton Hejtmancik, Battelle
Ernie Hood, Bridport Services
Marc Jackson, ILS

June 21, 2012

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met June 21-22, 2012, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Dr. David Eastmond served as chair. He welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. He welcomed new BSC members Drs. Robert Chapin, David Dorman, Dale Hattis, and Sonya Sobrian, who were present, and Dr. Jack Harkema, who would attend the next BSC meeting in December 2012. Dr. Lori White, BSC Designated Federal Officer, read the conflict of interest policy statement.

IV. Report of the NTP Director

A. Presentation

Dr. Linda Birnbaum, Director of NIEHS and NTP, updated the BSC on developments regarding the NIEHS Strategic Plan, which will provide direction for NIEHS for the next five years. She reported that the plan is basically done, with the three major phases having been completed, and the focus is turning now to implementation. She noted that it had been a very different Strategic Plan development process, being extremely inclusive, with multiple opportunities for all stakeholders to participate. She credited Drs. Rick Woychik and Sheila Newton for their hard work in getting the plan done.

She summarized the 18-month process, including the broader themes and the eleven strategic goals that emerged during the process and were ultimately included in the Plan. She went through the goals, noting that almost all of them involve multiple themes.

She said that the Strategic Plan is currently available on the NIEHS website. The implementation strategies are now being devised, which will determine "what we will do, when we will do it, and how much it will cost." The NIEHS divisions have developed implementation strategies to advance the plan's goals, and NIEHS leadership has been meeting to consider the implementation strategies, identify areas of collaboration, and set Institute priorities. Those deliberations will provide a framework for budgetary allocations by leadership.

B. BSC Discussion

Dr. Melissa McDiarmid asked about the possibility of collaborations with other agencies in exposure assessment. Dr. Birnbaum said NIEHS couldn't do everything in environmental health sciences by itself, so collaborations would be conducted in the future. Exposure science needs more investment by NIEHS, so there may be new investment in that area going forward. Dr. Birnbaum confirmed for Dr. Howard that both the extramural and intramural programs would receive such investment, probably more in Funding Opportunity Announcements than in new Request for Applications (RFAs), which require certain amounts of money to be set aside and fall within specific time windows.

Dr. Dorman asked how strategic planning was being informed by the relatively low rates of funding for the extramural programs, with the threat that poses to existing and emerging programs from the academic stakeholders. Dr. Birnbaum said interested parties could read the Strategic Plan; implementation plans would be available shortly. She noted the extramural branch puts out RFAs if there is an interest in moving into a particular area, with associated workshops to further explore the topic. She cited the example of current interest in the intersection between environmental chemical exposures and infectious disease, about which a workshop was held in 2011, with an RFA forthcoming. The extramural community will have many opportunities to learn about the new areas of research for NIEHS, and the extramural program officials are always happy to speak with members of the academic community about funding directions.

Dr. Birnbaum added that NTP has a unique mission, and the ways to accomplish that mission would naturally change over time.

V. Contract Concept Review: Genetic Toxicity Testing (ACTION)

A. Presentation

Ms. Velvet Torain, NIEHS Office of Acquisitions, provided the BSC with NIH guidelines for conducting project concept reviews. Ms. Kristine Witt, Biomolecular Screening Branch, presented the Genetic Toxicity Testing concept for review to the BSC. She noted that NTP has been conducting genetic toxicity studies using a contract mechanism since 1979. Findings from NTP genetic toxicity studies are considered authoritative worldwide. These studies have generated a large database, comprised of 5492 assays completed since 1979, which is available to all researchers and regulatory scientists. All chemicals that enter NTP testing are evaluated for genotoxicity using the existing contract. The contract assists NTP, NIEHS, and other governmental scientists in evaluating chemical toxicity and investigating mechanism of action. Genotoxicity data are considered in developing NTP test strategies, and are included in all NTP Technical Reports (TRs) as well as in chemical evaluations conducted by the Office of the Report on Carcinogens (ORoC). The data also appear in most toxicity databases and predictive software packages.

She described the evolution of genetic toxicity testing at NTP since the initial test battery used from 1979 through 2000. The current approach employs bacterial mutagenicity assays, *in vivo* mouse and rat peripheral blood erythrocyte micronucleus assays, *in vivo* mouse and rat comet assays, and *in vitro* micronucleus and comet assays using non-human cell lines. Under the new contract, study capabilities would remain the same, with the following additions: (1) the capability to evaluate endpoints of genotoxicity in human cell lines *in vitro, (2) t*he capability to evaluate endpoints of genotoxicity in human blood samples that may be provided by collaborating laboratories, (3) an *in vivo* mammalian cell mutagenicity assay (*Pig-a* assay), and (4) a more flexible research and development component

She cited the examples of zidovudine (AZT) and methylphenidate studies as projects that would have benefited from the capability of evaluating genotoxicity in human cells and human cell samples. Noting that the NTP has a continuing need to conduct *in vitro* and *in vivo* genetic

toxicity studies and seeks to expand its current testing approach, Ms. Witt stated that NTP seeks approval from the BSC to continue these activities using a contract mechanism.

B. BSC Discussion

Dr. Lisa Minor, first lead reviewer, considered the modification of the proposal to include human testing and increase its research capabilities quite important and necessary to meet current standards. She asked Ms. Witt whether increasing throughput through the use of multiwell assays was part of the proposal. Ms. Witt replied that although some endpoints related to genotoxicity are examined as part of the NTP's High Throughput Screening (HTS) program, typically a large number of chemicals are not tested simultaneously in a genetic toxicity assay, so high throughput capability is less relevant to this contract. Dr. Minor asked if NTP requests data from laboratories responding to a Request for Proposal to help evaluate their suitability for conducting the required assays. Ms. Witt said laboratories would be asked about their experience and capabilities in terms of the desired assays.

Dr. Chapin, second lead reviewer, recognized that a thorough and state-of-the-art evaluation of the genetic hazard of a compound is an appropriate part of any total evaluation of a compound. He said it should be a continued part of that process within NTP's mission. He asked who uses NTP data, such as the State of California, International Agency for Research on Cancer (IARC), or the Environmental Protection Agency (EPA). Ms. Witt replied that all of those entities use NTP data. Dr. Chapin felt the proposal undersells the wide impact of NTP data, and suggested including more examples in future presentations of this nature. He asked if the AZT data had changed prescribing habits. Ms. Witt said it had not, but had highlighted the need to monitor children who were transplacentally exposed to the compound. She cited an ongoing study that is currently doing so. He recommended that the next contract focus on the most effective endpoints and assays, and said he liked the concept of having a methods development component in the contract.

Dr. Minor noted that the group publishes a great deal, and asked if the number of citations on NTP publications were tracked. Ms. Witt replied that she had not tracked this information.

Dr. Judith Zelikoff asked for more information on the contract effort dedicated to assay development. Ms. Witt said it was defined as an overall percentage of the contract sufficient to allow the group to maintain state-of-the-art approaches in testing. Dr. Zelikoff inquired about the reliability, validation status, and regulatory acceptance of the *Pig-a* assay. Ms. Witt said the assay has been undergoing validation at 14 laboratories around the world for the past four years, and has shown an outstanding ability to detect mutations. The international genetic toxicology community has been enthusiastic about the *Pig-a* assay, and is incorporating it as a standard approach to evaluating *in vivo* mutagenicity. Ms. Witt said the assay had not yet been formally adopted, but several pharmaceutical companies are involved in the validation process and the FDA has been enthusiastic about it. The validation process should be complete later in 2012, at which time adoption should take place by various regulatory agencies. Dr. Paul Howard concurred regarding the universal acceptance of the *Pig-a* assay and noted that the

entire December 2011 issue of the journal *Environmental and Molecular Mutagenesis* was devoted to the assay.

Dr. Dorman asked about the absence of discussion about the use of partial or whole genomic data to identify genetic risk factors. Ms. Witt said there is in-house genomic studies capability, as well as groups that are studying environmentally related diseases, at NIEHS.

Dr. Hattis supported the effort to extend the assays into human tissues and asked what adducts might be derived from human DNA, to begin the process of tracing those adducts to exposures. Ms. Witt said tracing adducts are being done in animal studies, and that it would make sense to do the same in human studies as well. Dr. Bucher added that the idea fits with NIEHS' Strategic Goal extending NIEHS/NTP activities into exposure assessment. One of the goals of the Tox21 program is to change from single gene investigations to multiplex genomic platforms to look at systematic biological changes in cells, in response to thousands of chemicals.

Dr. McDiarmid asked whether this would be a single, overarching contract with the assumption that the responders could get the partners needed to conduct human studies, or whether the contract might allow for more flexibility in terms of the vendors. Ms. Witt said that previously human samples had been made available by collaborating laboratories, and that approach would likely be continued under the new contract. The NTP would not want to enter into a clinical trials approach, unless it was in conjunction with studies conducted by Division of Intramural Research scientists through the NIEHS Clinical Center.

Dr. Dorman asked whether there would be a tissue repository maintained for the tissues used under the contract, particularly the human tissues. Ms. Witt noted the NTP has a huge archive of animal tissue and to extend it to human samples would make sense. Dr. Bucher added that the NTP Epidemiology Group also has a large number of samples banked from their studies.

Dr. Eastmond said that as a genetic toxicologist, he has found the NTP's work in the area to be quite valuable, particularly in chemical carcinogenesis. He asked whether the current or proposed contracts provide sufficient flexibility to pursue some of the newer types of analyses. Ms. Witt replied that there is a certain amount of flexibility in the current contract, but that the increase in flexibility in the new contract would allow NTP to take advantage of any new technologies that emerge, and even to lead in the development of some of the new methods.

Dr. Minor asked about the duration of the proposed new contract. Ms. Witt said that it is slated to run five to seven years.

Dr. Eastmond said that it would also be important to re-examine some of the existing genetic toxicity methods, filling in the background information for some of the current standard tools such as the enzyme levels in induced rat liver S9. Dr. Minor moved to approve the contract concept and Dr. Chapin seconded the motion. The BSC voted unanimously (8 yes, 0 no, 0 abstentions) to approve continuing this activity using a contract mechanism.

VI. Environmental Enrichment in NTP Studies

A. Presentation

Dr. Angela King-Herbert, Cellular and Molecular Pathology Branch, briefed the BSC on modifications to the NTP animal care and use program to include environmental enrichment in NTP rodent studies. Environmental enrichment can be defined as any measure that promotes expression of natural species-specific behavior and a decrease in or disappearance of abnormal behaviors. NIH policy is driven by *The Guide for the Care and Use of Laboratory Animals*, 8th edition (*The Guide*), which was adopted January 1, 2012. Major changes in the 8th edition include a section on environmental enrichment for all species. Also, the NIH Animal Research Advisory Committee has suggested guidelines for housing rats and mice in the laboratory, which include socially housing whenever possible, housing mice on nestable bedding, and providing rats with increased structural complexity. Dr. King-Herbert described the natural behaviors of the rodents under consideration for enrichment, noting that enrichment programs should be based on those behaviors. Ultimately, environmental enrichment will allow animals to better cope with environmental stressors. She showed the BSC several examples of enrichment items for rats and mice and described plans to enhance NTP's current enrichment strategies, which are to be phased in over a period of time, starting with short-term range-finding studies, followed by 90-day studies and then 2-year studies. Enrichment items are to include natural crinkled kraft paper for rats and mice and polycarbonate rectangular shelters for rats. Studies will also be conducted to assess practical considerations for environmental enrichment in inhalation studies.

B. BSC Clarification Questions

Dr. Hattis asked whether the NTP tests plastic enrichment materials for releases of plasticizers or polymers. Dr. King-Herbert said contaminant screening would include plasticizers. Dr. Bucher added the NTP is very aware of bisphenol A (BPA) issues, and that polycarbonate cages and enrichment devices would be looked at very carefully for any signs of wear or clouding that may presage BPA release.

Dr. Chapin said he was less concerned about inhalation or dermal exposures related to enrichment devices, but more concerned about gnawing behaviors. Dr. King-Herbert said there is anecdotal evidence but no studies indicating that gnawing was a problem. She said the NTP is aware of the issue and will monitor it as polycarbonate materials are phased in. Dr. Chapin asked whether organizations would be able to opt in or opt out of the use of enrichment within the animal care and use protocol. Dr. King-Herbert said investigator would have to opt out, and would need to provide a justification for doing so.

Dr. Zelikoff asked about the possibility of the nestlets and/or crinkle paper having estrogenic properties. Dr. King-Herbert said the NTP is not considering nestlets and would be alert to the potential for estrogen exposures from the crinkle paper. Dr. Zelikoff said the NTP should be aware of any potential estrogenicity in the enrichment material used in any reproductive or immunological assays.

Dr. Sobrian noted that many of the changes found with enrichment are sex-, strain- and age-dependent. She asked whether any pilot studies were planned to explore strain-related differences. Dr. King-Herbert said the F344 rat is rarely used at NTP, and that the default rat strain is currently the Harlan Sprague-Dawley, which have been the subjects of many studies of the effects of enrichment devices. Dr. Sobrian asked whether reported physiological changes have been considered. Dr. King-Herbert confirmed that many of those parameters would be evaluated to help determine the impact of the devices.

Dr. Richard Miller asked for clarification on how the test article might influence the enrichment paradigm for any given study. Dr. King-Herbert replied that test articles would be considered for their potential impact, citing the example of a study of plasticizers precluding the use of polycarbonate materials. Dr. Bucher added that study design teams would need to consider the potential for interaction between test articles and enrichment devices. Dr. Birnbaum observed that the use of these new approaches would stress the importance of the concurrent controls as opposed to historical data.

Dr. Minor asked if there had been any evidence of an impact on dose response in solid-bottom cages due to animals eating their feces. Dr. King-Herbert said she was not aware of any studies indicating that. Dr. Howard said it is not currently in the guidelines to use wire-bottom cages, so the coprophagia is a possibility.

Dr. Dorman asked about the watering system in use when housing rats with the enrichment devices. Dr. King-Herbert said depending on the type of study, a water bottle or an automated watering system might be used. One reason for the phasing in of the use of the devices is so adjustments could be made as studies are ongoing

C. Public Comment

Dr. Alka Chandna, People for the Ethical Treatment of Animals (PETA), commented by telephone. She noted that the use of social housing and environmental enrichment are important both from the perspective of animal welfare and from the perspective of minimizing confounding variables in data. She said PETA appreciated Dr. King-Herbert's preparation of the environmental enrichment report, and the fact that she had included references to numerous studies that document psychological, physiological, and behavioral improvement in the wellbeing of animals when enrichment devices are implemented. PETA requests that the detailed guidelines for environmental enrichment, which are currently under review, be made public, with explicit guidelines for a variety of specific areas. It has been PETA's experience with various companies that a "mish-mosh" of enrichment is being provided, without checks and balances to ensure the various species-specific requirements are being met. PETA is concerned about some of the language used in the initial description of environmental enrichment at NTP, which alluded to the issues of economics and human convenience related to environmental enrichment. She noted *The Guide* calls for use of enrichment devices even if they necessitate additional staff time or monetary expense. PETA hopes that investigators conducting NTP studies will make a concerted effort to address the species-specific physiological and psychological needs of animals.

D. BSC Discussion

Dr. Miller, first lead reviewer, said environmental enrichment seems like a very simple concept on the surface, but is actually very challenging. He suggested conducting workshops on best practices, particularly with so many biomedical organizations in the Research Triangle Park area that might share the concern. He recommended gradual implementation of enrichment and careful documentation during studies of what happened and why changes might be made.

Dr. Sobrian, second lead reviewer, asked whether the enrichment would take place from weaning through adulthood. Dr. King-Herbert said studies begin right after weaning, and that is when the animals typically arrive at the testing facility, so that would be when enrichment begins. Dr. Sobrian pointed out that the literature reveals that some institutions provide enrichment of limited duration, as little as 2 hours a day, Monday through Friday. She said that concept might be useful to consider in some of the inhalation studies. She reiterated that there are some major differences in sex and strain results related to enrichment. She endorsed the idea of enriching breeding pairs and recommended the collection of data. She agreed that historical controls may not be useful, and that good record keeping would be essential.

Dr. Dorman, third lead reviewer, endorsed the use of environmental enrichment, but noted that it seems to concentrate on housing enrichment, while there is a totality of other aspects that should be considered. Dr. King-Herbert clarified that the social housing requirements are already part of NTP prescribed protocols. Dr. Dorman said one of the challenges will be what metrics of performance will be used to give the scientific community a sense that there is control and understanding of changes in the large historical database, because that is one of the enormous strengths of NTP. He suggested it might be useful to consider which studies might be more impacted by the use of environmental enrichment, and that modest changes in study design, such as use of increased number of animals, might be helpful to offset that impact.

Dr. Dorman advised to chose the correct metrics to assess what changes should be made and when. He said it would be critically important to look at a broad range of responses including P450 expression and stress hormone reactions. He mentioned caveats concerning coprophagia and urinary elimination and noted the potential for ergonomic effects on animal care staff resulting from changes related to environmental enrichment. He questioned to what extent enrichment devices might lose their impact over time, particularly as they are employed in 2-year studies. He noted that rotation of devices might be a two-edged sword, as the change in environment may turn out to be a stressor in itself. He also pointed out that the addition of enrichment devices might impact cage open square footage requirements. He felt the addition of the shelf unit in inhalation studies could become challenging, as animals could use it as a lounging area, potentially changing activity levels and respiration rates. He also recommended pilot studies exploring the issue of cage environment and temperature homeostasis in rodents as a potential confounder.

Dr. Zelikoff concurred with Dr. Dorman regarding whole body inhalation studies and the use of a shelf unit, which, she pointed out, could also absorb gases or particulates.

Dr. Chapin noted that all changes to be measured would not necessarily be bad – some would be normalization away from the conditions that research animals have been kept for the last fifty years. He expressed full support for environmental enrichment and noted that determining fecal corticosterone concentrations would be a good, non-invasive biomonitor for changes in the stress levels of individual animals.

Dr. Howard supported the environmental enrichment effort, but cautioned that there could be unintended consequences, including the release of known, or perhaps unknown, contaminants. He said the paper used should be carefully considered, in that it is typically a complex mixture. The potential consequences of the effort should be carefully considered, as they could invalidate studies in some instances. He was concerned that it might invalidate or weaken the power of the NTP historical controls database, which could have a direct bearing on prior or future decisions. He applauded the initiative, but cautioned that NTP should move slowly and carefully and perhaps include control groups with environmental enrichment in some upcoming studies to assess whether there is any change in historical controls within a study. Dr. King-Herbert said including a group with unenriched cages would be considered in pilot studies.

Dr. Miller thought the historical control database would become less valuable, but agreed that the enrichment must be done. He said that short of having a non-enriched concurrent control in every study for years to come, the compromise of the historical control database would be unavoidable. Dr. Birnbaum said it would be extremely expensive to provide a non-enriched concurrent control in every study, but it would need to be done at the beginning of the effort.

Dr. Nigel Walker noted the NTP had changed the standard rodent diet in the late 1990s, creating a transition period in which the historical database was rebuilt. The default rat strain was also changed, with a subsequent diminishment and rebuilding of the historical database. He said the historical database is a rolling 5-year database, and so it would eventually include enrichment.

Dr. Eastmond noted the overall strong support from the BSC for moving forward with the project. He noted the BSC's caveat about being cautious, at least initially, but said the effort needs to be done. He said that as it goes forward, a valuable historical record would be built up. The key point, he said, was that NTP be diligent in its record-keeping, carefully documenting the changes being made.

VII. Report on the NTP Technical Reports Peer Review Panel Meeting, February 8-9, 2012

A. Presentation

Dr. Michelle Hooth, Toxicology Branch, briefed the BSC on the NTP Technical Reports (TRs) Peer Review Panel Meeting that took place at NIEHS February 8-9, 2012. She said the panel had reviewed five chronic studies and two studies of shorter duration conducted in genetically modified mouse models. The charge to the panel was to review the scientific and technical elements of each study and its presentation, and to determine whether the study's experimental design, conduct, and findings support the NTP's conclusions. She provided an overview of the

level of evidence categories, to provide the context for her subsequent summary for each compound, which included information on its use, the draft NTP conclusions for each sex and species, and the panel's recommendations. She noted that TRs are revised and finalized following review and consideration of the panel's comments, public comments, and audit findings, with the possibility that additional data or analyses may be included in the report as they become available. All NTP staff recommendations are still under consideration by the NTP Associate Director and Director, who will make the final decisions.

B. BSC Discussion

Dr. Eastmond asked if 45-week studies are now being routinely conducted with the p53 heterozygous mouse model, rather than 26-week studies. Dr. Bucher said the 45-week study was found to be more sensitive than the 26-week study, and seemed to be right for that model.

Dr. Miller, BSC liaison to the TR Peer Review Panel Meeting said he felt the panel had done a good job and the process had gone well. He noted there were debates during the meeting, with thorough discussions, and that he was satisfied with how the issues were resolved.

Dr. Eastmond commented that by dealing separately with adenomas and carcinomas, the two combined, along with hepatoblastomas, the combination of all three, and hepatocholangiocarcinomas, there arises a risk of multiple comparison or comparison-wise Type 1 errors, which could affect the quality of the calls, which are very important. Dr. Bucher agreed, particularly regarding data from the mouse liver, where the background rate is fairly high and variable. Thus, background rates should be considered in relation to the stage of malignancy in the tumors being dealt with, looking at it as a continuum. He said the selection of the most appropriate combination and the most appropriate statistical evaluation is very difficult, and something NTP has struggled with.

VIII. Report on Carcinogens (RoC) Concepts

A. Introduction

Dr. Ruth Lunn, Office of the Report on Carcinogens (ORoC), briefly summarized the new RoC process and defined the RoC monograph and concept documents; the concept lays out the approach for preparing the monograph. She reported that the updated process for preparation of the RoC was released in January 2012 following input from the BSC and the public. Among the key elements of the process are opportunities for interagency or external scientific input, for public comment, and peer review of the monograph. The four major steps in the process are nomination and selection of candidate substances, scientific evaluation of candidate substances, public release and peer review of draft RoC monographs, and HHS approval and release of the latest edition of the RoC.

Dr. Lunn said the NTP is currently in the first stage of the process, nomination and selection of candidate substances, and noted that anyone can nominate a substance. The NTP solicited public comment on 15 nominated substances in January 2012, and has now developed draft concepts for five substances proposed for review.

She described a monograph as consisting of two major components, the cancer evaluation component and the substance profile, which includes the preliminary listing recommendation and discussion of the key evidence used to reach that recommendation. The approach for developing a monograph is tailored to the complexity of the substance, and is outlined in the draft concept document for that substance.

Dr. Lunn went over the elements of a draft concept. She noted that it provides only an overview of the types and scope of the available studies and does not provide detailed information on the studies; it does not evaluate the scientific information or make a recommendation for listing status. The ORoC will establish a website for each candidate substance and the NTP listserv will be used to communicate when new information is added to the website. The NTP will use a variety of mechanisms to obtain scientific and public input including technical advisors, information groups, *ad hoc* presentations, and listening sessions. She detailed the types of approaches that would be employed for the five candidate substances to be considered at the meeting. Following the BSC meeting, the NTP will evaluate comments from the public and the BSC, and the NTP Director will finalize the list of candidate substances. The ORoC will revise the concept documents based on the comments, and will initiate the cancer evaluation component of the process.

B. BSC Discussion

Dr. Eastmond noted that under the new process, the BSC would now be at both ends of the process – very early, and then again fairly late.

Dr. Dorman asked if the new process changes the timeline, and if it is an improvement over the previous process. Dr. Lunn said the purpose of the concept is to get input early in the process so the NTP will know it is heading in the right direction and not wasting time by missing key elements. Dr. Bucher said he did believe it is an improved process, noting that the creation of the RoC Monograph meets a need that was unclear in the prior process. The background document that was part of the prior process did not lead to a listing decision. The RoC Monograph, on the other hand, includes all of the relevant information along with assessment and evaluation of the information in a clear way to see how a listing recommendation was reached. The other big advantage is that the new process does not lock NTP into one process for every chemical evaluation; this allows information gathering tailored to the complexity of the database involved. Dr. Eastmond added that another change is ample opportunities for public comment throughout the process.

Dr. Hattis asked whether there had been consideration of adding a mode of action hypothesis section to the concept document. Dr. Lunn said that element would be developed later as part of the cancer evaluation.

Dr. Eastmond asked why only NTP advisors were to be consulted for cumene, as opposed to outside technical advisors. She replied that the literature search had revealed that most of the expertise for cumene is within NTP.

C. Pentachlorophenol

Dr. Gloria Jahnke, ORoC, presented the pentachlorophenol (PCP) draft concept. PCP and its sodium salt are polychlorinated phenols primarily used as wood preservatives. It is a restricted use pesticide used primarily in treatment of utility poles, cross-arms, railroad ties and wharf pilings. It is proposed as a candidate substance for the RoC based on widespread past and current U.S. exposure, and an adequate database of studies in humans and animals for evaluation of its potential carcinogenicity. One U.S. company produces an estimated 3 million pounds annually of PCP, which is available in both technical grade and commercial grade (which contains approximately 90% PCP plus contaminants formed during production). IARC (1991) and the U.S. EPA Integrated Risk Information System (IRIS, 2010) have conducted authoritative reviews of PCP, and NTP has received one public comment related to disagreement with IRIS conclusions. In human cancer studies, the tumor sites of interest are non-Hodgkin's lymphoma (NHL) and soft tissue sarcoma. Recent studies, including cohort studies and case-control studies, have focused on PCP exposure involving both PCP production workers and PCP users, with potential co-exposures in both groups. Dr. Jahnke reviewed the experimental animal studies, both in technical grade and commercial grade PCP with its contaminants, along with data from NTP studies of pure PCP, which still included some impurities. She went over the metabolism and mechanistic data, and described the key scientific questions relevant for cancer evaluation: what are the levels of evidence of carcinogenicity from human and animal studies, what are the tissue sites of cancer, can the effects of contaminants be separated from the effects of PCP, what are the potential modes of action, and does the mechanistic data support the findings in experimental animals or humans.

The approach proposed by NTP to answer those questions includes a web-based public symposium to receive public and scientific input on human studies and an informational group of scientists to review animal data on PCP and any toxicological data on the contaminants.

When the draft monograph is completed, it will undergo interagency review and be released for public comment. Then, NTP will convene a peer review panel to review the monograph. The panel will consist of members with the appropriate expertise in several areas. Time will be set aside at the peer review meeting for discussion of scientific issues raised in public comments.

D. BSC Discussion

Dr. Eastmond noted that the goal of the concept proceedings was to evaluate the concept and approach in general.

Dr. Dorman asked what might trigger the "future forums to address scientific issues" and expressed concern that it could delay the process if there were no set specifications. Dr. Jahnke said there were no set guidelines, but new data or information on a new approach could trigger a forum. Dr. Bucher added that the concept website would be continuously updated as new data emerged, and that new information would need to be sufficiently significant in NTP's judgment to convene another review group.

Dr. Eastmond asked whether the proposed webinar would be a physical meeting that would be webcast, or whether it would be entirely remote. Dr. Lunn said the format would depend on the

situation, but the webinar would not necessarily be a large public meeting where people would gather physically.

Dr. Minor asked for clarification on where NTP is in the process currently. Dr. Jahnke said an initial literature search for the nomination had been conducted, the major literature search has just started, and public comment on the nomination has been solicited. Dr. Lunn noted that the technical advisors would be identified at the beginning of the process for preparing a monograph, and the web-based symposiums and information groups would be convened to obtain advice for special issues. Dr. Minor asked whether the proposed special forums or webinars would be open to the public or invitation-only. Dr. Lunn said they would be open to the public via the web, and that speakers would be invited to address specific issues related to their expertise.

Dr. Miller, first lead reviewer, said that the information cited indicated that exposure to PCP in the U.S. is significant. He felt the information on carcinogenicity was muddled by the fact that so many of the animal and human studies have a contaminant or co-exposure situation, although that is readily acknowledged in the concept. He said the relevant scientific issues were identified and felt a multi-faceted approach is appropriate, with triggers being defined in progress. The question of separating the effects of PCP alone from the mixtures should be a higher priority in the approach, as well as increased emphasis on metabolites. He said the approach to obtaining input was adequate, as long as metabolism experts were included. His overall rating for the concept was “moderate.”

Dr. Dana Loomis, second lead reviewer, agreed that the information provided indicates there is significant exposure, and that there is adequate information to proceed with the evaluation. He agreed the key issue is the extent to which it is possible to separate exposure to PCP from its contaminants. He wondered whether it might be possible to find human studies in populations exposed to PCP but not the contaminants, or to be able to quantify the relative levels in relevant populations exposed to both. He also wondered about the inherent potential for delays as a result of the complex new process. Overall, he rated the evaluation concept as “moderate.”

Dr. Jahnke said metabolites are looked at for genotoxicity, and that that is part of the literature search. She said there are some studies of workers exposed to PCP but not to some of the other chemicals, so there is a way to separate out some of the co-exposures.

Dr. Dorman noted that in assessing epidemiology studies, there might be some workers exposed to both methods of treating wood, from chromate and copper arsenate to PCP, which could be a confounder.

Dr. Hattis said the potential confounding by co-exposures to TCDD and other dioxins is a quantitative issue, with the need for a plausible range of the co-exposures, including the compounds’ relative potencies. He suggested it might not be possible to identify pure exposures, so it would be more practical to try to measure the ratios of likely exposures and potencies, and perform a fair quantitative uncertainty analysis.

Dr. Eastmond said that because PCP was an uncoupler of oxidative phosphorylation, some toxicity should be expected with the compound, including the possible formation of micronuclei *in vivo*. He suggested when there is EPA IRIS or IARC documentation, a brief summary should be included in the concept document, to give a sense of what was seen. Also, human biomonitoring information should be included. He suggested using TOXLINE for literature searches, since it may contain information not included in PubMed.

Dr. Birnbaum said this was the first time this process had been employed, so there would be a natural learning process involved. She noted that with PCP, exposure in the real world would always be to a technical mix, so there would always be contaminants, which could be as far as the evaluation needs to go.

Dr. Jahnke noted that PCP is quite toxic, and the primary route of exposure is dermal. Dr. Eastmond said there is evidence from other phenols that they can cause micronuclei through non-DNA-reactive mechanisms.

In summary, Dr. Eastmond said that the reviewers had both given the proposal a moderate priority for subsequent review, and that there was concern about the contaminants and the ability to separate out the direct effects of PCP. He noted Dr. Birnbaum's comment that exposures would virtually always be to mixtures, so the question may be more academic than of public health relevance.

Dr. Zelikoff said she would consider PCP evaluation a high priority, and wondered why the reviewers had rated it moderate. Dr. Loomis said he had done so due to relatively low exposure levels, and that new studies were only moderately likely to provide relevant new information. Dr. Miller agreed with Dr. Loomis, and noted that the one animal study showed carcinogenicity at the only highest exposures.

Regarding concern about TCDD confounding, Dr. Hattis said much is known about the tumor sites related to TCDD exposures; that information may be useful to separate the effects of TCDD from PCP.

Dr. Birnbaum and Dr. Eastmond pointed out that in this case, the debate is as to whether the evaluation should go forward. Based on that, Dr. Zelikoff reiterated her impression that the priority should be high. Dr. Miller said that that had been the basis of his ranking, and that he felt there were some other compounds under consideration that should be rated as higher priorities in comparison.

E. Cumene

Dr. Jahnke presented the RoC cumene draft concept. Cumene is a liquid with a gasoline-like odor, primarily used in the synthesis of acetone and phenol. It is a candidate substance due to widespread current and past U.S. exposure, and an adequate database of animal studies for evaluation of its potential carcinogenicity. An IARC review was recently published that classified cumene as possibly carcinogenic to humans. Environmental exposure stems from contaminated air from combustion and evaporation of fossil fuels, release with production, use and transport, and in tobacco products and some foods. The primary route of exposure is

inhalation of ambient air. Occupational exposures occur in production processes in several industries. U.S. production is more than one billion pounds per year. There are no epidemiological studies on human cancer and exposure specifically to cumene, and there is one animal study, an NTP Technical Report from 2009, which showed some treatment-related carcinogenic effects. Dr. Jahnke described other relevant data from metabolism and genotoxicity studies. She described the potential mechanisms of carcinogenesis related to cumene. The key scientific questions relevant for cancer evaluation are: what is the level of evidence (sufficient or not sufficient) for the carcinogenicity of cumene from animal studies, what are the tissue sites, what are the potential modes of action by which cumene may cause cancer, is there evidence that the mode of action is not relevant to humans, what is the level of evidence that renal tumors in male rats are caused by an α_{2u}–globulin-associated nephropathy, and are there other potential mechanisms by which cumene could cause renal cancer.

The proposed approach is to convene a group of NTP scientists with specific expertise on cumene to independently evaluate data relevant to cumene exposure in adult male rats using IARC criteria and the U.S. EPA sequence of events for α_{2u}–globulin nephropathy. Public comments have been requested on the nomination and draft concept, and a RoC website will be established. Future forums may be convened to address any additional scientific issues.

When the draft monograph is completed, it will undergo interagency review and be released for public comment. Then, NTP will convene a peer review panel to review the monograph. The panel will consist of members with the appropriate expertise in several areas. Time will be set aside at the peer review meeting for discussion of scientific issues raised in public comments.

F. BSC Discussion

Dr. Hattis, first lead reviewer, said that exposure is highly likely to be significant, given the chemical's high production volume, although he noted that the term "significant" is not defined in the charge question. He said exposure information would benefit from information about relative exposures based upon production and use of cumene and auto exhaust exposures. He felt the NTP should shift its emphasis from the qualitative issue of whether specific substances have some carcinogenic activity to the quantitative issue of how potent they are likely to be. He suggested assembling information on the comparative pharmacokinetics of cumene in the experimental animals used for the cancer testing and humans, including the generation of DNA-reactive metabolites, adduct formation, and other possible steps in the causal chain for mutagenic versus other pathways to carcinogenesis. He cited industry claims, i.e., Cruzan *et al*., 2009, that the induced lung tumors are "mouse specific" and generated by cytotoxic rather than mutagenic mechanisms. He suggested a careful and quantitative evaluation for their human risk implications. Citing the Hong *et al*., 2008 and Wakamatsu *et al*. 2008 papers, he recommended careful evaluation of the changes in the specific mutations in lung tumors induced by cumene for their mode of action implications. He asked to what extent do the different mutation spectra in cumene-induced tumors indicate a mutagenic mode of action, or are they result of differential selection of the mutated tumor types found to be more prevalent in the cumene-induced tumors. He recommended more emphasis on quantifying the extent and intensity of exposure, in addition to mode of action and potency evaluation to help decision-

makers consider appropriate prioritization for cumene exposure control efforts. In terms of overall significance, he said he could not do so without some quantitative estimation. He said he has the impression that it is important, but could not rate it without a comparative quantitative analysis.

Dr. Dorman, second lead reviewer, said in terms of evaluating exposures to cumene, it might be valuable to tie it in with data from the Gulf oil spill. He noted that this concept and some of the others might benefit from some consideration of the compound's persistence in the environment, as well as non-cancer endpoints that might drive decision-making in whether a compound is significant. He encouraged identification of individuals with specific expertise regarding α_{2u}–globulin nephropathy. He said the scope and focus were appropriate, but was concerned about being able to mitigate the ability of people who will try to delay the process. He was surprised that there was not more discussion about specifically soliciting peer-review comments from within the Federal government. Dr. Lunn replied that interagency review is a part of the process. She also mentioned that some of the technical advisors throughout the process could be interagency advisors. Dr. Dorman rated that the significance of the project as "high."

Dr. Jahnke said there is a plan to discuss CYP2F2 in the document. Regarding the *ras* mutations mentioned in the Hong paper, it was found that the spontaneous tumors were different, lending credence to the possibility that the other tumors were cumene exposure-related. Dr. Hattis agreed that that was the issue. Dr. Birnbaum noted that despite differences between mouse and human CYP mechanisms, they might still be very relevant.

Dr. Miller liked the idea of bringing non-NTP experts into the evaluation process. Dr. Eastmond agreed that although the vast majority of studies had been done by NTP, it would useful to consult outside experts to gain other points of view. Dr. Birnbaum added that with this and other compounds, it would be important to look at them in the context of other structurally related chemicals.

Dr. Eastmond noted that cumene is actually an ultra-high production volume compound, which adds to the importance of evaluating it. Dr. Dorman said it might also be helpful to tie it in with the Toxic Release Inventory (TRI). Dr. Jahnke said they do have TRI data, which was not included in the concept document.

Dr. Hattis mentioned that it was also important that the chemical is in cigarette smoke, in terms of pathway to human exposure. Released indoors, he noted, it has about one thousand times the efficiency of getting into people versus outdoor release.

Dr. Eastmond summarized the discussion, stating that one reviewer felt it was an important compound to follow up on, but would feel more comfortable if there were quantitation to rely upon. The other reviewer gave cumene a high priority. The BSC felt it would be important to follow up on the proposed mechanisms.

G. Trichloroethylene

Dr. Lunn presented the RoC trichloroethylene (TCE) draft concept review. It is a chlorinated alkene used primarily as a metal degreaser. Exposure is widespread, as it is present in the environment, food, numerous consumer products and the workplace. Based on its pervasiveness, it is a potential public health concern, with significant U.S. exposure. Listed since 2000 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from experimental animal studies and limited evidence from studies in humans, is proposed for re-review for the RoC. Over 20 cancer studies in humans have been published since 2000, thus creating the need for re-review for the RoC. There have also been major evaluations since 2000, by the National Research Council (NRC) in 2006, the U.S. EPA in 2011, and the NRC in 2009. Each of those evaluations suggested an association between human exposure to TCE and kidney cancer. Dr. Lunn noted that one public comment received by the NTP disagreed with the EPA's conclusions on TCE carcinogenicity.

TCE is ubiquitous in the environment, and exposure to TCE can stem from inhalation of outdoor or indoor air, ingestion of drinking water and food, volatilization from tap and shower water, and dermally from bathing water. The highest levels are found in the workplace. TCE is a high production volume chemical, with 100 million to 500 million pounds produced annually. Cancer sites of concern are non-Hodgkin's lymphoma (NHL) and cancers of the kidney and liver. The current literature database includes over 75 studies. The mechanisms by which TCE causes kidney, lymphoma, liver, and lung cancer in experimental animals and possibly in humans can be explained in part by its metabolites. Metabolism occurs by two major pathways: oxidation by cytochrome P450 and conjugation with glutathione.

Dr. Lunn briefly reviewed the proposed mechanisms for TCE potential carcinogenicity. She said that cancer evaluation would focus on human and mechanistic data for specific endpoints. The assessment will be limited to NHL, kidney cancer, and liver cancer, and will focus on the human cancer studies and mechanistic data. The level of evidence of carcinogenicity (sufficient) from studies in experimental animals will not be reevaluated, but the findings will be integrated into the overall synthesis of cancer studies in humans and mechanistic data. The key questions and issues to be addressed include: what is the level of evidence of human cancer studies; what are the major strengths and limitations in the individual studies and how do they affect the study findings; what are the potential mechanisms by which TCE may cause lymphoma and cancers of the kidney and liver; is there evidence that the mechanisms by which TCE causes cancer in experimental animals may not occur in humans; is there mechanistic evidence in humans that would support the associations observed in some human cancer studies; and is there any evidence that TCE-induced immunologic effects are related to cancer development.

The ORoC will use a variety of sequential approaches to receive scientific and public input. Public comments have been requested on the nomination and draft concept and a website will be established. Appropriate technical advisors will be identified, and there will be a listening session to receive comments on proposed topics to be included in the monograph and a preliminary list of references. The ORoC will convene webinars on each of the three cancer sites, consisting of invited speakers presenting their views on the strength of evidence (mechanistic and epidemiologic) for the association between TCE and cancer. When the draft

monograph is completed, it will undergo interagency review and be released for public comment. Then, NTP will convene a peer review panel to review the monograph. The panel will consist of members with the appropriate expertise in several areas. Time will be set aside at the peer review meeting for discussion of scientific issues raised in public comments.

H. BSC Discussion

Dr. Chapin asked what would be the next higher level of confidence should it increase as a result of the evaluation, compared to the current *reasonably anticipated to be a human carcinogen*. Dr. Lunn said the next level would be *known to be a human carcinogen*, and there would need to be sufficient evidence to support that conclusion. So upon re-review, the call could stay at the same level or be elevated, or possibly the compound could be de-listed.

Dr. Miller asked about the role of mechanistic data in animals. Dr. Lunn said it could be used in an evaluation, and is considered important. Dr. Birnbaum noted when mechanistic data are available, NTP likes to include it, and the absence of such data does not mean that a call cannot be made.

Dr. Eastmond said that in order to list a substance, the preference appears to be multiple tumor sites in multiple species, but he asked whether that is a requirement. Dr. Lunn replied that there can be multiple routes or multiple sites or multiple species, and that it just happens that all of those requirements are met for TCE.

Dr. Loomis, first lead reviewer, said it was his impression that exposures are significant with TCE, providing sufficient basis for the proposed re-evaluation. He felt the scientific issues are adequately identified in the document. He wondered whether any of the new studies mentioned included exposure response data. He felt the proposed scope was good and he applauded the introduction of the web-based approach. He rated the significance and public health impact of the evaluation as “high.”

Dr. McDiarmid, second lead reviewer, said the exposures are very significant, noting that as a clinician, TCE is one of the most common exposures in her practice. She said the pertinent scientific issues were laid out well and she agreed with the proposed scope of the evaluation. She felt the approach for obtaining scientific and public input was exceptionally complete. She rated the overall significance and public health impact as “high.” She called attention to a recent paper by Ward *et al.* (*Environ Health Perspectives, 2010, 118(10), October 2010)* that included reference to TCE.

Dr. Miller, third lead reviewer, concurred with Drs. Loomis and McDiarmid and agreed that exposures to TCE are significant. He felt the scientific information was clearly described and adequate. He said the relevant scientific issues were identified, although he felt more attention should perhaps be paid to peroxisome proliferator-activated receptor alpha (PPARα). He said the scope and focus were great, and strongly supported the approach based on target organs. He recommended consideration of including target organ experts. He concurred with the other reviewers regarding the approach to obtaining scientific and public input. He ranked the concept as “high.”

Dr. Lunn said there are some studies looking at exposure response relationships, which are higher-quality studies than were available in 2000.

Dr. Hattis noted genetic evidence of an apparent hot spot for mutation in a kidney tumor suppressor gene associated with TCE exposure and also an association of kidney cancer risk and a polymorphism in the glutathione metabolism gene. He said those are unusual mechanistically relevant circumstances. Dr. Eastmond mentioned some kidney-specific toxicity measures have recently been reported that have an exposure response relationship associated with them as well.

In summary, Dr. Eastmond felt there was consensus that TCE is an important chemical, particularly with its high production volume, high exposure, and high public interest. He noted all three reviewers gave it a high priority. They were all positive about the web-based approach to acquiring information. There was strong support for the target organ-specific approach, and for focusing on specific mechanisms, inviting people with relevant expertise to participate. Generally, there was sufficient information to move forward and make this a high priority evaluation.

I. *ortho*-Toluidine

Dr. Lunn presented the RoC *ortho*-toluidine concept review. *ortho*-Toluidine is an aromatic amine used to make dyes, rubber chemicals, and herbicides and is proposed for re-review for the RoC. It has been listed in the RoC since 1983 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. Since 1983, numerous human cancer studies have been published including an IARC review in 2010 that concluded that *ortho*-toluidine is carcinogenic to humans. Public comment received to date supports the nomination. It is a high production volume chemical (10 million to <50 million lbs.) in the U.S. with widespread usage, and exposures in the workplace, in consumer products, tobacco products and medical products, and in the environment.

Human studies available at the time of the initial listing were inadequate to evaluate cancer risk, but now several cohort studies of workers from five different industries, and two population-based case-control studies are available. These studies have focused on urinary bladder cancer. Metabolism data and mechanistic data, including a large database on genetic effects are also available. The monograph will focus on human cancer studies and mechanistic data. Key questions and issues include: what is the level of evidence for the carcinogenicity of *ortho*-toluidine from studies in humans, what are the potential confounders for evaluating urinary bladder cancer risk and can the relationship between bladder cancer risk and exposures to *ortho*-toluidine be exposure to these substances, what are the potential mechanisms by which *ortho*-toluidine may cause cancer in animals, and is there evidence that these mechanisms occur in humans.

The findings from the animal studies will be integrated into the overall synthesis of cancer studies in humans and mechanistic data, but the level of evidence of cancer studies in experimental animals will not be re-evaluated, because no new studies that would change the conclusions made in 1983 were identified.

The ORoC will use a variety of approaches to receive scientific and public input. Public comments has been requested on the nomination and draft concept and a website will be established. Appropriate technical advisors will be identified, such as scientific experts in dye chemistry and/or manufacturing, and scientific advisors internal or external to the government with knowledge related to *ortho*-toluidine, dyes, or arylamines and expertise in relevant scientific disciplines. Future forums may be convened to address any additional scientific issues. When the draft monograph is completed, it will undergo interagency review and be released for public comment. Then, NTP will convene a peer review panel to review the monograph. The panel will consist of members with the appropriate expertise in several areas. Time will be set aside at the peer-review meeting for discussion of scientific issues raised in public comments.

J. BSC Discussion

Dr. McDiarmid asked for clarification regarding confounders in exposure assessment. Dr. Lunn said although there are many occupational co-exposure, not all of these are potential confounders. The evaluation of the human studies would consist of first identifying which of these co-exposures are real confounders by researching whether these substance have the potential for causing cancer, and then assessing their influence on any association between *ortho*-toluidine and cancer.

Dr. Loomis, first lead reviewer, said the information presented suggested that exposure is reasonably significant. He felt the information provided was adequate, and the description of the scientific issues was good. He appreciated the need to identify real confounders as opposed to simply presenting a laundry list of substances that could be confounders. He said that *ortho*-toluidine is a "tricky" substance, and that it could be difficult to separate its effects from some of the other chemicals used in industrial settings. He recommended consideration of not trying to focus strictly on the single chemical, but instead examine mixtures containing it. He wondered if there were enough good new studies available. He said he struggled a bit with how to rate the significance of the evaluation, but ultimately decided it is "moderately high."

Dr. Lunn reiterated that there had been several human studies published since the original listing, including a NIOSH study that contained a subset of workers exposed only to *ortho*-toluidine and aniline. Dr. Howard asked if those exposures were measured in the workers' urine or the work environment. Dr. DeBord confirmed that the exposures were measured in the urine, and added that hemoglobin adducts were also measured in that study.

Dr. Hattis, second lead reviewer, said he found the information mentioned by Dr. DeBord to be very important for quantification of exposures, adding to the significance of the exposure information. He also emphasized the recent information that suggested general population exposure, and said it would be important to determine where that exposure is coming from, and to quantify it. He noted the recent findings of DNA adducts in bladder epithelium of people who died of phantom causes that may be attributed to exposure. He felt that integrative quantitative analysis of the human epidemiological data, including the industrial hygiene and biomarker studies, is vital to the effort, and should be done in relation to the relative potencies in

exposures. He rated the concept "pretty high" because of the evidence of general population exposure.

Dr. Eastmond noted that *ortho*-toluidine is actually a metabolite of *ortho*-nitrotoluene. His general sense of the BSC's ranking for the concepts was medium high to high, and there was a feeling that it would be valuable to try to integrate the various types of studies, and to try to identify the source of exposure in the general population. He said that identifying the true effects of the compound independent of confounding factors would be challenging.

K. 1-Bromopropane

Ms. Diane Spencer, ORoC, presented the RoC 1-bromopropane draft concept. 1-Bromopropane is a brominated hydrocarbon used as a solvent in a variety of industrial applications. There is significant and increasing exposure in the U.S., with inhalation the primary route, but dermal exposure is also possible. It is a high production volume chemical. It has been measured in the air in industrial settings, and a metabolite has been detected in the urine of exposed workers. Exposure is increasing because it is being used as an alternative solvent to known or suspected carcinogens or ozone-depleting chemicals.

There have been no epidemiological studies identified that examined the relationship between human cancer and 1-bromopropane. Since the increase in its use is recent, epidemiological studies would not yet be able to evaluate cancer risk, which is usually associated with a long latency period. There are, however, cancer studies in experimental animals, including an NTP 2-year bioassay that identified treatment-related effects due to inhalation in male rats and female rats and mice.

There are several metabolism and mechanistic studies available, which delineate the chemical's formation of metabolites – more than 10 urinary metabolites have been identified. Genotoxicity studies are also available. Immunosuppression has been observed in both rats and mice. The key scientific questions and issues relevant to the cancer evaluation are: what is the level of evidence for the carcinogenicity in experimental animals, what are the potential target tissue sites, what are the potential mechanisms by which 1-bromopropane may cause cancer and what is the level of evidence for these mechanisms, is there evidence that these mechanisms are not relevant to humans, and do the alterations in immune surveillance in rodents play a role in tumor development.

The approach to the cancer evaluation will involve review and assessment of the scientific literature, discussion of the scientific issues, assessment and integration of the relevant scientific evidence, and the application of RoC listing criteria to reach a preliminary listing recommendation. The focus will be on studies in experimental animals and mechanistic data. The ORoC will use a variety of approaches to receive scientific and public input. Scientific and technical expertise will be used, including advisors external or internal to government. Public comments have been requested on the nomination and draft concept and a website will be established for communication of project status and as a mechanism for public input. When the draft monograph is completed, it will undergo interagency review and be released for public comment. Then, NTP will convene a peer review panel to review the monograph. The panel

will consist of members with the appropriate expertise in several areas. Time will be set aside at the peer review meeting for discussion of scientific issues raised in public comments.

L. BSC Discussion

Dr. Zelikoff asked for more information on the genotoxicity studies and if they were positive. Ms. Spencer said there were a number of *in vivo* and *in vitro* tests and some of them were positive; the NTP feels there is a sufficient database to evaluate the compound's genotoxicity.

Dr. Eastmond asked if NTP had considered putting the compound in the context of the larger group of halogenated propanes, many of which have previously been evaluated by NTP. Dr. Bucher said that was a good idea, and should be considered. Dr. Birnbaum concurred, adding that a comparison based upon structure may be useful.

Dr. Zelikoff, first lead reviewer, noted the production volume for the compound is extensive and is well described in the draft concept. She said although ambient levels are important, more information on blood/tissue levels in humans would be useful. She felt the total weight of evidence comes from the 2-year NTP assay. She mentioned the adenomas of the large intestines and increased incidence of epithelial neoplasms of the skin in rats; the adenoma and carcinoma in female mice; the lack of increase in tumor incidence in male mice; the increase in the number of non-neoplastic lesions; the unusual inflammatory lesions in the nose and skin of that suggested immunosuppression; and other changes in immune response such as decreased total spleen cell numbers and T-cells and reduced antibody production. The immunologic observations were not convincing in terms of cancer outcomes, but should be investigated further. She said it was difficult for her to determine the overall significance and she recommended that other possible mechanisms of action be considered, as the compound is "a big black box." She agreed with the emphasis on animal models, but said comparisons with structurally similar compounds may yield insights on human effects. She felt the proposed search strategy and approach to gaining input were adequate. Due to the lack of information on hand, she rated the concept as being low-to-moderate in priority and recommended inclusion of an immunotoxicologist on the peer review panel, due to the suspected immune effects.

Dr. Dorman, second lead reviewer made a general comment about the difficulty in determining what is the level of detail needed in a concept document, which is the proposal for developing a monograph. He said the write-up, as it stood was adequate to make a case for moving the evaluation of 1-bromopropane forward. He wondered whether the proposed EPA rule that may change the industrial availability of the compound might influence carrying it forward, potentially altering the decision to proceed with the review. He thought the presentation of the scientific issues was adequate, but wanted more information about the rare intestinal tumors. He felt the scope and focus were complete, as was the approach to obtaining input. He reiterated his concern that the opportunities for future public forums may be used to delay the process. He rated the overall significance as "moderate, with low enthusiasm."

Ms. Spencer said that despite potential EPA regulation, which would address aerosolized versions of the compound, there would still be enough expected exposures from other sources to justify the review. Dr. Lunn added that historical exposures are also important, due to the

long latency of cancer. Dr. Dorman agreed, but suggested the language in the document reflect that, despite the expected decrease in usage, the chemical remains an important potential source of cancer risk. Dr. Zelikoff asked how long ago in time people have been exposed to the compound. Ms. Spencer said the original use was in closed systems, but that usage has increased greatly in the last 10-15 years due to 1-bromopropane being a substitute for the other compounds. Dr. Zelikoff noted there is no epidemiological literature but asked if there was any human clinical or anecdotal data available. Ms. Spencer said there was some exposure assessment information from NIOSH workplace surveys. Dr. Lunn noted there are toxicity data on the compound. Dr. McDiarmid added that the compound is an acutely toxic and a reproductive toxicant, and from a public health standpoint should be rated at a minimum as moderate, since a hazard has been replaced by a hazard, and should be reviewed.

Dr. Dorman noted there could be other mitigating factors such as toxicity that could help support the proposal, which were missing from the concept document. He felt non-cancer endpoints were important to include. Dr. Zelikoff observed that the charge was to assess the adequacy of the information provided in the concept document to support moving forward. She said it was a new process, and a "slippery slope" to provide enough information to make a decision without "giving away the whole show." Dr. Eastmond said it's a difficult process, because NTP is trying to conduct it without showing substantial bias. Dr. Chapin said the right point in terms of information provided in the concept document probably differs among the various BSC members, so he questioned why NTP was doing this step. Dr. Bucher said in the past the BSC had been informed as to the list of chemicals that were under consideration for review, but this is the first time the BSC has been asked to help reach that decision. Dr. Birnbaum asked BSC members to let the NTP know how much information they think should be in the concept document. Dr. Miller said he was comfortable with the level of information provided, since there were references included. Dr. Dorman was also comfortable with the level of detail, but felt what was missing was a template approach that NTP could follow to help guide decision-making, adding a bit more information specific to the individual chemicals. He said that would help prioritize for moving forward.

In summary, Dr. Eastmond said 1-bromopropane was a challenging compound. He said the low to moderate ratings by the reviewers might have been influenced by the write-up. There is no human cancer epidemiological data, but there are animal data with some unusual patterns. So the decision comes down to being driven by mechanistic data, which is what Dr. Zelikoff requested to help support the proposal. By not biasing the process by going into that level of detail, he observed, the document fell short. Overall, his sense was that the proposal would be moderate priority, but perhaps would be more compelling if more information was presented in the concept document.

Dr. Birnbaum reminded the panel that for the RoC, there are 2 levels of listing – *known* or *reasonably anticipated to be a human carcinogen* and that for *reasonably anticipated* all three triggers (sufficient animal data, human data, and mechanistic data) are not necessary, and sufficient animal carcinogenicity data are adequate. Dr. Zelikoff did not feel the animal data were concrete enough to go into that category. Dr. Birnbaum noted that when NTP starts an evaluation, it is not sure that the chemical will end up being listed. In this case, it was felt there

was sufficient information to present it to the BSC to solicit its input regarding going forward with the full evaluation. Dr. Dorman observed that it might not be appropriate to ask the BSC to rate the concepts as high, low or moderate – that at this stage, that may not be the right question, since there are no set criteria. Dr. Bucher said that issue had been under discussion, and that it may be appropriate to eliminate the rating question. Dr. Eastmond said he felt there was some value in the ranking, even if it is crude, in order to be able to give NTP some sense from the BSC of where it stands.

Dr. Wolfe asked the Board for general comments regarding the new process for review of concept documents. Dr. Eastmond said it might be helpful to strengthen the documents in particular areas that may be perceived to be light, to lend more understanding about why NTP thinks the concept should move forward. Dr. Zelikoff mentioned that the BSC members had been told it would not be necessary to read any supplementary materials, and felt that advice from NTP to make the review process more efficient would be helpful. Dr. Birnbaum reiterated that the RoC concept process is "a work in progress," and thanked the BSC members for their comments. Dr. Eastmond thanked the NTP staff for being well-prepared and providing clear presentations.

June 21, 2012

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

The discussion continued the following morning, as Dr. Zelikoff expressed concern that there was information about 1-bromopropane that the BSC had not been privy to. She asked for explanation or further discussion about it. Dr. Eastmond reiterated his statement from his summary of the prior day that this was a compound where the mechanisms would be very important to driving decisions. He felt it had been conveyed effectively to NTP that they needed to flesh out that part of the document if they were to go forward. Dr. Walker asked Dr. Zelikoff to elaborate on her concern. She felt there had been more information given for the other compounds being considered, and that the 1-bromopropane concept document stood out from the others as being lighter in terms of the content provided. Dr. Birnbaum said it is difficult to balance the desire to have a great deal of information versus what will be provided when the monograph itself is written, because at the concept document stage, all of the research has not yet been done, but enough has been done to say that it is appropriate to conclude that a monograph should be done. She said it was inevitable that some concept documents would be more frustrating than others. She asked for BSC members to pass along their suggestions about how to achieve the appropriate balance.

Dr. McDiarmid suggested the slides used to summarize the rationales for each compound be standardized.

IX. Report of the NTP Associate Director

A. Presentation

Dr. Bucher briefed the BSC on recent NTP activities. Recent meetings included the NTP Technical Reports Peer Review on February 5-6 and the Society of Toxicology meeting March 11-14. Upcoming meetings include the Scientific Advisory Committee on Alternative Toxicological Methods meeting on September 5-6 and peer review of the draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy, which is scheduled for October 1-2.

Dr. Bucher reviewed progress on the revised RoC process since the last BSC meeting. The review process was finalized and published in the **Federal Register** on January 11. There was also a **Federal Register** notice on January 19 requesting comments on the 15 substances nominated for evaluation in the RoC. He summarized the progress on the draft concepts for the five proposed candidate substances, which culminated in the BSC's review.

He reported that on April 25, Dr. Birnbaum spoke at a joint hearing of the Committee on Science, Space, and Technology Subcommittee on Investigations and Oversight and the Committee on Small Business Subcommittee on Healthcare and Technology, which was convened to examine the impact of the RoC on small business jobs.

He introduced the systematic review (SR) process that has been developed by the NTP Office of Health Assessment and Translation (OHAT). OHAT has held webinars to disseminate information about the SR process, and has developed web-based tools to facilitate systematic review and evidence assessment. A BSC working group has been established to provide input on the approach for decision-making in evidence assessment. The approach will be shared with agencies in the fall of 2012, and with the NTP Executive Committee on November 8. The final information will be presented to the BSC at its next meeting on December 11-12.

Dr. Bucher reported that the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) has issued its Biennial Progress Report, as required by law. Also, a draft Five-year Plan for 2013-2017 has been released by ICCVAM and the National Toxicology Program Interagency Center for the Evaluation of Alternative Methods. Also, the NTP Annual Report for 2011 will be released shortly.

He summarized recent staff changes at DNTP: Drs. Michael Shelby, Joseph Roycroft, Frank Johnson, and Po Chan have retired and Dr. Aris Martone has been hired in the Program Operations Branch.

B. BSC Discussion

Dr. Bucher confirmed for Dr. Miller that the SACATM meeting in September would be open to the public. Dr. Chapin asked whether there would be a presentation for the BSC on how the anticipated large number of retirements would impact the NTP, and if there is a plan to manage that development. Dr. Bucher replied that much depends on what happens with the NIH budget. A small reduction would allow strategic hiring to replace retiring staff, but an 8-10%

reduction would be “an entirely different ballgame.” Planning is taking place for both scenarios, but an overall plan has not yet been formulated. Dr. Birnbaum agreed, and noted that several more retirements are anticipated shortly, with not all open positions being filled in anticipation of the potential budget cut. She said approximately 90% of the NTP’s intramural budget is devoted to salaries and benefits, so there’s not a great deal of flexibility in the event of a large budget cut. She said there might be a presentation at the December BSC meeting on this matter, along with information on how DNTP will be working to implement the new strategic plan initiatives.

Dr. Dorman asked how NTP could leverage its systematic review process with other Federal entities such as IRIS to come up with a shared process. Dr. Bucher said the NTP is in contact with IRIS, particularly in interagency workgroups considering the process. He said NTP is probably further along than most of the other groups in development of systemic review tools, and felt that the other agencies are anxious to continue to work with the NTP on the process. Dr. Birnbaum added that former NIEHS/NTP Director Dr. Ken Olden would be in charge of the IRIS program at EPA, starting July 2.

X. Systematic Review and New Tools for Information Management and Data Display

A. Presentation, Part One - Overview

Dr. Kristina Thayer, Office of Health Assessment and Translation, briefed the BSC on OHAT’s development of a new systematic review (SR) process. She provided background information about OHAT, which incorporates and expands the scope of the former Center for the Evaluation of Risks to Human Reproduction (CERHR). It is designed to conduct literature-based evaluations, using a flexible process tailored to meet the needs of each project. The main conclusion presented in an OHAT document is an NTP level of concern, which is integrated from a conclusion on evidence for toxicity and extent of human exposure and other factors, on a 5-point scale ranging from *serious concern* to *negligible concern*, with an additional category for *Insufficient Data*. She said it was extremely likely that the framework would be updated in the next year or so, as follow-on to implementation of SR. OHAT issues other products containing peer-reviewed conclusions and other reviews including monographs on specific topics of concern, workshops, and journal publications.

Dr. Thayer defined SR as a scientific investigation that focuses on a specific question and uses explicit, pre-specified methods to identify, select, assess and summarize the findings of similar but separate studies. SR is used to develop conclusions, clinical or public health recommendations, and clarify need for additional research; may or may not result in a quantitative meta-analysis; and is traditionally used for assessment of healthcare interventions. She noted that much of the SR methodology has been developed in clinical epidemiology to analyze data from randomized clinical trials. OHAT is trying to extrapolate the methodology to environmental health with its different evidence streams, including human studies that are often not randomized clinical trials, along with animal studies and mechanistic data.

Adoption of SR and use of new data extraction and display tools will enhance transparency of the evaluations and will allow more consistent data collection and more efficient information

management. The new information management tools can provide the infrastructure for development of a publicly accessible data extraction repository, which could help reduce duplication of efforts across agencies and the research community. To develop SR, technical experts have been engaged and interagency communication has been ongoing, including webinars and an Information Management Workgroup co-chaired by George Woodall of EPA and Andrew Rooney from DNTP. She noted that an SR will *not* eliminate the need for expert judgment, guarantee reproducibility of conclusions, provide guidance on how to reach evidence of toxicity or hazard identification conclusions, or provide guidance on how to integrate evidence across human, animal, and mechanistic studies.

Dr. Thayer said it is important to have a protocol for an SR, which is analogous to the methods in an experimental study. It is a pre-defined approach for conducting the SR, which is by its nature an iterative process, with modifications to the protocol expected and tracked. The SR methodology is oriented toward a specific question, with an identified "PICO": *p*atient population, *i*ntervention, *c*omparison, and *o*utcomes. Since environmental health questions are often broad, there must be a strategy to refine the topic's scope, which could involve use of previous evaluations to identify "added value" analysis questions, an exploratory screening of the literature stage, and the engagement of technical experts and the public early in protocol development.

OHAT is considering a phased approach for topic selection, which would start with release of a **Federal Register** notice announcing a topic under consideration and asking for public comments. A draft protocol would then be developed with the assistance of technical experts, which would be presented to the BSC, with an opportunity for public comment. Then, following any modifications to the draft protocol, the SR would begin.

B. BSC Questions

Dr. Hattis said in his experience with risk assessment, there is a need to treat quantal endpoints differently than continuous endpoints and recommended that OHAT's methodology should recognize the distinction.

Dr. Chapin compared the OHAT approach to the Cochrane process and asked if Cochrane had influenced OHAT. Dr. Thayer replied that OHAT reviewed that process, and some of the technical experts consulted had come from Cochrane.

Dr. McDiarmid asked how this SR process differs from what OHAT does now. Dr. Thayer said it is a big change, with more exploratory screening to identify the added-value questions, as well as laying out more transparently how study quality is assessed.

C. Presentation, Part Two – Methodology and Infrastructure Tools

Dr. Thayer said to expedite the literature search a librarian trained in systematic review is enlisted to construct the search itself, which is biased not to miss studies, but is iterative, with the search tweaked to avoid irrelevant studies. Dr. Thayer described a document flow of information chart, which depicts the number of records included in various stages of the

process. Development of the flow chart is a critical and difficult step if not considered in advance of screening the literature. It is important to determine inclusion and exclusion criteria early. Two independent reviewers screen studies and there is a strategy for resolving conflicts. OHAT has sought a software solution to help with the process, and chose one called DistillerSR, which is an industry standard package that greatly facilitates the screening process. She noted that the software could also be used to develop customizable data extraction forms, and customizable reports for tracking, reporting, and data display. She displayed several examples of DistillerSR forms, and provided details about their use and features.

D. BSC Discussion

Dr. Dorman asked whether there was any intention for NTP to make the software tools being created publicly available, despite the fact that the software itself is proprietary. He said that OHAT has developed a very powerful tool that could be used by a lot of investigators. Dr. Thayer replied that the front-end screening part of the software could not be shared because it is proprietary, but the data collection aspects could be disseminated, e.g., in an Excel format. Dr. Wolfe asked if the actual questions that were asked on the forms could be shared. Dr. Thayer said they could, easily through excel format, although viewing on-line via the Distiller interface would require access to the software. Dr. Dorman discussed an example of how an outside investigator might effectively utilize the SR process. He recommended that the NTP proactively consider how to make this tool available to the broader community. Dr. Thayer said the NTP wants to share the data extraction files so people can use them as data mining resources and to update reviews.

Dr. Eastmond observed that the most valuable use of the system would be to help coordinate between different agencies that conduct similar sorts of reviews. He said the real issue for him was the nature of the questions being asked, and whether the questions are sufficiently similar that the SR system would be extremely helpful, or whether questions are different enough that individual agencies would still need to perform their own reviews. Dr. Thayer said she imagined it would be some of both. Dr. Bucher added that even if the questions are not exactly the same between agencies, at least the information that has been systematically extracted from a particular set of studies can be utilized without having to re-do the extraction. Dr. Wolfe added that NTP is engaging agency partners early in the process to communicate questions and areas of interest and to identify potential commonalities.

E. Presentation, Part Three – Assessing Study Quality and Synthesizing Results

Dr. Thayer said to assess the “quality” of individual studies predefined criteria would be used to assess risk of bias, also referred to as internal validity, which addresses confidence in the study findings. Studies are assessed with a domain-based approach, with single summary scores of studies strongly disapproved. Risk of bias is assessed for individual studies and across studies. She depicted a draft Agency for Healthcare Research and Quality document illustrating the risk of bias assessment, and OHAT forms illustrating risk of bias for individual studies and risk of bias across studies, with green fields delineating low risk of bias, and red high risk. She described the next steps to be taken in methods for evaluating risk of bias, noting that most of

the risk of bias guidance is developed for human studies of medical interventions, i.e., randomized clinical trials (RCTs). OHAT would continue to assess the applicability of the existing guidance to environmental health studies, and the potential of modifying RCT elements for animal studies. The RCT guidance could also be used as a basis for potentially excluding studies or conducting stratified analysis. Consistency of response across reviewers would also be assessed for risk of bias, and risk of bias tools would be compared.

For synthesizing results, the next step is to evaluate the body of evidence across studies for each major outcome. The elements to be considered include risk of bias, precision, directness, consistency, dose-response associations, impact of confounding, magnitude of association, and publication bias. OHAT is currently examining what would be the approaches for NTP products, incorporating the philosophy embodied in existing guidance where possible (e.g., Grading of Recommendations Assessment, Development and Evaluation [GRADE]), but also seeking to integrate human, animal, and mechanistic data, and hopefully to include links to evidence of toxicity, hazard identification, and level of concern conclusions.

F. BSC Questions

Dr. Dorman asked about reviewer-to-reviewer bias, and whether there would be training sets developed to standardize data extraction in large projects. Dr. Thayer said the software allows the tracking of conflicts at the data extraction level, which would help with that issue. Dr. Dorman added that the use of systematic reviews would increase over time, with investigators and agencies being pushed in that direction. He said that NTP might want to consider trying to identify what features in the SR actually drive professional judgment and decision-making. He suggested development of a scorecard by which NTP can judge the strength of other individual SRs. Dr. Thayer said that is something to consider although OHAT collects many variables in its data extraction, so it would be difficult to make “apples-to-apples” comparison in terms of the data extraction elements.

Dr. Andrew Rooney, OHAT, asked Dr. Dorman to clarify his question – whether he meant that OHAT should identify for each individual review the key elements for risk of bias or decision-making that may have contributed to a certain outcome, or the key elements that the individual reviewers may have differed on. Dr. Dorman related his recent experience with an NAS committee evaluating lead. The committee, he said, is using the NTP monograph as a starting point, but must judge whether they trust that monograph. He noted that for influencing a panel, inclusion and exclusion criteria might be more important than judgments of individual bias in studies. He said there is a science behind the process of how panels work and judge reviews. Dr. Wolfe pointed out that it is also difficult to decide how to use the somewhat weaker studies in the overall process.

Dr. Hattis said it was important not to consider bias judgments as “clean/dirty” dichotomous decisions, because sometimes it is important to recognize a bias and counteract it in the analysis. He cited the healthy worker effect as an example. Dr. Chapin discussed some of the behavioral science research from the 1970s by Daniel Kahneman that addressed decision-making being based more on evolution than rational thought.

G. Presentation, Part Four - Data Dissemination and New Tools of Data Display

Dr. Thayer reiterated that when an SR is conducted, OHAT wants to make publicly available the outputs of the data extractions. Part of the process is time-intensive and expensive, taking anywhere from a half-hour to two hours to perform data extraction on a single study, conducted by experienced, highly trained personnel. The data extraction files can be imported into statistical packages, can be used to create customized summary or appendix tables, and can accommodate visual data mining in MetaData Viewer. That software is free and publicly accessible, taking Excel file input.

Dr. Thayer related the next steps anticipated for SR and integrating evidence. First, with the foundation of SR established, the plan is to develop a framework for reaching evidence assessment conclusions to address environmental health questions. There is a BSC working group being created, and by late summer 2012, the plan is to obtain review of a draft framework. Later, the approach will be shared with agencies and the NTP Executive Committee. By the December 2012 or June 2013 BSC meeting, the approach will be presented to the BSC for its review. Next steps in information management will include beta testing of data extraction forms, beta testing the utility of the forms for data mining, and development of a process for quality assessment of data extraction files and their storage in the Chemical Effects in Biological Systems (CEBS) database.

H. BSC Discussion

Dr. Miller applauded the NTP SR project and asked whether authors were contacted if there were questions about key elements of study design. Dr. Thayer said that had been done in the past, and there would probably be more in the future. Dr. Miller asked whether environmental enrichment, which could be a huge source of variability, was being well captured. He suggested that NTP take a leadership role in encouraging journals to add that element into materials and methods sections. Dr. Dorman added that dietary information in rodent studies would be a useful element to extract from studies.

Dr. Birnbaum recognized the excellent work by Dr. Thayer and her collaborators and said it would be important to look at making the process publicly available once it is ready. She said it would be wonderful if there were a harmonized SR method that everyone could use. Dr. Chapin agreed that it should be publically available and observed that the SR process would be transformative. He said that the need for it cannot be overstated – the global need for a tool that, without bias and with transparency, will help people summarize a literature and focus on the better studies.

Dr. Hattis, first lead reviewer, said he had considerable enthusiasm for the prospect, along with considerable fears about how to pursue the learning curve so that it is used effectively and accurately. He recognized that it would be a tool for iterative learning, with many technical elements to be incorporated into the software over time. He said NTP should by all means proceed with the project.

Dr. McDiarmid, second lead reviewer, agreed with the enthusiasm that had been expressed. She said the SR would standardize not only NTP work product but also the work product of others doing similar evaluations. She added it would also help refute any criticism of the work products.

Dr. Dorman was concerned that whatever the problem being addressed, there is a danger of being overwhelmed by the literature base. He noted that an SR may not necessarily need to be all-inclusive and recommended coming up with a strategy to rapidly focus the data to avoid dealing with a huge database that may not be very informative. Dr. Thayer agreed, but noted that the group is tolerant for getting a large number of hits, citing a recent search that brought back 23,000 hits. She said they would be focused on how to limit that response in subsequent projects. Dr. Dorman said Dr. Thayer's example illustrated his point, and that it is a dilemma that will only get worse. He felt that the SR should be more hypothesis-driven, to limit the number of hits, stressing that, "more may not be better in this particular case." Dr. Bucher said one way to limit the search might be to do it in two different directions – one all-inclusive, and one focused on the kernel of what is being addressed.

Dr. Chapin said one advantage of the large SR database is that the data then go into CEBS, which is mineable by other entities for other questions. Those searches would be one way to measure impact.

Dr. Hattis recommended a series of experiments to explore some of the issues being discussed, using a set of analysts to study how they use the SR software, and what their needs are. He also recommended inviting analysts from other agencies to try the system, as part of marketing efforts.

Dr. Eastmond observed that for him the real value is more for the exclusions than the inclusions. He said it would be useful to be able to track the exclusions and understand why they were excluded. He said there was frequently personnel turnover on large projects, so it would be valuable to go back and look at what earlier personnel did, and why. Dr. Howard agreed that that is a very significant advantage, in that it has been a criticism of NTP reports in the past that there was no way to backtrack and understand why particular studies may have been excluded. Dr. Eastmond summarized the discussion, stating that the BSC is very supportive and enthusiastic about the SR process.

XI. NTP Monograph on Health Effects of Low-Level Lead

A. Presentation

Dr. Rooney briefed the BSC on the *NTP Monograph on Health Effects of Low-Level Lead*. NIOSH had originally nominated low-level lead for NTP evaluation, a project that was unanimously supported by the BSC. The evaluation focused on epidemiological data for health effects at blood lead levels <10µg/dL. The monograph represents an overview of the science to date on potential health effects from low-level lead exposure. Dr. Rooney delineated blood lead level, which reflects current exposure, from bone lead level, which reflects cumulative exposure

but is much more difficult to measure. The majority of the available data on exposure are blood lead data and therefore the monograph refers primarily to blood lead levels.

The monograph is comprised of the following sections: Executive Summary, Methods, Exposure, and five Health Effects Sections – Neurological, Immune, Cardiovascular, Renal, and Reproductive and Developmental Effects. An independent expert panel conducted a peer review of the draft monograph on November 17-18, 2011, at NIEHS. The panel agreed with the draft NTP overall conclusions on health effects associated with blood lead <10µg/dL for cardiovascular, renal, and immune effects. The panel recommended changing the draft summary conclusion from *sufficient* evidence of an association at blood lead <10µg/dL to blood lead <5µg/dL for neurological effects in children and reproductive effects in adult women. The NTP concurred with the panel on all of its recommendations.

The main findings of the monograph were that both children and adults are vulnerable to the effects of lead, that there is evidence for many adverse health effects in both children and adults at blood lead levels <10µg/dL, and for some <5µg/dL. The NTP findings are consistent with and extend what other agencies have found in recent reviews (ATSDR, 2007; EPA, 2006 and 2012 draft update).

Dr. Rooney presented all of the conclusions included in the monograph. The NTP's conclusions for major health effects are that there is evidence that blood lead levels <10µg/dL are associated in adults with adverse effects on renal function, cardiovascular function, and lower birth weight babies. In children, there is evidence of decreased cognitive function, decreased hearing, reduced growth, delayed puberty, and increased attention-related and problem behaviors.

B. BSC Discussion

Dr. Hattis said his impression is that the way the data were presented, in weight of evidence form, is not as helpful as it might be to some kinds of decision-makers, particularly those who want to evaluate the costs and benefits of different measures to control lead exposures. He urged the inclusion of material to give the decision-making community metrics on how much benefit they might get from incremental efforts at control. Dr. Rooney replied that the monograph did a good job of answering the questions that had been put to it, and that the measures Dr. Hattis described would be beyond the scope of the project, but would be a valuable follow-up. Dr. Hattis added that it would be a good candidate for a SR. Dr. Bucher noted that cost-benefit analyses would be increasingly important under the new NIEHS/NTP Strategic Plan.

Dr. Dorman asked how this type of monograph might influence NIEHS funding decisions both intra- and extramurally. Dr. Birnbaum said her vision for NIEHS has been a "one NIEHS" approach, so it would be natural for cross talk to occur. She did not see an increase in lead research intramurally, although there would probably be some extramural interest in filling some of the gaps identified in the monograph. Dr. Dorman added that this would be a good opportunity to capture some of the added value that NTP provides. Dr. Birnbaum agreed, and

noted the impact would go beyond NIEHS and NTP to the larger community, including other interested Federal agencies.

Dr. Zelikoff, first lead reviewer and BSC liaison the expert panel meeting, said she was impressed with the monograph. She said the NTP is to be congratulated for taking the external panel's comments to heart, and applying them to the document. She said there was some confusion as to whether it was designed to be a SR, which it was not. The expert panel had also been concerned about references to causality in the initial document. The panel preferred "association," and those suggested changes were incorporated into the monograph. There had been some concern about the fact that there were only blood lead level data available, and some of the conclusions were changed as a result. Another concern was that there were too many reviews used without identifying them as reviews in the references. Dr. Zelikoff noted that that had been addressed in the final document. She applauded the use of animal data. All in all, she said, although some of the conclusions were downgraded from the initial monograph, the final document was excellent. Dr. Rooney agreed that the panel had been extraordinary. He noted that there were 61 conclusions in the monograph, and that the expert panel had changed only five of them.

Dr. Chapin, second lead reviewer, said he had not been at the peer review meeting, but saw the monograph as the first of a great many examples of the expansion of the former CERHR review process into something beyond just reproductive and developmental toxicology, with a real potential to have an impact on public health. He noted that lead seems to be the only compound where exposures are rated at a certain level or below, and he asked about no-effect levels. Dr. Birnbaum replied that there is no evidence of a no-effect level for lead, and noted that many of the studies in the area are population studies, with concerns raised about population risk, as opposed to individual risk. Also at low levels, there is the issue of measurement error.

Dr. Hattis mentioned that there has been a tendency for slopes to increase over time as dose-effect relationships are determined at lower levels. Dr. Birnbaum pointed out that the Centers for Disease Control and Prevention has not set an action level for lead, but has expressed concern about anything above the 97.5th percentile in the population, which is currently in the neighborhood of 5µg/dL.

Dr. Eastmond said he found the criteria that had been used to establish "an association" somewhat unusual. He was curious as to why the panel had wanted references to causality removed, since that is a standard in summaries like this, and is ostensibly the key element. Dr. Zelikoff said at least one or two of the panelists were very insistent that there need to be animal studies that clearly show the link to get causality to confirm the feasibility of an association seen in epidemiological studies. Dr. Rooney noted the monograph is based on the human literature, with animal studies referred to in order to support associations, rather than an absolute causal link. Dr. Eastmond said it sounded like this was a special case, and so the panel did not want to be tied down to specific mechanistic or established evidence. Thus, he hoped this would not be seen as a precedent going forward in terms of evidentiary requirements. Dr. Hattis reiterated that causality is important for considering public health control efforts, and added that perhaps a

Bayesian approach to inferring causality would be useful. Dr. Rooney said that as evidenced by the current discussion, it is a complex question, with which the panel had also struggled. He agreed that it is a special case, and that in a potential future SR, the evidence from the human, animal*, in vitro,* and mechanistic studies could be integrated, with the causality vs. association questions being considered.

XII. Adjournment

Dr. Birnbaum and Dr. Bucher thanked the BSC and the NTP staff for their excellent contributions and hard work during the meeting. Dr. White noted that the next BSC meeting is December 11-12, 2012.

Dr. Eastmond adjourned the meeting at 11:45 AM.