National Toxicology Program

Board of Scientific Counselors

Summary Minutes

December 15, 2011

National Institute of Environmental Health Sciences

Research Triangle Park, NC

Table of Contents

I. Frequently Used Abbreviations and Acronyms

ACC	American Chemistry Council
ADME	absorption, distribution, metabolism, and excretion
AK	Alaska
ATSDR	Agency for Toxic Substances and Disease Registry
BSC	Board of Scientific Counselors
CDC	Center for Disease Control and Prevention
DERT	Division of Extramural Research and Training
DIR	Division of Intramural Research
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
FACA	Federal Advisory Committee Act
FDA	U.S. Food and Drug Administration
HHS	Health and Human Services
HPV	high production volume
IARC	International Agency for Research on Cancer
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
NOAEL	no-observed-adverse-effect-level
NTP	National Toxicology Program
OEL	occupational exposure limit
OHAT	Office of Health Assessment and Translation
ORoC	Office of the Report on Carcinogens
OSHA	Occupational Safety and Health Administration
PBZT	phenolic benzotriazole
PCB	polychlorinated biphenyl
PCPC	Personal Care Products Council
PETA	People for the Ethical Treatment of Animals
POP	persistent organic pollutant
PPAR	peroxisome proliferator-activated receptor
PPB	parts per billion
PPRTV	Provisional Peer Review Toxicity Value
RoC	Report on Carcinogens
SAR	structure-activity relationship
TK	toxicokinetic
TMSD	trimethylsilyldiazomethane
TR	Technical Reports

II. Attendees

Members in Attendance:

David Eastmond, University of California - Riverside (Chair)
Elaine Faustman, University of Washington (by telephone)
Stephen Looney, Georgia Health Sciences University
Melissa McDiarmid, University of Maryland School of Medicine
Richard Miller, GlaxoSmithKline
Lisa Minor, *In Vitro* Strategies
Mitzi Nagarkatti, University of South Carolina School of Medicine
Ruthann Rudel, Silent Spring Institute
Gina Solomon, Natural Resources Defense Council
Judith Zelikoff, New York University School of Medicine

Members not in Attendance:

Nicholas Jewell, University of California Berkeley
Dana Loomis, University of Nebraska Medical Center
Justin Teeguarden, Pacific Northwest National Laboratory

Pending BSC Member:

Miguel Fernández, University of Texas Health Science Center at San Antonio

Other Federal Agency Staff:

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

National Institute of Environmental Health Sciences (NIEHS) Staff:

Linda Birnbaum
Jack Bishop
Chad Blystone
John Bucher
Raj Chhabra
Helen Cunny
Paul Foster
Dory Germolec
William Gwinn
Ernie Hood
Michelle Hooth
Paul Jung
Angela King-Herbert
Grace Kissling
Ruth Lunn
Robin Mackar
Scott Masten
Aubrey Miller
Cynthia Rider
Robert Sills
Cynthia Smith
William Stokes
Kris Thayer
Ray Tice
Molly Vallant
Michael Waalkes
Nigel Walker
Suramya Waidyanatha
Lori White
Mary Wolfe

Public:

Perry Bennett, Molded Fiberglass Companies
Nancy Bordelon, Battelle
James Bus, The Dow Chemical Company
Neepa Choksi, Integrated Laboratory Systems
Barry Clayton, Reichhold
Laurie Haws, ToxStrategies
Chuck Hebert, Southern Research Institute
Milton Hejtmancik, Battelle
Linda Loretz, Personal Care Products Council
Joseph Manuppello, People for the Ethical Treatment of Animals (by telephone)
Timothy Nelson
Steve Risotto, American Chemistry Council
Lorenz Rhomberg, Gradient
John Schweitzer, American Composite Manufacturers Association
Julie Skare, The Procter & Gamble Company
Jack Snyder, Styrene Information and Research Center

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met December 15, 2011, 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. Dr. Lori White, BSC Designated Federal Official, read the conflict of interest policy statement and noted that Drs. Lisa Minor and Judith Zelikoff are now full voting members of the BSC.

IV. Report of the NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, updated the BSC on developments since the last meeting. In staff developments, she noted the appointment of Dr. Darryl Zeldin as the new NIEHS Scientific Director, as of October 23, 2011. Dr. Zeldin had been the acting NIEHS Clinical Director, and a selection process to fill that vacancy is currently underway. In June 2011, Ms. Joellen Austin was appointed to be the NIEHS Associate Director for Management and Executive Officer.

Regarding the NIEHS/NTP budget, Dr. Birnbaum reported that the institute has been working under a Continuing Resolution since September 30, which represents a 1.5% decrease in funding, or approximately 3-4% accounting for inflation. Compared to other parts of the federal government that is a modest decrease, she noted. NIEHS buying power has actually been flat for several years. With the continuing tough economy, she said, increases in the budget are unlikely, and the best hope is that it will continue to remain relatively flat.

She updated the BSC on the status of the NIEHS Strategic Planning process, which will guide the institute's activities over the next five years. The process was designed with three phases. In the first phase, stakeholder input was solicited, both online and through a series of stakeholder meetings. Now draft mission and vision statements are on line, as well as draft pillars, with paragraphs describing the pillars. As material is added to the website, there is opportunity to provide input to the process. The Visionary Ideas site was open from March 1 through April 30, 2011,and 231 Visionary Ideas were received. A Stakeholder Community Workshop was held in July, with more than 180 participants. It employed a Modified Open Space format, and ultimately yielded a slate of 13 "big topics" for further development. In October, a smaller strategic planning workshop was held, with the goal of drafting the mission statement, the vision statement and "tag line," and the supporting pillars. Dr. Birnbaum shared the current drafts of the Mission Statement, Vision Statement, and Supporting Pillars with the BSC, and solicited members' input.

In recent NIEHS news and highlights since the last BSC meeting, Dr. Birnbaum reported that Representative David Price, who represents the NC Triangle area in the U.S. Congress, held a town hall meeting with staff at NIEHS in June and returned in August for a meeting with grantees to discuss the benefits of federal research for the economy. The *12th Report on Carcinogens* (RoC) was released in June. Led by NIEHS, the National Research Council's Committee on Emerging Science for Environmental Health Decisions held a workshop in July on chemical mixtures, as well as a workshop on exposomes held in early December. There

have been two recent meetings of the NIEHS Nanotechnology Consortium. Also, NIEHS won the FY2010 U.S. Department of Health and Human Services (HHS) Green Champions Award for outstanding efforts related to sustainability.

In ongoing programs responding to the Deepwater Horizon oil spill in 2010, the large intramural GuLF Study focusing on up to 50,000 cleanup workers is continuing. Additional funding was recently received to examine a sub-cohort of 1,000 subjects, looking at their current exposures to several chemicals. A cross-NIH effort involving eight sister institutes and centers has been launched, which is an academic community consortium looking at issues in different populations in the Gulf. The lead universities are Louisiana State University (women and children), Tulane University (resilience of the Gulf community), the University of Florida (eastern Gulf Coast communities), and the University of Texas Medical Branch at Galveston (a variety of related health risks). There are also more than 120 community groups involved in the academic research efforts.

Dr. Birnbaum thanked BSC members who had completed their tenure and presented certificates of appreciation to Dr. Mitzi Nagarkatti, Ms. Ruthann Rudel, and Dr. Gina Solomon, and thanked Dr. Justin Teeguarden, who could not be present.

She noted that the reorganization of NTP as a separate intramural division within NIEHS had been finalized.

V. Report of the NTP Associate Director

Dr. John Bucher, NTP Associate Director, provided an update to the BSC since the last meeting. The Public Health Service Act, Section 301(b)(4) (1978) directed the HHS Secretary to annually publish a list of carcinogens. This was changed to a biennial report in1992. Its preparation is managed by the Office of the Report on Carcinogens (ORoC) within the Division of the NTP (DNTP) at NIEHS. The 12th RoC, published in June 2011, has 240 listings, 54 of which are listed as *known human carcinogens* and 186 of which are listed as *reasonably anticipated to be human carcinogens*. The 12th RoC added 8 listings, for which there has been highly coordinated communication plans, fact sheets, a dedicated website, media teleconferences, wide news coverage, and a high volume of downloads of RoC-related information.

Dr. Bucher described joint the DERT/NTP workshop *Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects*, held in September 2011 in Chapel Hill, NC. The workshop goals were to identify and focus on key issues that present challenges in mixtures research and to inform the development of an intramural and extramural research strategy. The new tools discussed for mixtures toxicology included Toxicology in the 21st Century, exposure sciences, and computational sciences. Future plans for mixtures study at NTP include target tissue approaches, sufficient similarity evaluations, use of high-density information, and cross-disciplinary collaborations.

Dr. Bucher updated the BSC on the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods-Interagency Coordinating Committee on the Validation of Alternative

Methods International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing, held in Ames, IA at the National Centers for Animal Health in October 2011. The workshop, which hosted 80 participants from 12 countries, addressed refinement (less pain and distress), reduction, and replacement of animal test methods. Highlights included refinement and reduction of the NIH challenge test by using anesthesia, analgesics, earlier humane endpoints, and reduction of the numbers of mice used. Replacement options for the challenge test are the serum virus neutralization test and *in vitro* antigen quantification methods.

The NTP held a peer-review meeting in November 2011 to review the draft NTP Monograph on Health Effects of Low-level Lead prepared by the Office of Health Assessment and Translation (OHAT), NIEHS/DNTP. NIOSH nominated lead at blood levels <10µg/dL for evaluation for adverse reproductive and developmental effects (the Center for Disease Control [CDC]'s definition of elevated blood lead is ≥10µg/dL for all ages). The NTP expanded the scope to include neurological effects, immune effects, cardiovascular effects, renal effects, and reproductive and developmental effects. OHAT sought to identity (1) the blood level associated with the health effect, (2) the life stage at which the effect is identified, (3) data to evaluate the association between bone lead and the health effect and, and (4) the association of bone lead exposure with blood lead. Dr. Bucher described the methods used in the assessment and highlighted some of the conclusions.

VI. Report on the NTP Technical Reports Peer Review

A. Presentation

Dr. Nagarkatti, BSC Liaison to April 15, 2011 NTP Technical Reports (TRs) Peer-Review Panel Meeting, provided a brief report on the meeting. The panel was charged to peer review the scientific and technical elements of the study and its presentation and to determine whether the study's experimental design and conduct supported the NTP's conclusions regarding the carcinogenic activity of the substance tested. Four draft TRs were reviewed at the meeting: senna, a nondecolorized whole leaf extract of *Aloe barbadensis Miller (Aloe vera),* acrylamide, and combinations of AIDS therapeutics (3′-azido-3′-deoxythymidine [AZT], lamivudine [3TC], and either nevirapine [NVP] or nelfinavir [NFV]). The panel recommended the NTP's draft conclusions for all four reports and the NTP accepted the panel's recommendation.

B. BSC Discussion

Dr. Solomon asked about disagreement on the panel regarding the AIDS therapeutics, particularly the minority view on some of the endpoints. Dr. Nigel Walker replied that one of the reviewers had felt one of the "no-calls"—the AZT/3TC/NFV combination—should have been "equivocal."

Dr. Eastmond inquired about the panel's split vote on senna. Dr. Walker said there had been concerns about whether the haploinsufficient p53 model used was a viable model for intestinal tumors. One of the reasons for using that model was to test it on behalf of the FDA. Dr. Eastmond noted that senna had been tested previously in a conventional animal bioassay, and asked about the results. Dr. Rajendra Chhabra, NTP Toxicologist, stated senna was negative in

rats. At the behest of FDA, the NTP had selected the transgenic p53 mouse model, which he said has been accepted as an alternative to the two-year mouse bioassay. Dr. Bucher explained that years ago in an NTP study of the laxative phenolphthalein, the two-year bioassay was considered insufficient, and a p53 had been conducted as well, which led the FDA to regulate use of the compound. Since senna was the substitute for phenolphthalein in laxatives, there was also a desire to look at results for senna in the p53 mouse model.

VII. NTP Research/Testing Concepts: Introduction

Dr. Scott Masten, Director, Office of Nomination and Selection, NIEHS/DNTP, provided an introduction to NTP research concepts. The NTP selects for study individual or classes of chemical, biological, or physical substances that are judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity. Gaps exist in the toxicological knowledge of these substances and additional studies would aid in assessing potential human health risks, e.g., by facilitating cross-species extrapolation or evaluating dose-response relationships. There are also issue-based nominations to enhance the predictive ability of NTP toxicology studies, to address mechanisms of toxicity, and to inform risk assessment approaches.

Research programs are developed in response to external and NIEHS/NTP nominations. The nominations undergo multiple levels of review to determine the merit and priority for study. Not all nominations lead to a research program. The NTP uses an iterative approach to design, conduct, and analyze studies. Typically the research programs are phased with multiple review and decision points. More frequently, NTP's research programs incorporate novel and alternative testing approaches, to inform and prioritize chemical and study endpoint selection, and to allow integration and interpretation of multiple data types in a comprehensive toxicological characterization.

Dr. Masten reviewed the NTP study nomination review process, explaining the sources of nominations, use of Federal agency points of contact, solicitation of public comments, and review by the BSC and NTP Executive Committee. He then described the format of this session (1) introduction to concepts, (2) presentation of the research concept by the NTP project leader, (3) public comments, (4) comments from BSC reviewers, and (5) BSC discussion. Dr. Masten briefly outlined the three nominations and reviewed the charge to the BSC: *To review and comment on draft research concepts and determine whether the proposed research projects are an appropriate use of NTP testing program resources.* The BSC was asked to comment on the clarity and validity of the rationale for the proposed research, the merit of the proposed research relative to the NTP mission and goals, the overall significance and public health impact of the proposed research, and the scope of the proposed research program.

VIII. NTP Research/Testing Concept: Sulfolane

A. Presentation

Dr. Chad Blystone, Toxicologist, NIEHS/DNTP, stated that sulfolane was nominated by the Alaska (AK) Department of Environmental Conservation with support from AK's Department of

Health and Social Services, the Mayor of Fairbanks North Star Borough, a Senator from the State Legislature, and the Agency for Toxic Substances and Disease Registry (ATSDR) due to concern over insufficient developmental and chronic toxicity data. Sulfolane is a solvent used primarily in natural gas/petroleum refining, fractionalization of wood tars, curing of epoxy resins, and production of electronics and polymers. Production in the U.S. in 2006 was between 10 - 50 million pounds.

Sulfolane is a highly polar chemical with a low vapor pressure and is miscible in water. It is presumed not to break down easily in groundwater due to low oxygen and nutrients. It does not accumulate in aquatic food chain, but is taken up by plants. Occupational exposure may by through inhalation. The groundwater in North Pole, AK has been contaminated with sulfolane possibly for up to around 20 years and it is present in other sites within Canada. In North Pole, it was detected in nearly 300 drinking water wells and the Flint Hills Refinery is providing other sources of water to residents.

Dr. Blystone reviewed the animal studies for sulfolane. Toxicokinetic (TK) data are limited, but suggest a short half-life, placental transfer, and large volume of distribution. Some studies observe neurotoxicity indicated by convulsions/seizures, hyper/hypo-activity, and hypothermia. Subchronic inhalation studies of aerosolized sulfolane (3% water) showed mortality in monkeys and dogs, chronic lung inflammation in all species studied, chronic liver inflammation in rats, decreased white blood cells and increased fatty liver in guinea pigs and a NOAEL of 20 mg/m^3. He described results of studies from 28-day exposures, 90-day oral exposures, and a 13-week rat drinking water exposure. Sulfolane reproductive and developmental toxicity has also been reported. Chronic toxicity and carcinogenic activity have not been assessed in sulfolane and genotoxic assays are mostly negative. An intermediate in the production of sulfolane, 3-sulfolene, was associated with poor survival in both rats and mice in a chronic study (NTP TR-102).

Dr. Blystone explained that sulfolane exposure and human health effects have not been characterized; AK is currently reviewing cancer and birth defect rates. ATSDR reviewed toxicity data in 2010 and 2011 and the U.S. Environmental Protection Agency (EPA) is developing a Provisional Peer Review Toxicity Value (PPRTV).

Key issues in understanding sulfolane toxicity are (1) species differences in response to exposure: limited evidence suggests guinea pigs are more sensitive than rats; (2) sex differences: previous studies suggest that the immune system is more sensitive in females than males; (3) species differences in sulfolane kinetics, metabolism, distribution, and metabolism: route specific kinetics and tissue distribution of sulfolane need to be improved; and (4) a lack of data for human exposure and potential health outcomes coupled with logistical challenges.

The specific aims and proposed approach are:

- Evaluate rodent species (mice, rats, guinea pigs) sensitivities in short-term *in vivo* assays via an oral route of exposure, which would include an evaluation of immunotoxicity in adult animals. Sulfolane was included in the 10,000 chemical library evaluated in Tox21.

- Evaluate the route of exposure influence on internal dose and tissue distribution to relate to potential toxicity and improve the TK and absorption, distribution, metabolism, and excretion (ADME) data sets.
- Evaluate the potential reproductive and developmental toxicity, developmental immune and neurotoxicity, chronic toxicity, and carcinogenic activity. NIOSH will be consulted regarding the possibility of an occupational exposure study.

Dr. Blystone explained that the study would address the uncertainties (e.g., species sensitivities) and lack of developmental and chronic toxicity data for evaluating sulfolane toxicity. By incorporating an assessment of rodent species sensitivities, influence of route on internal dose, and incorporating a developmental exposure, these studies will provide much needed data for a sulfolane risk assessment.

B. BSC Clarification Questions

Dr. Blystone clarified for Dr. Elaine Faustman that the production volume sulfolane was 10-50 million pounds.

Dr. Fernandez asked Dr. Blystone to comment on the chemical's environmental persistence, its half-life in different environmental compartments such as groundwater or surface water, and its presumed mechanisms for neurotoxicity. Dr. Blystone said it is not believed to be very persistent in surface water, but that due to the low oxygen and nutrient environment in groundwater, it is believed to persist longer. He noted that since it is miscible in water it tends to be highly mobile, leading to the concern that sulfolane may spread easily from groundwater at the refinery. Sufolane was first detected in 2000 on the site of the refinery at North Pole, AK, and was identified outside the site in 2009, when work began to define the plume within the groundwater. Regarding the neurotoxicity of sulfolane, Dr. Blystone said it had not yet been systematically evaluated.

Dr. Solomon asked to hear more about exposure issues, particularly why sulfolane might be more persistent in groundwater than in surface water, whether volatility might be a factor, and the potential for dermal exposure. Dr. Blystone said the chemical is not expected to be very volatile, and that the ADME involved and the various routes of exposure are issues to be addressed. Dr. Fernandez noted that sulfolane has low volatility and low dermal absorption due to its polarity. He added that absorption of aerosolized sulfolane from contaminated well water could still be an issue, leading to inhalation exposures. Dr. Blystone said ATSDR believed that to be a minor route of exposure.

Dr. Birnbaum asked whether, as high production volume (HPV) solvent, sulfolane is one of the compounds being used in hydraulic fracturing, or "fracking." Dr. Blystone said it may be used downstream of the fracking itself, but in terms of on-site fracking, he did not believe it was being used. Dr. Howard asked for clarification as to where the chemical is being used in terms of distribution. Dr. Blystone said it is estimated that sulfolane is used at approximately 150 extraction units across the U.S. and Canada.

Ms. Rudel asked whether sulfolane is included in standard drinking water tests in the U.S., in that given its widespread use, it may be a more common contaminant than just the one known

town in AK. Dr. Blystone said its distribution has not been assessed. Dr. Nagarkatti asked about the exposure levels in humans, and how they would compare to the levels used for testing. Dr. Blystone that the highest level seen in drinking water wells was up to 269 parts per billion (ppb).

C. Public Comment

Dr. Laurie Haws, Principle Health Scientist, ToxStrategies, Inc., said she had been involved with toxicity research on sulfolane since 2009 and cited a study (Andersen *et al*., 1977) that assessed exposure to aerosolized sulfolane. The compound is thought of as non-volatile, leading regulatory agencies to conclude that an inhalation pathway need not be assessed. She said that from a risk assessment perspective, the inhalation pathway is viewed as "very negligible and not one of concern." She added that the literature suggests that sulfolane is poorly dermally absorbed, and therefore of little risk from dermal exposure. The pathways of reasonable concern for human exposure, she said, are oral exposures in drinking water and ingestion of sulfolane in produce that has been irrigated with sulfolane-contaminated groundwater. She said most of the exposures would be "fairly low," and there is no evidence of widespread environmental contamination.

Dr. Haws reviewed the toxicity data available for sulfolane and said the EPA had derived a PPRTV for sulfolane, and due to the many studies available, had reduced its database uncertainty factor from the typical ten to a value of three. She advised that data from existing studies should be used to guide any additional testing, future research should reflect targeted research, and that the focus should be on gathering critical data for risk assessment, by employing environmentally relevant doses. She noted that gathering blood and tissue concentrations of sulfolane and metabolites would help develop TK models for estimating dose metrics and would improve extrapolations from animals to humans.

She questioned the use of guinea pigs for assessing species sensitivity and questioned data from studies using inhalation and intraperitoneal injection as routes of human exposure. She described the results of a neurotoxicity study and three reproductive toxicity studies. She suggested that NTP thoroughly review available data and identify actual risk assessment data needs prior to making decisions about future studies, focusing on endpoints where the overall weight of evidence demonstrates a clear need. She also cautioned the NTP not to fall into the trap of conducting research for the sake of research.

D. BSC Discussion

Dr. Faustman, first lead reviewer, said she appreciated the supplemental materials provided with the concept document. She felt that sulfolane was "an exceptionally interesting compound," and that the rationale and background documents were very supportive of the need to look further at the compound. Particularly, the fact that exposures have been documented but not quantified to understand risk supports the need for more research. She noted that the estimated exposure levels in the water supply in the contaminated drinking wells are actually much higher than the levels recommended for drinking water by the ATSDR. She felt that the merits of the proposed studies fit the mission and goals of the NTP. In terms of overall public

health significance, she said there is “a very strong case” for looking at the exposure routes. However, she characterized as “fairly low” action levels and recommendations for impact of additional research on the already-affected population. On points of uncertainty, a compelling case had been made in the documents that there is minimal evidence of genotoxicity. There is evidence of droplet formation, which suggests a non-genotoxic mechanism. She said the available reproductive studies suggest that that is not an endpoint of interest, but noted that implications of immunotoxicity are important. She pointed out that many of the other endpoints were hematological, and wondered whether NTP was thinking about those questions as part of the immunotoxicity studies. She was struck by the consistency of the thermal regulation modification, which was reported not to be related to central nervous system-based effects, suggesting an unknown mechanism at work. She said the inability to detect an effect does not equate to no evidence in humans. Overall, she argued for a high level of support for going forward, with the caveat that between specific aims 1 and 2 there should be discussion about whether the research is impacting quantitative risk assessment measures.

Dr. Melissa McDiarmid, second lead reviewer, endorsed Dr. Faustman’s comments, and said “this is precisely the situation the NTP is supposed to serve.” With the concentrations at the contaminated site three to ten-fold higher than recommended levels, it is definitely a situation that needs to be examined, she pointed out. She recommended that between specific aims 2 and 3, NTP identify endpoints of concern for the chronic studies, including the heme endpoints Dr. Faustman had mentioned. She felt that renal endpoints would also be worthy of consideration. She reiterated Dr. Faustman’s concern about no evidence conclusions, as the power of the studies to date has not been adequate to say there is no evidence in humans. Routes of exposure need to be more fully characterized, including the potential for double exposures, i.e., occupational plus environmental exposures. She had “high enthusiasm” for the proposal.

Dr. Zelikoff supported looking at heme endpoints, but felt that the immunotoxicological studies need to go further, looking at some of the basic factors beyond white blood cell count, such as bone marrow, and not focusing necessarily on functional changes until some evidence is seen.

Dr. Fernandez said the aerosol route of absorption should not be minimized, and should be looked at more carefully.

Dr. Nagarkatti asked whether the NTP was considering testing human peripheral blood for toxicity to white blood cells. Dr. Blystone replied that would be beyond the scope of NTP’s studies. Responding to some of the other comments, he said there would be a comprehensive evaluation including hematology, perhaps utilizing the modified one generational study, which would include developmental exposure.

Dr. Dori Germolec, Immunology Discipline Leader, NIEHS/DNTP, said the NTP would take a very focused approach because the data are consistent for immunotoxicological effects. One focus would be to determine whether a specific leukocyte population is targeted. Responding to Dr. Nagarkatti’s suggestion, she said the NTP would consider her suggestion to conduct a human *in vitro* study.

Ms. Rudel recommended the nomination of sulfolane to the EPA's Unregulated Contaminant Monitoring Program for drinking water supplies. She said listing it may be a way to get some new exposure information.

Dr. Eastmond summarized the discussion, stating the BSC has strong support for the NTP to investigate the toxicological effects of sulfolane; however, at some point during the process, there should be a pause to consider how to proceed with the follow-up chronic studies. He said a study is warranted since sulfolane is an HPV chemical with potential for occupational exposures throughout the U.S. and clear environmental exposure in the one Alaskan population.

IX. NTP Research/Testing Concept: Phenolic Benzotriazoles

A. Presentation

Dr. Blystone explained that the phenolic benzotriazole (PBZT) class was nominated by NIEHS due to widespread use as UV stabilizers, industrial additives, food contact polymers, cosmetics, sunscreens, and fragrances. He described the levels of PBZT production, the Log P values for ten of the compounds, and the PBZT class structures. The class is made up of chemicals with single substitutions on the phenolic ring, double substitutions on the phenolic ring, double substitutions on the phenolic ring that includes an ester bond, and a collection of other PBZTs with various substitutions. PBZTs have low water solubility and low vapor pressure. Some are thought to be environmentally persistent, but human exposure data are lacking. PBZTs have been measured in marine wildlife, seafood, and sediment. There are little PK/ADME data; two-ester linkage PBZTs had short half-lives in rats.

Dr. Blystone reviewed the PZBT toxicity studies, which indicate that target sites of subchronic exposures included the liver, kidney, reproductive organs, and hematopoietic system. No comprehensive reproductive toxicity studies have been completed. Prenatal toxicity studies showed limited developmental effects with no maternal toxicity. In tests for chronic toxicity and carcinogenic activity, seven PBZTs were negative for genotoxicity. A two-year drometrizole feed study showed no increase in tumors.

Key issues in the study include (1) identifying which chemicals in the PBZT class should undergo toxicity evaluation and what types of toxicity evaluation, (2) evaluating specific chemicals with the highest potential for hazard and/or internal exposure instead of testing all chemicals within the class, and (3) identifying specific potential toxicities (e.g., reproductive) and tailoring further testing to these toxicities to allow a more targeted approach to the PBZT class evaluation.

The specific aims and proposed approach are:

- Evaluate the PBZTs class in short-term *in vitro* and/or *in vivo* assays to prioritize chemicals on the basis of potential toxicity and accumulation potential
- Select which chemicals will undergo toxicity evaluation, which may include reproductive, prenatal, and subchronic toxicity evaluations in order to anchor the short-term assays

- Evaluate the ADME and PK of selected PBZTs via oral and potentially dermal routes of exposure and between males and females to better understand the influence of route of exposure and sex on internal dose
- A chronic toxicity study may be warranted based on extensive exposure and limited chronic toxicity and carcinogenicity evaluation for the class

Dr. Blystone explained that study of this class is significant because the presence of these chemicals in the environment, with the potential for accumulation, and some use in cosmetics and sunscreens requires a better understanding of any hazards. A class evaluation that incorporates a prioritization or ranking of hazard in combination with anchoring to *in vivo* evaluations will aid in the risk assessment of PBZTs. The identification of PBZTs with a hazard concern and evaluation of pharmacokinetic parameters will also provide a basis for selecting chemicals as substitutes in products.

B. BSC Clarification Questions

Dr. Richard Miller asked how the activity of at least some of the PBZTs in the peroxisome proliferator-activated receptor alpha (PPARα) pathway might reflect in the testing paradigm, or whether Tox21 testing might shed light on that. Dr. Blystone replied that the potential for peroxisome proliferation had been seen for some PBZTs and that pathway would be examined, to potentially match that response to the *in vitro* potency seen.

Dr. Minor asked whether the ADME and TK tests would be done prior to conducting even the short-term animal studies, so that exposure levels and doses could be characterized for the studies. Dr. Blystone said the issue had not yet been thoroughly discussed, but some short-term ADME and PK data may be derived. Dr. Minor asked whether NTP was also planning to link structure-activity relationship (SAR) with *in vivo* potential, versus *in vitro* assay data. Dr. Blystone said some of those experiments were planned. He added that the NTP would be evaluating tissue levels as well as plasma levels.

Dr. Solomon asked whether any environmental monitoring data in humans exists for any of the chemicals, and if not, whether that might be worth considering, potentially in collaboration with CDC or others. Dr. Blystone said he was not aware of any such data.

C. Public Comment

Mr. Joseph Manuppello, Research Associate, People for the Ethical Treatment of Animals (PETA), commented by telephone, noting that the PBZTs were a category in the EPA's HPV chemical testing program. PETA's main concern was that selected PBZTs were to be evaluated for developmental and/or subchronic toxicity in parallel to the *in vitro* studies used to prioritize the 29 compounds for further testing. He said in the research concept, the 90-day study in rats on DitPe-BZT mentions increases in testes weight, but those increases were judged to be largely a result of decreases in body weight, and not considered to be of toxicological significance. With DeMeEtPh-BZT, the research concept states reduced fetal weights and delayed skeletal maturation had been seen, but fails to mention that in the absence of effects in the high-dose group, the effects were considered to be incidental to treatment. Overall, he felt

that the concern over potential reproductive and developmental effects was overstated, and that the *in vitro* tests of PBZTs should be conducted before further testing is considered.

D. BSC Discussion

Ms. Rudel, first lead reviewer, said that the PBZTs are a large family of chemicals with significant exposure potential and "fairly shallow" toxicology data, so it is a good choice for further study. She felt that the proposed approach to start with *in vitro* studies and then use those data to prioritize *in vivo* studies is good. She recommended that NTP consider starting with ADME and TK studies to inform the first step and added that to do the *in vitro* screens, it should be known whether the active agent is the parent compound or a metabolite. Starting with the ADME would also allow the potential identification of biomarkers, which could then be considered by the National Health and Nutrition Examination Survey to give a sense of human exposure levels. She asked whether it was known how stable the chemicals are in the environment. She found the tables summarizing the toxicology data in the concept document to be very helpful. She suggested that NTP explore the use of drug discovery computational tools that might predict pathways or mechanisms based on SARs.

Dr. Minor, second lead reviewer, concurred with Ms. Rudel and suggested that building a SAR on the class itself is the priority, so it should be considered to test all 29 compounds in the *in vitro* assays. She also suggested the use of kinetic solubility assessment to ensure that the maximum concentration used would be soluble in the assay to be run. She said the specific assays to be used were not discussed, and since liver toxicity came up often in the data, she asked that NTP include some human and rat liver assays to examine different features of toxicity in order to generate a predictability model for the class. She asked for more details on assays to assess accumulation. She echoed Ms. Rudel's comments regarding the need to assess metabolic stability in mouse, rat, and human *in vitro* studies, and recommended metabolic studies in liver as well. She suggested a testing funnel using primary tests and secondary tests, where currently the protocol is comprised of several primary tests. She asked for identification of the primary tests and what would trigger movement into the next assessment. The ADME properties or PK should be determined prior to conducting that step. For the longer-term testing, she also felt that the trigger points for moving from one stage to another need to be determined. If reproductive endpoints are to be assessed, she asked which parameters would be examined and how the doses would be chosen. She rated the proposal as "moderate-to-high," depending on pulling together the several pieces she mentioned, to ensure that there is a real rationale for running the many proposed tests.

Dr. Nagarkatti, third lead reviewer, felt that the rationale for the studies was clearly articulated. She echoed the concerns the other reviewers had expressed, but felt that Dr. Blystone's presentation had helped to clarify many of her concerns. She was unclear as to what basis had been used to select the 29 compounds to be tested, or how they would be narrowed down to the one to three chosen for further study. She was also uncertain which *in vitro* assays were to be used, or what cell lines. She agreed with the other reviewers that ADME and TK studies should be conducted prior to any reproductive, prenatal, or subchronic toxicity testing, and suggested that the chronological order of the specific aims be changed to reflect that order. She was also concerned that the proposal failed to include immunotoxicological studies,

especially as the toxic effects following oral or dermal exposure may lead to sensitization. Citing several specific examples, she said she felt that the document lacked some of the details and cohesiveness she would like to have seen. In terms of the merit of the proposal, she felt that the proposed program would be "of immense value to all consumers as well as industries." She said that although some of the chemicals appear to be non-toxic, others appear to be toxic, warranting further evaluation as the public health impact may be significant. She said each of the 29 PBZTs should be evaluated on an individual basis, and then prioritized for further testing. Since only some of the chemicals would be selected for testing, the scope of the research appeared to be limited and may not provide comprehensive data. She was also unclear whether both rats and mice would be used for the *in vivo* toxicity testing.

Dr. Miller supported Dr. Minor's suggestion of a "testing funnel." For example, he said that by performing a PPARα assay, it might be possible to screen out liver effects, to the point that doing *in vitro* hepatocyte testing may be unnecessary. Dr. Birnbaum noted that there might be other mechanisms at work aside from PPARα activation. Dr. Miller agreed, but said the assay may be a useful tool for prioritization.

Dr. Howard read a consensus statement from the FDA, in which "the FDA supports the nomination of PBZTs as a class of compounds to the testing program for additional toxicology testing." In the statement, the establishment of an FDA-NTP working group for the class of compounds is proposed, to facilitate the identification of data gaps and priorities. He noted that such an approach had been used successfully in the past.

Dr. Eastmond commented on the potential for bioaccumulation, noting that the compounds' metabolites may be of even more concern, as they may fall into the range of maximal bioconcentration. Dr. Minor agreed and recommended that the issue be kept in mind as the program moves forward, perhaps by identifying additional molecules that could be tested as metabolites are determined.

Dr. Blystone thanked the BSC and said the NTP would follow the recommendations on issues addressing study design, such as quality control, stability, and purity. He said they would also address the issues of metabolism and metabolites. There is interest to develop a funnel and to identify appropriate triggers for further research. Environmental stability information will be used in moving forward in the testing paradigm. In terms of the reproductive testing, several flags in the literature support moving forward, the class is lacking in information, and the group feels those tests should go ahead.

Noting that Dr. Blystone had mentioned that several of the chemicals were among those to be screened in Tox21, Ms. Rudel wondered whether any of them are in ToxCast. Dr. Masten said that none of the PBZTs were in ToxCast Phase I, but there may be a few in ToxCast Phase II.

Dr. Eastmond summarized the BSC's comments, stating there was good support for going forward with the proposed program to develop a predictive model on SARs for the toxicity of this class of compounds. He reiterated the discussion regarding balancing the need for *in vitro* studies with the need to conduct TK and ADME studies.

X. NTP Research/Testing Concept: Trimethylsilyldiazomethane

A. Presentation

Dr. William Gwinn, Biologist, NIEHS/DNTP, briefed the BSC on the research concept for trimethylsilyldiazomethane (TMSD), a synthetic methylating reagent used by chemists for organic synthesis and in analytical methods. TMSD was originally developed as a potentially less toxic substitute for the highly unstable (explosive) and toxic compound diazomethane. The toxicity of TMSD has not been characterized, though occupational exposures can occur though dermal contact or inhalation. The Occupational Safety and Health Administration (OSHA) nominated TMSD largely as a result of recent deaths (due to acute and progressive respiratory distress from pulmonary injury) of two chemists who were exposed to TMSD in the workplace. It is unknown whether the pulmonary toxicity was caused by TMSD or by diazomethane and/or other chemical species generated by the breakdown of TMSD. The goal of the study is to characterize the inhalation toxicity of TMSD and to establish its inhalation exposure limits.

Key issues regarding the study include (1) the health and safety of individuals performing stability and toxicity studies with TMSD as well as chemical containment, (2) the stability and breakdown of TMSD into diazomethane and/or other chemical species, (3) the effect of the solvent carrier for TMSD on toxicity and in the generation of pure TMSD vapor, (4) the feasibility of generating a specified atmospheric concentration of TMSD vapor to perform an acute inhalation toxicity study, and (5) nose-only versus whole body exposure.

Specific aims of the study are to (1) characterize the availability, purity, and stability of TMSD; (2) determine the feasibility of generating controlled atmospheric concentrations of pure (and stable) TMSD vapor and characterize the stability of TMSD in artificial lung fluid; (3) perform a two-week inhalation study to assess acute lung toxicity in male and female rats and mice; and (4) perform additional *in vitro* and *in vivo* studies with TMSD to evaluate (a) inhalation toxicokinetics, (b) mechanisms of TMSD-induced pulmonary toxicity, (c) acute dermal toxicity (skin irritation and corrosion) *in vitro*, and (d) eye irritation *in vitro.* Due to limited information available for TMSD, specific aims 1 and 2 will be addressed prior to performing an acute inhalation toxicity study (specific aim 3). Because of TMSD's acute toxicity, a subchronic inhalation study does not appear to be warranted.

Dr. Gwinn stated the data obtained on TMSD could be used to update material safety data sheets (MSDSs, and other chemical reviews), establish an inhalation occupational exposure limit (OEL), and to provide risk assessment and regulation. He noted that if TMSD is found to be unstable and readily forms diazomethane, then an acute inhalation toxicity study would likely not be necessary. Diazomethane has previously been shown to be highly toxic (and lethal) upon inhalation. An OEL for diazomethane is already established and can be used to provide further risk assessment and regulation of TMSD. Further evaluation will be needed if TMSD is unstable and breaks down to yield chemical species/toxic products other than diazomethane.

B. BSC Questions and Discussion

Dr. Zelikoff asked whether there would be real-time monitoring, as a safety issue. Dr. Gwinn replied that there would be real-time monitoring outside the chambers during any whole-body

exposure tests. Also, it will be recommended that anyone in the room containing the chambers be in full respirators.

Noting that TMSD is normally sold in solution, Dr. Solomon was curious whether there had been any consideration of looking at that mixture to see if the toxicity would be different. Dr. Gwinn said such comparisons were possible.

Dr. Nagarkatti asked whether it would be important to look at other organs besides the lungs, since the compound contributes to multi-organ failure. Dr. Gwinn said liver effects had been described for diazomethane.

Regarding the accidents that had occurred with the two investigators, Dr. Minor asked if it was known what the solvents were and whether they had been used in a hood. Dr. Gwinn said the U.S. exposure solvent was ether and the Canadian exposure solvent was hexane. In the U.S. case, in which a spill had occurred, it was not required to be in a hood. Dr. Fernandez noted that the U.S. case had actually been a non-functioning fume hood exposure.

Dr. Zelikoff, first lead reviewer, recommended shortening the experimental acute exposures to less than 14 days, and that if the compound is found to break down to diazomethane, experiments with animals should go no farther given the well-established toxicity associated with that compound. Regarding the proposal's clarity and validity, Dr. Zelikoff addressed her comments to the individual aims included. She said determining the availability, purity, and stability of TMSD seemed reasonable. Noting some of the potential problems that could arise, she wondered how NTP would address them and how the research would proceed. She pointed out the potential flaws in the second aim, noting that simulated lung fluid often does not match actual lung fluid. Lung cells may be necessary, as they are primarily responsible for the metabolism of TMSD. For the third aim, she reiterated her recommendation of shortening the duration of exposure to make it more relevant for acute exposures. Since the effects are progressive and some are delayed, she recommended performing histological evaluations at multiple time points both during exposure and post-exposure up to seven days. For the fourth aim, she was unsure why subchronic studies would be necessary. She also suggested including lower doses than those proposed. She felt the studies fit well with the NTP's mission given the extreme pulmonary toxicity associated with diazomethane. She gave the research a high priority, but given the low number of exposures to the compound, she rated the public health impact of the research as moderate. Overall, she felt that aims 1 and 2 should be accomplished relatively quickly, and then it would be obvious as to whether studies should progress. She felt the subchronic studies in aim 4 were unwarranted at this time.

Dr. Fernandez, second lead reviewer, supported the need to check all metabolites, including those that might not be expected. He mentioned the possibility of intracellular formaldehyde formation and felt that cardiotoxicity should also be evaluated, either in the conduction system or in the cardiac tissue itself. He pointed out that in the second case report, the chemical was in an admixture that included methylene chloride, which metabolizes to carbon monoxide. He recommended that NTP include carbon monoxide in the evaluation, since it may have been responsible for some of the observed adverse effects.

Dr. Nagarkatti said that due to the acute toxicity of the compound, more tests might need to be included beyond the histopathology. Dr. Miller suggested looking at subtle pulmonary effects at low doses, which may not be evident in histopathology.

Dr. Gwinn agreed with the BSC's comments. Responding to Dr. Zelikoff's comment regarding stability, he said it would be a good idea to check the other solvents to see if any are more ideal in stability. He said that if there were unexpected breakdown into diazomethane, moving forward with further studies would need to be reconsidered. He agreed with Dr. Zelikoff's concern about the use of simulated lung fluid, and added that perhaps there is a cell-based assay that could be employed to look at metabolic breakdown *in vitro* versus chemical degradation in solution. He noted that doses had not yet been set for the toxicology study, and would largely depend on what sort of atmospheric concentrations can be generated from 10% solution. He also agreed that there would probably be fewer doses administered over less time.

Dr. Eastmond said the general impression of the BSC was that there was support for going forward with the project. The major concern was for the safety of the staff conducting the studies, to ensure that they are adequately protected, particularly from an aerosolized form. There was concern about stability, and the potential to look at non-lethal endpoints, both for animal welfare and for the opportunity to see effects at lower concentrations.

Dr. McDiarmid reiterated that the personal protection of the workers should be thoroughly considered in advance, as "this is a very high-hazard undertaking."

XI. Report on NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

A. Presentation

Dr. Kristina Thayer, Director of the Office of Health Assessment and Translation (OHAT), NIEHS/DNTP, briefed the BSC on the NTP-sponsored workshop, *Role of Environmental Chemicals in the Development of Diabetes and Obesity*, which was held January 11-13, 2011, in Raleigh, NC.

She related background information on the increasing prevalence, incidence, and public health impact of diabetes and obesity, illustrating that the conditions are major risks to public health. Overall, the workshop was designed to evaluate the science associating exposure to certain chemicals or chemical classes (e.g., arsenic, bisphenol A, organotins, maternal smoking, persistent organic pollutants, pesticides, phthalates, and nicotine) with development of diabetes or obesity in humans. It was intended to provide input to NTP and NIEHS for development of a research agenda. In the months following the workshop, Dr. Thayer reported, there were three government reports that acknowledged the emerging literature in the field and called for more research.

The conference was designed to bring together diverse expertise, including epidemiologists, toxicologists, bioinformaticists, and experts in the pathobiology of disease, to discuss the pertinent issues. Most of the meeting consisted of breakout group deliberations, with plenary

reports from the breakout groups. The breakout groups were asked to evaluate the strengths and weaknesses, consistency, and biological plausibility in the literature, to identify best practices, and to identify data gaps and research needs. Dr. Thayer said a series of technical reports emerging from the workshop will be published in *Environmental Health Perspectives* in early 2012.

Data from Tox21 were integrated into several chapters of the background materials and meeting sessions, as a way to introduce the program to the researchers in attendance, and to stimulate discussion on how to best assess the applications of Tox21 data.

Overall, there was support for the biological plausibility of environmental chemicals having a role both of the health conditions. Positive associations in human epidemiological studies were noted, such as associations between maternal smoking during pregnancy and childhood obesity, arsenic in areas of high exposure and diabetes, and diabetes and certain chlorinated persistent organic pollutants (POPs). Biological plausibility was also supported by several animal and mechanistic studies. The workshop demonstrated that Tox21 is an intriguing tool for assessing biological plausibility and developing research questions.

Dr. Thayer provided more details about some of the conclusions. Maternal smoking during pregnancy is associated with increased risk of childhood overweight/obesity; several studies provided support for the plausibility of a developmental "obesogen" hypothesis. The phenotype seen in the human studies was largely recapitulated in many animal studies. The breakout group concluded that the association was likely causal. There was less support for a linkage to Type 1 diabetes in human studies. There were few human studies of Type 2 diabetes, but the animal studies showed effects on pancreatic beta cell mass and function. The breakout group felt that many of the potential disease pathways were largely unexplored.

The arsenic breakout group felt that there was "limited" to "sufficient" evidence of an association between arsenic and diabetes in populations with high exposure levels such as Bangladesh and Taiwan, but "insufficient" evidence for an association in lower exposure areas, such as the U.S. and Mexico.

Dr. Thayer reported that it had been challenging to prepare a text-based background document on human studies of POPs and diabetes, since the literature was complex, with many studies reporting findings on multiple chemicals. Using a new graphic software MetaData Viewer, the breakout group found evidence for an association with diabetes based on collective analyses of cross-sectional, prospective/retrospective, and occupational exposure studies. The strongest correlations of diabetes were with trans-nonachlor, dichlorodiphenyldichloroethylene, and dioxin, and dioxin-like chemicals, including polychlorinated biphenyls (PCBs).

Some of the groups considered chemicals thought to interact with PPARs. Organotins and phthalates interact with PPARs, but the nature of those interactions differs. The breakout groups found that human studies are "insufficient" for phthalates and "nonexistent" for organotins, although it was seen that there is strong mechanistic support for the classification of organotins as "obesogens." Pesticides were the most exploratory part of the workshop, with the

goal being to identify pesticides that can serve as “signposts” for metabolic effects, based on human and animal data, linking to ToxCast data when possible.

At the workshop, input was sought from the experts to help identify the most relevant Tox21 assay targets, focusing on the biological processes being considered. The experts were asked to help identify both the relevant assay targets already in Tox21, and others to consider including.

In summary, Dr. Thayer said there had been general support at the workshop for the plausibility of the obesogen hypothesis, a linkage of diabetes to certain chemical exposures, and the recognition of a common mechanistic basis for certain chemical classes. OHAT will submit a series of technical reports to *Environmental Health Perspectives*, oversee the targeted testing project, assess human exposure to organotins, assess the ability to investigate environmental exposures in ongoing cohort studies, and continue to develop and provide access to the Meta Data Viewer as a screening tool for human studies.

B. BSC Discussion

Dr. Stephen Looney asked if NTP had considered conducting a formal, systematic review of the data included in the forest plots that Dr. Thayer had shown. Dr. Thayer replied that the breakout group that had looked at PCBs had considered the feasibility of conducting a pooled analysis. Dr. Birnbaum noted that many of the studies, such as those with PCBs, are “apples and oranges,” with different populations and different congeners measured. Dr. Thayer added that in future analyses there would be an effort to convert data to a common effect size.

Ms. Rudel said it was a terrific project and complimented Dr. Thayer on her presentation. She found the mix of disciplines to be a real strength and supported the incorporation of Tox21 and ToxCast data.

Dr. Birnbaum confirmed for Dr. Miller that the AKT protein kinase assay was included in the insulin signaling study in pancreatic ß-cells.

Dr. Zelikoff cautioned about using nicotine as a surrogate for tobacco smoke. Dr. Thayer said the breakout group had felt that the literature for nicotine was sufficient to consider the relationship causal, although they recognized that other factors might strengthen the conclusion, such as cadmium. Dr. Zelikoff suggested that if nicotine is concluded to be a potent factor, smokeless tobacco should also be examined. Dr. Thayer said that had been a recommendation from the breakout group and would be included in the report.

Dr. Birnbaum publicly commended Dr. Thayer and her team on the entire effort, as well as the other parts of the institute that had contributed.

Dr. McDiarmid suggested the use of occupational populations for exposure data on organotins and perhaps some of the other candidate toxicants. She noted that occupational populations are the positive controls for environmentally exposed people, and NIOSH would be a good source of data.

Dr. Nagarkatti asked if the high-throughput screening would be restricted to genomics, or also include epigenomics. Dr. Thayer replied that it would depend on the systems being used by the various individual researchers, but that for the most part epigenetics would not be explored.

Dr. Solomon, the lead reviewer, also praised the workshop, which she had attended in part. She found the section she attended to be "creative chaos," with many interesting discussions. She said Dr. Thayer's conclusions reflected her own recollections, although with so much activity, it was a difficult meeting to summarize. One of the strengths of the approach taken with the workshop was bringing together basic science researchers with expertise in the disease in question and scientists with expertise in the potentially associated chemicals, which had provided much of the creative spark. She noted that incorporating the Tox21 program had helped to generate potential hypotheses and consideration of how a research agenda might be developed on the issue. She agreed with Dr. Zelikoff's comment about the inclusion of cigarette smoke and its components in the research. She concluded by asserting that the workshop began what will be "a hugely important area of research."

Dr. Eastmond summarized the BSC's comments by noting that it had been a very successful workshop addressing important areas of public health and bringing together environmental science and public health. It brought together people from many disciplines, and the hope is that the work will continue.

XII. Report on Carcinogens New Review Process

A. Presentation

Dr. Bucher presented the details of the revised proposed process for preparation of the Report on Carcinogens (RoC). He reminded the BSC that the RoC is a congressionally mandated, science-based report intended to be a hazard identification document, that it is prepared by the NTP for the Secretary of HHS, and that the 12th RoC was published in June 2011.

He showed a graphic depicting the proposed RoC review process, which was released for public comment on October 31, 2011. As in prior versions, it is comprised of four panels: (1) Nomination and Selection of Candidate Substances; (2) Scientific Evaluation of Candidate Substances; (3) Public Release of Draft RoC Monograph and Peer Review; and (4) HHS Approval and Release of the Latest Edition of the RoC.

Dr. Bucher said there had been adjustments in the proposed review process for the RoC, primarily to increase flexibility in the ways NTP can obtain information as the documents are prepared, particularly since the amounts of information available on individual substances can vary dramatically. The changes also seek to dispel confusion about how NTP reaches decisions.

Following announcement of the availability of the proposed review process in the *Federal Register* on October 31, 2011, with public comment invited at that time, there was a public listening session on November 29, 2011, which attracted 19 speakers. Written comments from 13 submissions were received by the deadline of November 30, 2011. The NTP considered all

of that input and made revisions to the proposed review process to change or clarify some of the steps in the process. Dr. Bucher reported that NTP had *not* made revisions in response to requests to solicit public comment on potential members of NTP panels, set time periods for solicitation of public comments, prepare a response to public comments document, open interagency reviews, or change the listing criteria.

Dr. Bucher detailed the changes that had been made to the proposed review process in response to public comments, referring both to the graphical representation and to specific paragraphs in the written document.

He began by discussing two new documents proposed to be part of the process. First, he described a concept document, which would be similar to the concept documents used for chemical nominations to the NTP testing program. Each substance proposed for review for the RoC would have a concept document prepared as a draft for public and BSC comment. The document would include the reason for the review of a substance for the RoC, including brief information on exposure and the extent of scientific evidence for evaluating the substance's carcinogenicity, along with any major, relevant issues such as proposed mechanisms or modes of action of carcinogenicity. It would also describe the proposed approach for obtaining external scientific and public inputs in development of the cancer evaluation component of the draft RoC monograph on a substance. Thus, prior to the detailed evaluation of a substance, the public and the BSC would have the opportunity to provide input. The second new document is a RoC monograph, which Dr. Bucher contrasted with the previously used background document. The background document contained all of the relevant information used in the listing decision; however, it did not provide an integrated analysis of this information to allow one to see how the information was used in developing a listing decision. With the revised process, each candidate substance reviewed for the RoC would have a RoC monograph, consisting of two parts—a cancer evaluation component and a substance profile. The cancer evaluation component includes all the information that may bear on listing decision, both positive and negative data, mechanistic information, and an assessment of the quality and sufficiency of the data. It will apply the RoC listing criteria to the relevant information and recommend a listing status for the candidate substance. The second part of the RoC monograph will be the substance profile, the three to five pages that would ultimately appear in the RoC. It contains the NTP's listing recommendation, and a summary of the scientific evidence considered key to reaching that recommendation. It also contains information about production, use, exposure, and current regulations. The monograph will be prepared as a draft that undergoes public peer review.

Dr. Bucher went over the specific changes in each of the four panels contained in the revised proposed RoC review process document. Under Nomination and Selection of Candidate Substances, page 1, paragraph 5 delineates public comment on the nominations in the *Federal Register*, which is not a new step, but is now more clearly defined. This invites submissions of publications and information about ongoing studies for a substance, invites nominations of scientists to serve on panels and/or provide advice, and maintains a website for nominations and public comments. Changes to page 2, paragraph 1 clarify the content of the concept document. A change to page 2, paragraph 2 clarifies the opportunity for public comment at BSC meetings and the time for comments.

Under Scientific Evaluation of Candidate Substances, changes to page 3, paragraph 1 clarify the components of the RoC Monograph. The substance profile in the past has not detailed information that was contrary to the listing. This has been a source of confusion previously because it was not understood that negative information has always been considered in listing decision-making. Additions to page 3, paragraph 4 clarify the cancer evaluation component of the RoC Monograph. The additions are in response to calls for a transparent approach to identifying studies, for the RoC Monograph to include both positive and negative studies, and for NTP to conduct an overall evaluation of the available evidence. Changes to page 3, paragraph 5 clarify the approach for development of the cancer evaluation component, and include response to calls for clarification of the use of Federal Advisory Committee Act (FACA) panels, and for public comments to be made available on the web and provided to advisory groups.

Under Public Release of Draft RoC Monograph and Peer Review, changes to page 4, paragraph 3 clarify the peer-review group and the use of FACA panels. The NTP had received comments both for and against the idea that the BSC should have a formal role in the RoC process, including listing recommendation, but ultimately decided that it would be more appropriate to use expert external scientific panels for peer review of the monograph. Changes to page 4, paragraph 4 delineate the commitment to set aside time at the meeting for discussion of scientific issues raised in the public comments. It also states that the peer-review panel will vote on (1) whether the scientific evidence supports the NTP's level of evidence for human studies or experimental animal studies and (2) whether the scientific evidence supports the NTP's preliminary listing decision. Those changes were made in response to concerns that public comments have little role in evaluations. Changes to page 4, paragraph 5 specify that the NTP will respond to the peer-review report, and that the response will be posted on the RoC website. Based upon the peer-review comments, ORoC prepares a revised draft RoC Monograph. The BSC will be provided information regarding the peer review at a public meeting. Following the meeting, ORoC, in concert with the NTP Director, finalizes the RoC Monograph on the candidate substance, including the cancer evaluation component and substance profile, and posts the final RoC Monograph on the RoC website. Those changes respond to public suggestions that the response to the peer-review report should be earlier than when the RoC is released, and that the BSC should have a formal role in the process.

Under HHS Approval and Release of the Latest Edition of the RoC, changes to page 5 define the NTP Executive Committee with addition of a footnote and delete text regarding release of the NTP's response to the peer-review report, which will now occur in part 3, Public Release of Draft RoC Monograph and Peer Review. Dr. Bucher pointed out that the NTP would like to establish a more continuous process for completion of reviews for candidate substances, not necessarily waiting until the end of the two-year time period between RoCs to provide listings to the Secretary. The law mandates a new RoC be published every two years; however, the NTP would like to make the RoC a living document so that as reviews are completed, substances approved for listing could be added to the report. Regardless of the outcome of that process, NTP will make the final RoC Monograph and the peer-review report on a substance available on the web before the Secretary actually decides what will go into the RoC.

B. BSC Clarification Questions

Dr. Zelikoff asked Dr. Bucher to clarify when the draft would be reviewed by the BSC. He said the BSC would see a draft RoC monograph that includes all of the thinking that goes into the listing decision and will have been peer reviewed by a scientific panel. That panel will produce a peer-review report, and the NTP will prepare a response to the peer-review report. All of that information will be brought to the BSC. The BSC will be informed about where NTP is in the review process for the substance. There will be an opportunity for public comment. The BSC's comments would be taken into consideration, and then the final RoC monograph would be completed. Dr. Bucher clarified that the expert panel constitutes an advisor to the NTP, but the ultimate decision on listing rests with the NTP. He noted that in the past, the substance profile had been brought to the BSC for a vote as to whether it supported the preliminary listing decision.[1] In some incidence, the NTP had not augmented the BSC with subject matter experts, nor was the BSC expected to read through the background information, come to its own conclusion on whether the listing recommendation was correct or not, and vote on the actual listing. The BSC was simply asked to vote on whether the material presented in the substance profile supported the listing. He said that has caused great confusion among the public, so it was decided to eliminate that step.

Dr. Eastmond said that as a member of the BSC, he has found the role of the BSC in past process confusing. He said NTP would be well served by having the opportunity for the BSC to make its comments and give its advice early in the process, not necessarily in a voting sense, but in giving advice to go forward. Dr. Birnbaum noted that the BSC would have the opportunity to review the draft at a public meeting, with NTP staff and she listening and taking into account the BSC's comments prior to finalizing the document.

Dr. Fernandez asked how the composition of the expert panels would be determined, and what protections would ensure that the public's interests are best represented. Dr. Bucher replied that NTP evaluates the literature to see who is publishing in a given area and at subject matter experts. The NTP keeps information on experts who might be considered for inclusion on a panel. When a concept document is brought to the BSC, it would outline the scientific issues that NTP has determined need to be addressed in the review of a particular substance for listing. The public will be asked for comments and recommendations of scientists to comprise panels. There are many resources and names available to NTP. The expertise of identified individuals will be matched with the substances and scientific areas under consideration. Typically there will be need for an exposure expert, a statistician, an epidemiologist, and a toxicologist. Individuals are identified and go through an evaluation for any potential conflicts of interest, whether financial or in terms of a pre-formed opinion or bias, which could potentially disqualify them. Dr. Mary Wolfe, Deputy Program Director for Policy, NIEHS/DNTP, added that a search of companies is also conducted, to ensure that individuals being considered do not have consulting relationships, which would constitute a conflict. The individuals are informed about conflict of interest rules, and are required to sign pre- and post-meeting forms certifying that they have not had a conflict of interest during the time of their service on the panel.

[1] The statement refers to substance profiles having been brought to the BSC for comment.

Dr. Eastmond said he hoped that simply making public comments about an issue would not automatically disqualify someone from serving on a panel, which was an experience he had had previously. Dr. Bucher said he had not experienced that situation before, but the information being sought early in the process is aimed at determining the key scientific issues that need to be evaluated, not for making the listing decisions. In that early stage, public comments would not necessarily disqualify an individual from serving on the putative panel. Dr. Birnbaum elaborated that the idea was to not have someone on a panel that has already made a determination on the issues involved prior to hearing all of the input. Dr. Eastmond agreed with that concept.

C. Public Comments

Mr. Barry Clayton, Industrial Hygiene Manager, Reichhold, Inc., briefly described his company and its products. He noted that his ability to assess, manage, and communicate risk depends upon having accurate hazard information such as the RoC. He wished the BSC to be aware that the RoC has "real-world implications for manufacturers and downstream users of chemical products." As a result of the listing of styrene in the 12th RoC as being reasonably anticipated to be a human carcinogen, Reichhold has had to update its MSDSs and labels to reflect the new information, as required by OSHA standards. Explaining the relevance of the RoC listing to employees, plant neighbors, and customers is also a challenge. Noting that some other agencies came to different conclusions about styrene, he said it creates confusion when there are conflicting conclusions, undermining his credibility as a health safety professional as he seeks to give out accurate information.

He said he had participated in the NTP Listening Session that took place November 29, 2011. He noted that some of the concerns raised in that session had been addressed by Dr. Bucher, but that there was no reference in the revised proposed process to "weight of evidence," instead referring to more generalized terms such as "overall body of evidence." He urged that any revisions to the RoC process include rigorous and transparent reviews based on "full weight of the evidence evaluation" conducted in accordance with the guidelines in Chapter 7 of the 2011 National Academy of Sciences (NAS) *Review of the EPA's Draft IRIS Assessment of Formaldehyde*. He felt that any efforts to minimize the role of the BSC or to make the RoC process more discretionary than it already is would reduce its accuracy and accountability. He recommended engaging stakeholders and starting fresh to design a robust new process.

Mr. Steve Risotto, American Chemistry Council (ACC) Formaldehyde Panel, noted that some of his comments would address items Dr. Bucher had indicated that NTP had decided would not be changed, and that his group was recommending that the NTP reconsider. He said that the proposal reduces, rather than enhances, transparency by adopting a discretionary, "tailored" approach to conducting cancer evaluations. Under the new system, the public is denied an opportunity to review the monograph until after there has been interagency review, preventing review of interagency comments. Also, he said it eliminated BSC review of the monograph and listing recommendations. He said the requirement to respond to public comments is dropped. He charged the proposal compromises the scientific integrity and rigor of the RoC process by replacing the background document with a concept paper, by removing the BSC from all but

substance selection, by blurring science and policy, and generally by further insulating the NTP and RoC reviewers from scientific debate of the issues.

He called for clarification of the listing criteria used, to include requirements for a biologically-plausible mechanism, an assessment of the quality of the study or studies, and a weight-of-evidence evaluation of all available information. He recommended more of a focus on scientific decision-making, as opposed to policy, again calling for a consistent weight-of-evidence framework to be employed, with a standardized approach to evaluating studies, as was recommended by the NAS. The ACC also asks that the NTP conduct an independent peer review with an expert panel chosen by a transparent process (such as the one many agencies employ involving the NAS in the selection process) to ensure the appropriate level and breadth of expertise, with NTP staff providing the panel with a summary of the main points of controversy, and allowing the panel to make the listing recommendation, not the NTP. He called for public comment at each stage of the review process, with NTP summarizing the comments clearly and concisely for the benefit of the groups of reviewers at each stage, facilitating a weight-of-evidence approach versus a strength-of-evidence approach.

Dr. Lorenz Rhomberg, Gradient, stated that his comments were his own, but were prepared under the sponsorship of the Styrene Information and Research Center. He said RoC listing decisions have profoundly important consequences for regulation and use of the listed substances. Thus it is crucial that the decision-making process be highly scientifically credible, with a sound process for open debate on all relevant data and input from stakeholders and the wider scientific community, and sound reasoning behind listing decisions. He argued that both the current RoC listing criteria and their scientific standards need to be reformed. He noted that the current proposals for revision of the process focus almost entirely on procedure, with little said about how the judgments are to be made and listing categories defined.

He echoed the other commenters' recommendations regarding using Chapter 7 of the NAS review of the EPA formaldehyde assessment. He noted some of those recommendations were included in recent changes to the NTP proposed process, but felt that it still falls short in terms of addressing how the judgments are to be made and how the listing categories are to be defined. He found the current definitions of the listing categories to be tautological and circular. He said the "reasonably anticipated" category has no defined lower limit, and recommended a defined "top" and "bottom" to that category. He called for use of a weight-of-evidence approach, versus the current strength-of-evidence approach. He felt that the NTP RoC process had not kept up with the advances in understanding carcinogenesis brought about by recent technological breakthroughs such as high throughput screening. He asked that the BSC recognize that criteria for listing need attention, aside from the procedures used to review substances.

Dr. James Bus, Director, Toxicology and Environmental Research and Consulting Unit, The Dow Chemical Company, said "the BSC needs to ask NTP to go back to the drawing board on these proposed procedures for the RoC." He felt the proposed revisions fall "considerably short" of the objectives stated in the NAS review and the 2009 Obama administration memorandum regarding the procedures of authoritative bodies.

He articulated three main areas of concern regarding the proposed draft revisions. First, there is the failure to commit to a weight-of-evidence approach for classification decisions. The weight-of-evidence approach demands standardized data presentation and analysis of all countervailing data. Second, he was concerned about the treatment of public comments in the proposed revision, and how public comments are valued. He called for public responses to public comments, including why NTP agrees or disagrees with comments and how they are treated in RoC documents under review. He noted the proposed revisions offer no guidance as to the timing of when external peer reviewers would be provided access to public comments. Absence of timely access to public comments by peer reviewers may marginalize the value of the comments to enhancing the quality of RoC documents.

Thirdly, he noted that under the proposed revisions, the BSC would review only the concept document, and would simply receive information thereafter, with an external peer-review panel reviewing the draft monograph. He was concerned there were no guidance criteria presented as to how the peer-review panels would be assembled, and that the proposed revisions eliminate interagency peer review of the monograph. He recommended the BSC be retained as the final check, also standing as an additional arbiter for any potential unresolved controversies related to the documents. He suggested that NTP organize a public workshop in concert with the BSC to catalyze interactive dialogue between stakeholders on opportunities to best identify means for making RoC classifications.

Perry Bennett, Health and Safety Manager, Molded Fiberglass Companies, said his company is very interested in the hazard and risk assessments of the chemicals they use, including the RoC, citing thorough peer review, public participation and transparency as critical elements of the review process. Flawed reporting of cancer risks could result in unnecessary concerns, which could seriously jeopardize the company's ability to stay in business. He said public perception of the NTP's analysis is that it addresses risk. He addressed the liability insurance issue with relation to the NTP's listing of styrene as being "reasonably anticipated" to be a carcinogen, reporting that some insurers had been reluctant to renew liability policies as a result, creating an impact throughout his industry. He agreed with other commenters' concerns about the dropping of the BSC as a reviewer, with the BSC having no opportunity to vote on the adequacy of the scientific evidence or listing criteria under the proposed revisions. He urged the BSC to stay involved in the RoC process, to ask the NTP to "go back and develop a better process that follows sound scientific principles for chemical review," such as those defined by the NAS.

D. BSC Discussion

Dr. Solomon thanked the NTP staff for its very clear presentation of the complex process. She wondered how the proposed process would be completed within the mandated two-year time frame. She approved of the concept of chemicals going through the process on a rolling basis, although it might mean that the more complex chemicals might get pushed back. She said she was confused about the number of public comment periods, and that her impression was that there were to be four rounds.

Dr. Bucher said NTP shares Dr. Solomon's concern about the two-year process, and that was one of the reasons the rolling chemical concept was attractive, recognizing that the more complicated the review, the longer it will take, and that some of the more complex reviews may not make the two-year time period, but that it would be preferable to hold to the next RoC edition than to rush a review for the sake of a deadline. All of the substances under review and their status at any given time will be on the NTP website, and those finished in two years will be gathered together for the next RoC.

Dr. Zelikoff asked whether NTP had considered using an outside group to select expert reviewers, in that it might eliminate the impression that reviewers are sometimes chosen on a basis other than their expertise. Dr. Wolfe replied that NTP, like other NIH groups, is responsible for its panels and manages the selection process internally.

Dr. Faustman said she was excited by many of the proposed changes. She noted that in the past there had been frustration about only hearing about the positive studies when there were equally robust negative studies, so she applauded their intended incorporation. She said the RoC has played a unique and important role in the field, particularly due to its timeliness. With that in mind, she shared concern about the delays in the RoC. She suggested having opening and closing dates for public comments, with a clear decision pathway.

Dr. Bucher clarified that in the past the BSC had passed judgment on the clarity and completeness of the substance profile, which provided the carcinogenicity data that supported a listing. He emphasized that the entirety of the data was considered in the listing decision, and it was always placed in the background document and discussed thoroughly during the development and peer review of the background document and the formulation of the listing decision. Dr. Faustman replied that as a user of the RoC, the final write-up that ended up in the RoC itself was heavy on the evidence for carcinogenicity, but light on negative studies.

Ms. Rudel noted that these were hard issues, and that the changes made, such as the rolling process, the broadening of the types of evidence to be put into the evaluation document, were positive. She approved of the concept of choosing expert panels to be suited to the particular chemical under consideration. She supported the idea of the NTP continuing to be the experts to make the ultimate listing decisions. Regarding the discussion about the weight-of-evidence versus strength-of-evidence approaches, she felt that the implication was that the commenters wanted to see a greater emphasis placed on negative findings. She said no one, including the NTP, would want chemicals to be named as carcinogenic that are not, and there is no motivation to list chemicals that don't have solid support for the idea that they are reasonably anticipated to be carcinogens. She alluded to a language problem within the field and with the public concerning "risk," including how to communicate whether a substance has been studied or not, versus strong or weak evidence of risk itself.

Dr. Eastmond commented that the process often seems like a train going forward–once it gets going it must be carried through to the end. He hoped that would not be the case with this process; that there would be multiple potential stopping points in the process if it became clear that the evidence was insufficient. Dr. Wolfe confirmed that the process states that the NTP

may defer or terminate the review of a candidate substance if relevant information becomes available that warrants its reconsideration.

Dr. Eastmond noted that there had been several comments about the perception of a fundamental shift in BSC responsibilities in relation to the RoC, now moving to simply providing advisory comments with no formal vote. He asked whether the other members of the BSC accepted that change. Dr. Miller said he was "very comfortable with the bottom line."

Dr. Eastmond summarized the major points of consensus; the BSC supports the efforts being made to change the process, with many positive changes such as the presentation of negative results, the rolling process, and multiple opportunities for public input at appropriate times prior to the final decision. He agreed that the decision is ultimately the responsibility of the NTP and its director, but there is adequate opportunity for feedback from the public, from expert panel members, and the BSC prior to making the decision. On the other hand, it is important to make sure that the process goes forward in a timely manner and does not bog down, taking many years. He felt that the proposed changes would make a reasonably efficient, straightforward process with appropriate input. He said it was his impression that the BSC supports the effort, and "supports you going forward."

XIII. NTP Concept: Workshop on Permanent Hair Dyes

A. Presentation

Dr. Ruth Lunn, Director of the ORoC, presented the draft workshop concept to the BSC: Exposure to Permanent Hair Dyes and Cancer: Needs and Approaches for Improved Hazard Characterization.

She discussed the rationale for the workshop, including the key issues and relevant background. There is considerable public concern and frequent inquiries to the ORoC regarding the safety and potential carcinogenicity of hair dye products. Congress showed concern about mutagens in hair dyes in the 1970s, with some hair dyes taken off the market in the 1980s because they were mutagenic or caused cancer in experimental animals. However, some of the dyes used today are in the same chemical classes as those taken off the market. There are three types of hair dyes: temporary, semi-permanent, and permanent, with the permanent hair dyes being the most commonly used. Exposure to hair dyes is actually exposure to a mixture of chemicals, including dye precursors, oxidants, fragrances, stabilizers, non-permanent hair dyes, and hair-related conditioners.

Dr. Lunn reviewed some of the existing knowledge about the chemicals' metabolism and key findings in humans and animals. She noted that some hair dyes are aromatic amines which can be metabolized via Phase I and/or Phase II enzymes, leading to the formation of nitrenium ion, which can bind DNA, forming adducts and leading to mutations. The NTP has tested 26 chemicals used in hair dyes, for example. A few of them are listed as *reasonably anticipated to be a human carcinogen* in the RoC or possibly carcinogenic by the International Agency for Research on Cancer (IARC). In a 2010 monograph, IARC concluded that there was limited

evidence of carcinogenicity of hair colorants from studies in experimental animals, although the group acknowledged methodological limitations in the studies they reviewed.

Although the safety of hair dyes has been a concern for a long time, and there are numerous studies in animals and humans, the state of the science is still unclear. The IARC review concluded, " . . . personal use of hair colourants is not classifiable as to its carcinogenicity in humans." In the NTP's initial review of the literature, several key issues in hair dye research were identified: (1) the large number of chemicals present in hair dyes, (2) topical exposure to a mixture of chemicals, (3) variation of dyes across commercial brands and shades, (4) types of dye used change over time, and (5) genetic susceptibility.

Thus, the proposed workshop would help advance the state of the science to answer the question whether hair dye use is a cancer hazard. It would include a focused discussion of data gaps, research strategies, and testing methods. The workshop would provide a forum to obtain cross-disciplinary scientific input from the private and public sectors for testing and research, and an opportunity to evaluate the utility of short-term assays, such as Tox21, for testing hair dyes' safety and to compare short-term testing to findings in other experimental systems. The goals of the workshop are to (1) identify knowledge gaps in testing and research evaluating hair dyes and cancer risk; (2) identify approaches to improve (a) toxicity testing of individual dyes and/or commercial products and (b) epidemiologic studies; (3) identify and propose mechanisms of cancer induction potentially applicable for hair dyes and research strategies to test them; and (4) foster multidisciplinary discussions to facilitate the use of toxicology to inform epidemiologic study design.

The pre-workshop, workshop, and post-workshop activities were discussed. Pre-workshop, there would be a workshop planning committee consisting of NIEHS scientists both from DNTP and other parts of the Institute, as well as representatives from other governmental agencies such as the FDA and the National Cancer Institute. A literature review document would be produced, taking advantage of the IARC document as a starting point, supplemented with updated information from Tox21 and other related materials. The workshop itself would consist of plenary sessions, presentations, and multiple sequential breakout groups, facilitating cross-disciplinary discussions and recommendations. After the workshop, there would be a final meeting report consisting of the literature review document and the working group recommendations for publication in the peer-reviewed literature.

The breakout group topics proposed for the workshop are: (1) toxicology testing: long- and short-term strategies, individual dyes or commercial products; (2) mechanisms of carcinogenicity: identification, proposal, and strategies to evaluate; (3) biomarkers of exposure, effect, and genetic susceptibility; and (4) epidemiologic studies.

B. BSC Clarification Questions

Dr. McDiarmid said she could understand why the group desired to expand the outcome measures beyond mutagenesis and cancer. Her group had reviewed the area just last year and came to the understanding that the excesses were only attributable to black dye prior to 1980, at which time there was a change in formulation. Dr. Lunn said that at least in the pooled

analysis, the role of the color was not clear. Most of the studies had found excess risk in people who had begun dye use in the 1980s. The issues of color and the dyes that had been taken off the market had not been fully resolved as yet.

Dr. Miller requested elaboration on the potential impact of the workshop on future testing strategies. Dr. Lunn said it was hoped the workshop would generate some recommendations for short-term tests, particularly in light of the current efforts in Europe.

Dr. McDiarmid called the workshop a potential "can of worms," and felt there were too many elements to be evaluated in the workshop setting. Dr. Lunn said the workshop would concentrate on personal use products, and not on occupational exposures of hairdressers. Dr. Birnbaum said that the complexity was one reason for holding the workshop, to bring many people together to try to determine what really needs to be investigated in the area.

C. Public Comment

Dr. Linda Loretz, Director, Safety and Regulatory Toxicology, Personal Care Products Council (PCPC), provided comments. The PCPC represents the cosmetics and personal care products industry, including hair dye manufacturers. She said the PCPC was very interested in the workshop and would be willing to participate, bringing its unique knowledge of hair dye chemistry, formulation, and ingredient use. She noted that the hair dye industry had contributed much of the hair dye chemistry information to the IARC review of hair dyes. The hair dye strategy started in Europe in 2003 required hair dye manufacturers to submit safety dossiers for each dye, and as the hair dye industry is global, the products used in Europe are relevant to products used elsewhere, including the U.S. The data submitted included genotoxicity tests, dermal absorption data, metabolism data, and TK. She emphasized that the industry stands ready and willing to participate, and believes it can make a unique contribution.

D. BSC Discussion

Dr. Miller, first lead reviewer, said he struggled with this concept a bit, and agreed with Dr. McDiarmid's characterization, making a workshop a good idea. He felt that the rationale for the workshop was appropriate, and that it is meritorious relative to the mission and goals of the NTP. He said there was a good communication plan for disseminating the key points and proposals to emerge from the workshop. He characterized the overall significance as "moderate," as there has obviously been a great deal of exposure, but the signal is rather weak, although controversial. He said the scope is broad, but that that was necessary, and a multidisciplinary approach is supported. With regard to modifications, he recommended more emphasis on metabolism in combination exposures in terms of the expertise recruited for the workshop. He endorsed the use of outside experts to help plan the workshop, including carcinogenesis, immunotoxicology and metabolism experts. He clarified that the suggestion regarding bringing in outside experts was not meant to imply that that expertise was not available in governmental agencies, but was intended to help focus the tough questions for the workshop. Regarding the proposed breakout sessions, he noted that given the absence of a confirmed carcinogenicity signal, it would not be appropriate for one of the groups to be

"Mechanisms of Carcinogenicity." He felt that it should be combined with metabolism, or that perhaps there should be a group strictly focused on metabolism.

Ms. Rudel, second lead reviewer, felt it was unrealistic to expect that there would ever be a really good human study of hair dye use due to the overwhelming number of confounders. Therefore, she suggested focusing on other developments: first, development of short-term exposure and early-effect markers for certain classes of hair dyes, testing strategies, and identification of chemical characteristics to avoid in hair dyes, to help direct the design of new formulations that would be less concerning.

Dr. Zelikoff, third lead reviewer, suggested starting with the knowledge gaps that had already been identified in the IARC document and going forward from there. She asked how this workshop would give an outcome different from IARC's. She wished to emphasize that whatever emerges from the workshop should be published in the peer-reviewed literature. She felt that there was much to be gained from having a multi-disciplinary event, by broadening out the scope a bit. She considered the overall significance was "high" and suggested including reproduction and development as areas of focus in addition to cancer, as many pregnant women dye their hair.

Dr. Lunn said she understood the criticism regarding the mechanisms breakout group and said that perhaps biomarkers and mechanisms could be consolidated into one breakout group. She said that while the IARC document was a good starting point in some ways, it did not address immune effects or short-term testing, so there would be some additional elements to examine beyond what the IARC did. She agreed that looking at metabolism would be important.

Dr. Howard said the FDA encourages and supports the concept of getting together to identify data gaps in this area. But it suggests not necessarily focusing just on cancer, but looking at the broad spectrum of potential effects.

Dr. Birnbaum said that some of the previous comments about expanding the scope of the workshop had resonated with her, and that it might be an opportunity for OHAT to work with ORoC on the workshop.

Dr. Eastmond summarized the discussion, stating there was general support from the BSC to move forward with the workshop. He noted the BSC's concern about how complicated the workshop would be due to the many confounding factors and different chemicals involved. The feeling was that the concentration should not be on cancer alone but expanded to include other endpoints as well. He noted the importance of including outside experts early in the process to help focus the workshop to identify data gaps and how to fill them.

XIV. Adjournment

Drs. Bucher and Birnbaum thanked the staff and the BSC members for their hard work. Dr. Eastmond adjourned the meeting at 5:00 PM.