



NTP
National Toxicology Program

Summary Minutes

NTP Board of Scientific Counselors

June 15-16, 2016

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I. Frequently Used Abbreviations and Acronyms

ADME	absorption, distribution, metabolism, excretion
BPA	bisphenol A
BSB	Biomolecular Screening Branch
BSC	Board of Scientific Counselors
CDMA	Code Division Multiple Access
CRU	Clinical Research Unit
DNTP	Division of the NTP
EBV	Epstein-Barr virus
EFSA	European Food Safety Agency
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HHS	Health and Human Services
HIV-1	human immunodeficiency virus type 1
HTLV	human T-cell lymphotropic virus type 1
IAA	interagency agreement
IARC	International Agency for Research on Cancer
ILS	Integrated Laboratory Systems, Inc.
IRB	Institutional Review Board
IVIVE	<i>in vitro</i> to <i>in vivo</i> extrapolation
JMPR	Joint Food and Agriculture Organization of the United Nations/World Health Organization Meeting on Pesticide Residues
KSHV	Kaposi sarcoma-associated herpesvirus
LAN	light at night
MCV	Merkel cell polyomavirus
NCTR	National Center for Toxicological Research
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OEHHA	California EPA Office of Environmental Health and Hazard Assessment
OHAT	Office of Health Assessment and Translation
ORoC	Office of the Report on Carcinogens
RoC	Report on Carcinogens
RFR	radiofrequency radiation
TK	toxicokinetic

II. Attendees*

Members in Attendance:

Cynthia Afshari, Amgen	Kenneth McMartin, Louisiana State University
Norman Barlow, Johnson & Johnson	Lisa Peterson, University of Minnesota (chair)
George Corcoran, Wayne State University	Kenneth Ramos, Arizona Health Sciences Center
Mary Beth Genter, University of Cincinnati	
Daniel Kass, New York City Department of Health & Mental Hygiene (by telephone)	James Stevens, Eli Lilly and Co.
Steven Markowitz, City University of New York	Iris Udasin, Rutgers University

*The meeting was webcast. Individuals who viewed the webcast are not listed, except as noted.

Member not in Attendance:

Katrina Waters, Pacific Northwest National Laboratory

National Institute of Environmental Health Sciences (NIEHS) Staff:

Mamta Behl	Gloria Jahnke	Robert Sills
Linda Birnbaum	Grace Kissling	Stephanie Smith-Roe
Abee Boyles	Kelly Lenox	Diane Spencer
Chad Blystone	Chris Long	Matt Stout
John Bucher	Ruth Lunn	Vicki Sutherland
Jed Bullock	Robin Mackar	Kyla Taylor
Warren Casey	Scott Masten	Kris Thayer
Natasha Catlin	Barry McIntyre	Sally Tilotta
Helen Cunny	Mark Miller	Erik Tokar
Mike DeVito	Esra Mutlu	Molly Valant
June Dunnick	Sheila Newton	Suramya Waidyanatha
Paul Foster	Rick Paules	Nigel Walker
Dori Germolec	Cynthia Rider	Vickie Walker
William Gwinn	Georgia Roberts	Lori White
Robbin Guy	Veronica Robinson	Cynthia Willson
Jean Harry	Andrew Rooney	Kristine Witt
Ronald Herbert	Kristen Ryan	Mary Wolfe
Michelle Hooth	Kelly Shipkowski	Rick Woychik

Other Federal Agency Staff:

Paul Howard, US Food and Drug Administration (FDA), National Center for Toxicological Research (NCTR) liaison to NTP

Elizabeth Whelan, National Institute for Occupational Safety and Health (NIOSH) liaison to NTP

NIEHS Contractors:

Dave Allen, Integrated Laboratory Services, Inc. (ILS)	Ernie Hood, Bridport Services
Greg Baker, Battelle	Kyathanahalli Janardhan, ILS
Roy Barnewall, Battelle	Rachel McIntosh-Kastrinsky, Kelly Services
Karen Elsass, Battelle	Jamie Richey, Battelle
Dawn Fellacara, Battelle	Pam Schwingl, ILS
Sanford Garner, ILS	Mayo Smith, Social and Scientific Systems
Amit Gupta, Battelle	Barney Sparrow, Battelle

Public:

Reshan Fernando, Research Triangle Institute	Amy Roe, Procter & Gamble
Laura Green, Green Toxicology, LLC	Karen VanderMolen, Procter & Gamble
Wendy Kuo, University of Pennsylvania	Sarah Weil
Alaina Perkins, Yale University	

June 15, 2016

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened in public session on June 15-16, 2016, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Dr. Lisa Peterson served as chair. She welcomed everyone to the meeting and asked BSC members and other attendees to introduce themselves. Dr. Lori White, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Report of the NIEHS/NTP Director

Dr. Linda Birnbaum, Director of NIEHS and NTP, briefed the BSC on recent developments at NIEHS and NTP. She said the Senate recently passed a bill that included a \$2 billion increase in National Institutes of Health (NIH) funding for FY 2017, but that much of the increase was earmarked for specific programs, with the remainder to be proportionately distributed among the NIH Institutes and Centers. If the increase is finalized, it would mean an approximately \$28 million increase for NIEHS funding. Superfund appropriation is anticipated to be flat. The 21st Century Cures Act is still under consideration in Congress. Dr. Birnbaum noted recent Congressional briefings on endometriosis awareness and bisphenol A (BPA).

She described recent scientific advances by NIEHS/NTP staff, including studies of neurite outgrowth in human induced pluripotent stem cell-derived neurons, allergic pulmonary inflammation in mice due to exposures to fungal bioaerosols, a histology atlas of the developing mouse hepatobiliary hemolymphatic vascular system, and a report on chemical reactivity and respiratory toxicity associated with popcorn flavoring agents.

She discussed the May 26 release of a NTP report on partial findings from NTP carcinogenesis studies of cell phone radiofrequency radiation (RFR) in rats, which received a great deal of media attention. She updated the BSC on NIEHS/NTP efforts related to the drinking water crisis in Flint, Michigan.

Recent special visitors to NIEHS included Dr. Yvonne Maddox from the Uniformed Services University of the Health Sciences and Dr. Janine Clayton, Director of the NIH Office of Research on Women's Health.

Dr. Birnbaum noted the 50 years of environmental health training at NIEHS, describing the fellowships provided, with a total training investment of \$28.1 million in FY 2015. She also described local and global training programs.

Dr. Birnbaum recognized retiring BSC member Dr. Iris Udasin, presenting her with a certificate and letter of appreciation for her service.

Mr. Kass asked about the appropriation in FY 2017 for the Worker Training Program. Dr. Birnbaum said the \$27 million for the Worker Training Program comes mainly from the \$77

million Superfund appropriation. In addition, the Worker Training Program typically also receives an annual pass-through of \$10 million from the Department of Energy for training at nuclear sites.

V. New NTP Research Projects

A. Presentation: NTP Research Problem Formulation

Dr. Scott Masten, NTP Office of Nomination and Selection, briefed the BSC on how the NTP identifies research problems and formulates a program of work designed to address critical data gaps.

Nominations to NTP come from many different sources through an open and transparent process in which anyone can nominate a substance or issue for study at any time. The nominations have a widely varying level of specificity. NTP studies individual or classes of chemicals, as well as undertakes thematic research aimed at improving predictive capability of current tools, addressing mechanisms and pathways of toxicity, and informing risk assessment approaches. Risk-based prioritization is determined by exposure potential and hazard potential. NTP spends time on formulating appropriate research questions in order to obtain useful and correct answers. Problem formulation involves iterative and interactive scoping activities.

Dr. Masten detailed the strategy and approach used in NTP research project development. He briefly described the three projects to be presented, and noted that they were less mature than what is typically presented to the BSC. He mentioned NTP's current interest in environmental and viral exposures such as Zika virus. Dr. Masten noted the importance of stakeholder engagement throughout the process, taking advantages of opportunities throughout project development and involving agency partners and the public. Planning and review documents for projects are available through NTP websites.

B. BSC Questions and Discussion

Dr. Markowitz asked if NTP tracked where nominations originate over the past five to ten years. Dr. Masten estimated that half of the nominations came from other federal agencies and half from the public.

Dr. Birnbaum noted that Dr. Masten has been one of the key members of the NIH team working on research on Zika, including large, prospective, longitudinal pregnancy studies, leveraging new cohorts of pregnant women in Puerto Rico.

Dr. Barlow asked what happens to a nomination if the substance is not studied at NTP. Dr. Masten said in the case of a decision to not study a nominated substance, the nomination still remains under consideration, because circumstances may change.

Dr. Howard noted that there are many levels in the nomination and selection process where other federal agencies are involved, because they help maximize the impact of a study and prioritize what should be done.

C. Presentation: NTP Research Concept: Thallium Compounds

Dr. Kelly Shipkowski, DNTP Toxicology Branch, briefed the BSC on the research concept for thallium compounds. She noted that the U.S. Environmental Protection Agency (EPA) Office of Land and Emergency Management nominated thallium compounds due to the potential for widespread human exposure and a wide spectrum of potential adverse health effects in humans. EPA requested data to support hazard identification and dose-response assessment and to derive toxicity values.

Dr. Shipkowski said human exposure could occur from both anthropogenic and naturally occurring sources, with contaminated drinking water exposure a major concern. Existing data indicate that thallium causes alopecia, may be a neurotoxicant, and may induce developmental and reproductive toxicity. A 2009 review from EPA's Integrated Risk Information System (IRIS) indicated low confidence in the available toxicity data and a lack of adequate toxicity studies. The proposed research program would evaluate the potential for water-soluble thallium compounds (+1 state) to induce neurological, reproductive, and developmental toxicity following oral exposure in rodents. The oral exposure route is most relevant due to concerns about exposure through contaminated drinking water. Specific aims are to: (1) select a representative thallium compound (potentially Tl_2SO_4) and evaluate its stability in drinking water formulations, (2) evaluate the subchronic toxicity of a representative thallium compound in rodents following perinatal exposure via drinking water, and (3) utilize *in vitro* approaches and lower animal models to assess the comparative biological activity of multiple thallium compounds. The third aim will include: (1) evaluation of the stability and speciation of multiple thallium compounds, (2) consideration of *in vitro* assays to evaluate cytotoxicity and genotoxicity, and (c) possible use of zebrafish models for evaluation of different biological targets. The significance and expected outcomes of the project are: (1) oral exposure to thallium compounds via drinking water and dietary sources may represent a significant human health concern, (2) EPA Office of Land and Emergency Management identified subchronic toxicity studies of thallium compounds as a key research need, and (3) the information provided by these studies will serve to reduce uncertainty in the available toxicological data, characterize dose response, and more fully assess the potential hazards of thallium compounds.

D. BSC Questions and Discussion

Dr. Cynthia Afshari asked about the peer review of the report on subchronic studies, including whether there had actually been a review of primary data and whether there had been any recommendations that informed this newer plan. Dr. Shipkowski said it is her understanding that the report was never published, but some findings may have indicated neurotoxicity; however, alopecia was the only treatment-related finding reported.

Dr. Norman Barlow suggested it would be preferable to conduct *in vitro* studies first, both to inform later *in vivo* studies and ensure that the correct compound is selected. He said the extent of potential human exposure is still not clear, and that the need should be balanced with the finite resources of the NTP. He noted that the project fits some of NTP's goals, but that it was

still not clear to him that it should be a high-priority program. He rated the project's overall significance as low.

Mr. Daniel Kass said the rationale for engaging in the project is solid, and it is convincing that thallium's presence in the environment is sufficiently widespread to warrant concern for human health effects, particularly since there is insufficient information to establish a reference dose. He noted that thallium is not a rare element, as established by National Health and Nutrition Examination Survey (NHANES) data, and that it is unclear whether it has public health significance, even at high doses. He approved of the approach proposed in the concept, which seems to appropriately cover hazard, exposure, outcome, and mechanism in a parsimonious way. He rated the project's significance and public health impact as moderate.

Dr. Afshari noted that thallium appears to still persist in the environment and exceed current limits. She said significant data gaps could be closed with the proposed studies, and they may ameliorate some of the concern. The ability to study stability may help mediate or moderate some of the concern that fuels the proposal. She felt the different components of the proposal were important and would help close the data gaps. She recommended starting the work with the third aim, the stability testing and *in vitro* assays. She agreed with the idea of testing stability in simulated body fluids, and noted that it should be conducted at body temperature to allow selection of the right species for the 90-day *in vivo* study. Closing the gaps in distribution and excretion data would present an opportunity to consider sensitive populations. Another important point in the proposal was one of the proposed mechanisms of action involving sodium-potassium ATPase, which could be studied *in vitro*. Those assays would be helpful for picking doses for further studies and for cross-species extrapolation. She said exploration of the sensitivity of the cardiovascular system is lacking in the proposal. She approved of the use of alternative models such as zebrafish, which would help to generate additional data to answer questions on reproductive and neurotoxicity, but she cautioned about the possibility of false negatives. She said if NTP undertakes the subchronic study, it would be an opportunity to collect samples to look for non-invasive endpoints of biomarkers. Regarding the alopecia endpoint, she recommended consulting with an expert to help design a study to evaluate it appropriately. Regarding assessment of inhalation exposure, she cautioned that impact from a particle route may be different from a blood level exposure route. She ranked the proposal's significance as moderate.

Dr. Shipkowski said the *in vitro* assessments are designed to be a read-across of the thallium compounds, rather than a prioritization exercise, particularly since there is limited information for thallium regarding the specific endpoints of toxicity. By performing the *in vivo* studies first, specific endpoints on which to base comparisons would be determined, then the *in vitro* approaches would be used to see if there are specific differences between any of the thallium salts. Regarding the significance of human exposure, she said although there is no complete understanding of human exposure currently, data from the Environmental Working Group indicated detection of thallium in treated tap water and data from NHANES suggested that human exposure is occurring. One goal of the project is to fill the data gap on continuous low-level exposure. There is also concern for exposure to thallium in sensitive subpopulations, including children and pregnant women. She said prevalence of exposure, limited data, and

concerns for sensitive subpopulations play a role in the significance of the project. Regarding the sodium-potassium ATPase mechanism, Dr. Shipkowski said it is known that thallium ions can replace potassium ions *in vivo*.

Dr. Kenneth Ramos asked about the rationale for narrowing the focus to developmental, neurological, and reproductive endpoints. Dr. Shipkowski said those are the endpoints listed in the nomination from the EPA, and they seem to be the most significant in the literature. Dr. Masten said the plan is to place extra emphasis on neurological and developmental endpoints, as opposed to excluding other endpoints. Dr. Ramos disagreed with the plan to conduct *in vivo* studies first. He recommended conducting initial screening *in vitro* and then using those data to guide selection of the *in vivo* studies. He said there is potential to proceed with a 90-day study using the wrong compound at the wrong dose for the not-most-sensitive endpoints.

Dr. Peterson summarized the BSC recommendations which were to give the project a low-to-moderate priority and to complete the *in vitro* studies before the *in vivo* studies.

E. Presentation: Synthetic Turf/Crumb Rubber Research Program

Dr. Abee Boyles, DNTP Office of Health Assessment and Translation (OHAT), briefed the BSC on the proposed research program for synthetic turf and crumb rubber. Synthetic turf, which is installed in indoor and outdoor facilities, is considered a substance of concern. Adults and children play sports on it, and crumb rubber can stick to skin, clothes, and hair. The potential exposure pathways are dermal, ingestion, and inhalation. A private citizen nominated crumb rubber for evaluation in November 2014. In November 2015, the California EPA Office of Environmental Health and Hazard Assessment (OEHHA) requested short-term *in vivo* and *in vitro* toxicology studies on crumb rubber with results available within the next 18 months. In March 2016, a private citizen requested a cancer bioassay for inhalation exposure and characterization of chemicals that can be extracted from crumb rubber.

A review of the human health literature revealed mainly injury and sports performance, with very few studies on health effects from exposure to chemicals in the turf. Dr. Boyles summarized risk assessment studies conducted in Italy (2011), Connecticut (2011), and California (2007), which found health risks due to exposure to benzo[a]pyrene, benzothiazole, and chrysene. OEHHA is conducting a study on the potential health effects of synthetic turf; it involves extensive field sampling and analysis and personal biomonitoring, and is expected to be completed in 2018. There is also a federal effort involving U.S. EPA, Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry, and Consumer Product Safety Commission, which seeks to fill data gaps, characterize the constituents of recycled tire crumb, and identify ways people might be exposed to tire crumb. A status report on that effort is expected later in 2016. The European Chemicals Agency is also assessing the risk resulting from skin, oral, and inhalation exposures to recycled rubber filling used on both open air and indoor sports grounds.

The NTP program goal is to conduct short-term *in vivo* and *in vitro* toxicology studies on crumb rubber, while not aiming to reach definitive hazard assessment conclusions. The intentions are to investigate exposure scenarios similar to human experience, complete the work within 18

months, and emphasize health outcomes of most concern to the public, such as blood and brain cancer. Dr. Boyles summarized the details of planned testing, including preliminary chemistry testing, exposure options, and *in vivo* and *in vitro* tests. She noted that there would be continued communication and cooperation with OEHHA and federal agencies. Analysis of the studies' findings and release of initial results are expected in 2017.

F. BSC Questions

Dr. Steven Markowitz asked if there were any published studies of workers at tire recycling plants. Dr. Boyles said no studies have been found, although there is much in the literature about rubber manufacturing. Dr. James Stevens mentioned a Taiwanese study of workers in a tire shredding plant. Dr. Birnbaum said there would be different types of exposures at different times, with a newly laid, artificial, indoor turf creating a higher exposure to volatiles than any similar surface outdoors or an aged surface. Dr. Boyles noted that it is unknown whether the release of volatiles would change over time. Dr. Birnbaum added that there has been concern recently about leukemias and lymphomas among female soccer goalies. Dr. Boyles said those reports have been in the lay press and not yet published in the scientific literature.

Dr. Udasin asked whether mucus membrane exposure has been considered, especially since the cancers of concern are blood cancers. She said it is a different exposure from dermal, which implies intact skin. Dr. Boyles said exposure via mucous membranes is not a typical route that is evaluated, but in this case should be included due to the occurrence of abrasions among athletes.

G. Public Comment

Dr. Peterson introduced Dr. Laura Green from Green Toxicology LLC, for public comment on the program. Dr. Green identified herself as a consulting toxicologist who has examined exposures to, and health risks from, crumb rubber used as infill in synthetic turf fields. Regarding a potential cancer cluster among soccer players, particularly goalies, she said there is likely a cluster, but the cluster will probably never be explained. She recommended including a representative from the tire industry in NTP's roster of experts consulted for this project. She discussed the prior research in the area and said inhalation was not a concern, since particles are typically too large to be inhaled. She noted that there should be much information available about benzothiazole, which will likely be the only volatile of interest. She recommended that dosing be conducted by suspending crumb rubber in water and administering it by gavage. She urged that NTP not bother with many *in vitro* tests, which would not be as informative as gavage exposures. She felt that administering more than one dose would be important, specifically three doses, along with controls of ordinary field dirt and other infills.

H. BSC Discussion

Dr. Mary Beth Genter felt there is a clear and valid rationale for conducting the studies because there are many stakeholders and a very engaged and concerned public. She recommended clarity in the vocabulary for describing crumb rubber and a focus on the tire crumb, since artificial turf has many components. She said a focused effort would be required to accomplish

an 18-month completion of analysis and release of initial results. She agreed with administering crumb rubber via gavage at multiple dose levels and said it would be important to determine what elements become bioavailable. She recommended building in genotoxicity assays in the research, urged establishment of a reference crumb sample, and endorsed conducting a limited number of *in vivo* tests evaluating dermal exposure endpoints, particularly using artificial sweat. Dr. Genter had moderate-to-high enthusiasm for the project, particularly since it involves a battery of short-term tests that could guide future studies.

Dr. Stevens said it is not clear why the previous studies of crumb rubber, which found little risk, were being discounted. If the studies are flawed, the flaws should have been explained. He was troubled by the 28-day study design, and felt that it would be better to be designed as an exposure study via gavage. He questioned how a dose-response relationship could be established in the absence of knowing what to measure. He said there is a body of literature on crumb rubber that evaluates downstream aquatic toxicology outcomes, and recommended exposing zebrafish to downstream water near artificial turf fields to assess toxicological effects. He advocated an ecotoxicology approach as a surrogate for understanding what concentrations might yield a biological response. He said that although the study could be conducted, he is unsure whether there is a hypothesis to test. Even with a hypothesis in place, he questioned whether the technical aspects of the design are sufficiently worked out to obtain data that would allow conclusions that help inform public health. Dr. Stevens had low enthusiasm for the project.

Dr. Kenneth McMartin said his support of the project fell between the first two discussants. Although there is relatively high public concern for health effects from exposure to crumb rubber, there are little data available in terms of the toxicity. He thought pursuing short-term *in vivo* and *in vitro* toxicity studies would be valuable. He endorsed Dr. Stevens' suggestion regarding zebrafish and ecotoxicological testing, since identifying what compounds leach off the crumb rubber is important. He was concerned about conducting any surrogate marker analysis of chemicals that might be in the rubber, as it is unclear what those components might be. He said surrogate marker studies should await completion of ongoing exposure studies, which should yield important information for follow up by NTP. He noted that solvent extraction would not be useful, although water extraction might be. He felt it would not be reasonable to compare the turf to other types of fields. Dr. McMartin said the rationale for the study is fairly clear, and that although exposure appears low, public health concern is high, so he thought the study of moderate impact.

Dr. Boyles said the NTP team had struggled with the vocabulary regarding crumb rubber and hoped to be more consistent in the terminology. She said there has also been difficulty with the bioavailability characterization, which is what some of the other agencies are working on; NTP has been asked to complement their work. The plan is to work on short-term studies now in response to the OEHHA request. The data generated will serve as a starting point for future studies. She said it would be useful to have a reference crumb sample, but it is difficult to determine one. She appreciated the recommendations regarding artificial sweat and an ecotoxicology approach.

Dr. Markowitz noted that all three discussants had referred to public concern, and added that with 11,000 fields in use and another 1,200 per year being added, there is potential widespread exposure. Having been on such fields, he said crumb rubber inevitably accumulates on skin and clothing.

Dr. Stevens agreed with Dr. Markowitz, but said that he is concerned about whether the proposed study would add anything informative to the necessary risk assessment. He was skeptical that a 28-day gavage study in rats would yield anything useful to decrease the level of uncertainty or alleviate public concern.

Dr. Barlow questioned the timing of these studies in light of the other work currently underway at NTP. He said it might be better to complete the studies at another time. Dr. George Corcoran shared Dr. Barlow's concern regarding the timing and noted that he considered the proposal premature.

Dr. Afshari said it is questionable whether a 28-day study would appropriately mimic the short-term exposures on athletic fields. She liked Dr. Stevens' suggestion of the ecotoxicology approach.

Dr. Nigel Walker noted that NTP has not actually proposed to conduct a gavage study, although it is one of the options under consideration as methodology is being determined.

Dr. Bucher said NTP's contribution in this area would be to shed light on exposure and help determine what might come off the particles and be absorbed. He was interested in the BSC's comments that inhalation should be excluded as a possible exposure route.

Dr. Peterson summarized the discussion, stating that the BSC has varying opinions on the program, and it is suggested that the *in vivo* studies would be premature at present.

I. Presentation: Glyphosate Research Scoping

Dr. Stephanie Smith-Roe, DNTP Biomolecular Screening Branch, gave the BSC a brief review of efforts by NTP to investigate whether to conduct studies of glyphosate and glyphosate formulations. Glyphosate is the most heavily used herbicide in the United States and around the world. It was first nominated to the NTP for testing in 1981, before the development of glyphosate-resistant crops. NTP conducted a series of short-term studies including 13-week toxicity studies of glyphosate in feed, which were published in 1992. At that time, few toxicological effects were observed and there was no evidence of genetic toxicity. The International Agency for Research on Cancer (IARC) concluded in 2015 that glyphosate is *probably carcinogenic to humans*, while the European Food Safety Agency (EFSA) stated that it is *unlikely to pose a carcinogenic hazard to humans*. In 2016, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Meeting on Pesticide Residues (JMPR) reached a similar conclusion. U.S. EPA is currently completing a new risk assessment for re-registration of glyphosate. The key difference in those evaluations was that the IARC evaluation was a cancer hazard identification, whereas the latter evaluations were comprehensive risk assessments. Additionally, IARC included glyphosate formulations in its evaluation.

Dr. Smith-Roe described the potential objectives of an NTP research program in terms of problem formulation: (1) compare toxicity of glyphosate versus formulations, and the toxicity of among various formulations of glyphosate, (2) provide publicly available toxicology data on cancer-related endpoints, (3) provide publicly available toxicology data on non-cancer endpoints, and (4) investigate mechanisms of how glyphosate and formulations cause toxic effects.

The proposed NTP approach involves *in vitro* screening assays to yield information about the effects of glyphosate and different formulations for a variety of endpoints, and to make direct comparisons among them. Based on what is learned about the test articles from rapid screening approaches, additional *in vitro* assays would be used to gain mechanistic information. Screening approaches would also identify which test articles are good candidates for *in vivo* testing. Short-term *in vivo* testing would involve guideline genotoxicity assays, gene expression assays, and assays for oxidative stress. Another key outcome could be the generation of robust dose-response data to aid risk assessment. Dr. Smith-Roe said NTP is proposing a very focused approach using *in vitro* assays and short-term *in vivo* studies to provide decision makers with information quickly.

J. BSC Questions and Discussion

Dr. Afshari asked if histopathology was conducted in the 13-week study, which concluded that no gross lesions were seen. Dr. Smith-Roe said no gross lesions at necropsy were reported, but there were microscopic lesions of the salivary gland in rats and mice.

Dr. Corcoran said he was impressed by the widespread exposure of individuals to glyphosate. He said the project is clearly highly aligned with NTP's mission and goals. He expressed strong support for some elements of the research plan, but needed more information about others. He felt the studies of glyphosate formulations would be of great interest, but very complex and possibly not yielding a clear outcome. He considered the use of publicly available literature for both cancer and non-cancer endpoints a potentially highly productive approach. He thought it was too early to be confident of identifying key mechanisms, particularly if formulations are considered the driver of any toxicity. The strong concurrence of NTP, EFSA, and JMPR findings of little carcinogenicity risk limited his enthusiasm for progressing forward at this point. He said it would be important to see the evidence from the IARC study reproduced. He discerned a significant emphasis on dietary exposure during the presentation, but missed any reference to occupational exposure. He felt the project is rationally designed, with an appropriate scope at this early stage and with potentially very high significance due to the high production level of glyphosate and the widespread exposure. Dr. Corcoran said he has some enthusiasm for the project, but it is significantly dampened by the conclusions from the agencies.

Dr. Masten noted that the agencies' conclusions are focused on the active ingredient. The agencies have called for further information on the formulations, especially since there are more than 750 products containing glyphosate in the United States alone. Dr. Bucher noted that NTP communicates extensively with its agency partners, so the project would not be done in isolation.

VI. Peer Review of NTP Technical Reports on Antimony Trioxide and TRIM® VX

A. Presentation

Dr. Chad Blystone, DNTP Toxicology Branch, reported on the peer review of the NTP Technical Reports (TRs) on antimony trioxide (TR 590) and TRIM® VX (TR 591), which was held February 16, 2016, at NIEHS. Dr. Jon Mirsalis chaired the peer-review meeting, and Dr. Corcoran served as BSC liaison.

Dr. Blystone reviewed the TR program, the levels of evidence of carcinogenic activity used in the reports, and the charge to the panel. He briefly summarized the antimony trioxide draft TR. The chemical is the primary form of antimony in the atmosphere and is the most commercially significant form of antimony, used primarily as a flame retardant. NTP conducted inhalation studies in rats and mice. The report's conclusions were *some evidence* of carcinogenic activity in male and female rats, and *clear evidence* in male and female mice. The peer review panel voted unanimously to accept the conclusions.

Dr. Blystone summarized the draft report on TRIM® VX, noting that is a metalworking fluid used in machining processes. NTP conducted inhalation studies in rats and mice. The report's conclusions were *equivocal evidence* in male and female rats, and *clear evidence* in male and female mice. The panel voted unanimously to accept the conclusions.

The final steps will be to edit the reports based on public and panel comments and publish them within the next 6-9 months.

Dr. Blystone described three TRs expected to be posted for peer review by the end of 2016: dietary zinc (TR 592), 2,3 butanedione (TR 593), and *p*-chloro-a,a,a-trifluorotoluene (TR 594). He also described NTP Toxicity Reports, which typically present the findings of 13-week studies and do not include the evidence categories. He mentioned four reports coming up for letter review, *o*-chloropyridine, *o*-phthalaldehyde, tetrabromobisphenol A-bis (2,3-dibromopropyl ether), and chitosan.

B. BSC Discussion

Dr. Corcoran felt the panel members represented a broad range of expertise and worked effectively together. They demonstrated a high level of familiarity with the draft TRs. He found the contributions of the panel members accorded appropriate credence and weight in a balanced, deliberative process. He noted discussion of the oral public comment at the meeting, along with several written public comments that were provided to the panel. Dr. Corcoran's overall conclusion was that the panel was a very effective group that worked seamlessly together, and had a very high degree of concordance in their opinions.

VII. Report on NTP Toxicology and Carcinogenicity Studies of Cell Phone RFR

A. Presentation

Dr. Michael Wyde, DNTP Toxicology Branch, briefed the BSC on NTP's toxicology and carcinogenicity studies of cell phone RFR emissions. The U.S. Food and Drug Administration (FDA) originally nominated cell phone RFR to NTP in 1999, due to widespread human exposure and a lack of knowledge about potential health effects of long-term exposure.

Dr. Wyde provided background information about the scientific context for the studies, including the 2011 IARC conclusion that cell phone RFR is *possibly carcinogenic to humans*. He described the design of the animal studies, which was developed in collaboration with the National Institute of Standards and Technology, and was intended to overcome some of the limitations of previous study methods. These studies are the largest and most complex ever conducted by NTP. Rats and mice were exposed to frequencies and modulations (Code Division Multiple Access [CDMA] and Global System for Mobile Communications [GSM]) currently used in cellular communications in the United States.

Dr. Wyde discussed the RFR reverberation chamber exposure facility and described the research program elements, which included three-phase (5-day pilot, 28-day prechronic, and 2-year) toxicology and carcinogenicity studies in Harlan Sprague Dawley rats and B6C3F₁ mice. He summarized the results of each of the three studies: (1) body weights at birth and throughout lactation in rat pups exposed *in utero* tended to be lower than controls; (2) in general, survival was greater in all groups of GSM or CDMA RFR-exposed rats compared to controls; (3) increased incidence of schwannoma was observed in the hearts of male rats; (4) there was a significant structure-activity relationship-dependent trend for increased gliomas in the brain of rats exposed to CDMA-modulated RFR; and (5) no exposure-related effects were observed in the brains or hearts of female rats.

NTP pathology peer review is underway for evaluation of all remaining tissues. Complete results from all of the rat and mouse studies will be available for peer review and public comment by the end of 2017, with a peer review of the draft TR in 2017 or 2018.

B. BSC Questions and Discussion

Dr. Markowitz asked whether the relation between hyperplasia and malignancy is known in terms of the gliomas seen. Dr. Wyde said the main difference appears to be simply the size of the lesions.

Dr. Afshari asked about the lower degree of confidence in the observation of the gliomas, and whether that was because the incidence occurred at the same level as in the historical controls. Dr. Wyde said the confidence determination came from the level of statistical significance, which was lower in the brain than in the heart. Dr. Afshari asked whether any comparison could be

reached with ionizing radiation regarding the decreased body weight. Dr. Wyde said the lower body weight is being investigated further.

Dr. Ramos believed that gliomas and glial hyperplasias are actually two different entities and should not be treated as comparable. He asked how the historical control data were used in interpreting the study data. It seemed that it was not used and he wondered why it was included in the presentation. Dr. Wyde said the glioma vs. hyperplasia question is a contentious issue, but the distinction would be determined by the pathologists. Regarding historical controls, he said they were incorporated into the evaluation, with consideration of background rates. Dr. Ramos said if historical controls were taken into account, then interpretation of some of the findings should be changed, because some of the signal seen in the results may actually be noise. He said it appears that there were drifts in the data set, and that use of data from historical controls may negate some of the conclusions that were reached. Dr. Birnbaum noted the limitations of these historical controls since there are few other studies using the Harlan Sprague Dawley rat, and the studies were done at different laboratories under different conditions. She said the conclusion on the schwannomas is “unequivocally clear.” She noted that molecular genomic studies are currently in progress, identifying molecular signatures for the gliomas in the rat strain. Dr. Bucher said the veterinary pathologists believe that the gliomas and hyperplasias are essentially the same lesions. He added that the majority of scientists who reviewed the dataset had felt that it is more likely that the schwannomas, with less confidence in the gliomas, were related to RFR exposure. He said NTP contracted with five pathology experts to review the data and form an opinion about the relationship between the hyperplasias and gliomas, and that they concluded that they were related, with the only difference being the size. Dr. Ramos said there should be no reference to historical controls, since they appear to be of no value and just cloud the issue. Dr. Birnbaum said there is a clear dose-response relationship with the schwannoma data that is not present with the glioma data.

Dr. Corcoran asked whether any of the brain lesions reached statistical significance. Dr. Wyde replied that the CDMA exposure for the gliomas is a statistical trend.

Dr. Markowitz wondered why the glial hyperplasias and gliomas could not be combined, given that they are on a clear continuum. Dr. Bucher said the pathologists separated the two based on size.

VIII. National Center for Toxicological Research (NCTR) Update on NTP Activities

A. Presentation

Dr. Paul Howard, the FDA/NCTR liaison to NTP, provided an update on the 23.5 year history, and perspectives on the future, of the interagency agreement (IAA) between FDA/NCTR and NIEHS/NTP.

He provided background information about the history and mission of FDA, and noted that NCTR was established in 1971 as a non-regulatory national resource managed by FDA. He described the mission and research strategy of NCTR. He discussed the IAA, which was established in 1992 to facilitate cooperation between NCTR and NIEHS/NTP on compounds of shared interest and to facilitate FDA regulatory decisions.

The goals of the IAA are to: (1) conduct toxicological studies at NCTR on FDA-regulated or FDA-interest chemicals/compounds, (2) ensure the design and conduct of toxicological studies are consistent with regulatory needs and goals of FDA, (3) provide oversight and ensure studies are conducted in the most rigorous scientific manner, and (4) ensure communication of study data to enable regulatory agencies to make science-based safety assessment and risk management decisions.

He noted that more than 260 peer-reviewed scientific publications and 19 TRs have been produced since 1992. He listed and described each of the programs of study under the IAA, which include Dietary Supplements, Food Contaminants, Enhancing Toxicology, Endocrine Active Agents, Drug and Device, AIDS Therapeutics, Nanoscale Materials, and Phototoxicology.

He described the many advantages of the IAA in utilizing the unique resources of the FDA/NCTR. Regarding the impact of the IAA, results have been used for regulatory decisions, and study results have generated debate regarding public risks. Dr. Howard said, in the future, the IAA should continue with studies of high interest and concern to FDA and NTP, and examine new methods and approaches for their ability to inform NTP and FDA about hazard and risk.

B. BSC Discussion

Dr. Afshari said she had been on the NCTR advisory board and observed some of the work mentioned as it was occurring. She complimented Dr. Howard on his presentation of the cooperation and synergy between the two agencies. Dr. Howard said the association with NTP has allowed NCTR to do a better job in making regulatory decisions.

Dr. Birnbaum called for a round of applause for Dr. Howard for his many years of collaborative work as FDA/NCTR liaison to NTP.

IX. Report on the Peer Review of the Report on Carcinogens (RoC) Draft Monographs on Selected Viruses

A. Presentation

Dr. Gloria Jahnke, Office of the Report on Carcinogens (ORoC), reported to the BSC on the peer review of the RoC draft monographs on selected viruses, which was held December 17, 2015, at NIEHS. Dr. Andrew Olshan chaired the peer review and Dr. Markowitz served as BSC liaison.

Dr. Jahnke provided background information about the RoC, the process for preparing the report, and the current status of the draft monographs on selected viruses. The viruses under consideration for listing are: (1) Epstein-Barr virus (EBV), (2) Kaposi sarcoma-associated herpesvirus (KSHV), (3) human immunodeficiency virus type 1 (HIV-1), (4) human T-cell lymphotropic virus type 1 (HTLV-1), and (5) Merkel cell polyomavirus (MCV).

She described the development of the draft monographs, which included several opportunities for public comment and expert review. The revised draft monographs, based on the peer review, were posted online May 13, 2016. She reviewed the RoC listing criteria. The peer-review panel agreed with the preliminary listing recommendation of *known to be a human carcinogen* for all five viruses. Dr. Jahnke provided more details about the level of evidence calls for each of the viruses and associated cancers. The panel identified two overarching scientific issues: (1) cancer causation by oncogenic viruses is not unusual; cancer does not need to occur in all exposed individuals for an agent to be carcinogenic and (2) the presence of an oncogenic virus alone can be sufficient for oncogenesis.

Dr. Jahnke said NTP anticipates submission of the 14th RoC to the Secretary HHS by late summer or early fall 2016. Newly reviewed submissions will include the five viruses, trichloroethylene, and cobalt and cobalt compounds that release cobalt *in vivo*.

B. BSC Discussion

Dr. Markowitz said the peer-review meeting was excellent, with well-done draft documents that were comprehensive and clearly written. The peer reviewers were outstanding with many decades of experience in the appropriate disciplines. The panel had many constructive comments and did not merely rubber-stamp the draft monographs. Dr. Markowitz noted there were some extensive discussions regarding the level of evidence calls for some of the viruses. He praised the quality of the webcasting and remote participation capabilities.

Dr. Udasin said in the case of EBV, perhaps the RoC conclusion would spur interest in development of a vaccine, given how common the associated cancers are. Dr. Bucher agreed that that was why it is important to list biological agents in the RoC.

X. NTP Projects Utilizing the NIEHS Clinical Research Unit (CRU)

A. Presentation

Dr. Kristina Thayer, DNTP OHAT, updated the BSC on NTP projects utilizing the NIEHS CRU. She provided background information about the CRU, which was established in 2009 and described three projects: BPA oral and dermal pharmacokinetic studies, the study to investigate BPA exposure in cashiers, and the NIEHS EPA pilot study of exposure to chemicals in consumer products.

Ms. Kristine Witt, DNTP Biomolecular Screening Branch (BSB), described an ongoing study of black cohosh use in women, which is the first collaboration between the CRU and the BSB.

Black cohosh is an herbal extract used by women worldwide and is the fourth most popular herbal product in the United States. Based on widespread use and lack of toxicity data, it was nominated to NTP by the National Cancer Institute and NIEHS in 2000. In 13-week toxicity studies, blood samples revealed significant dose-related increases in micronucleated red blood cells in female rats and mice. Given concerns raised by the animal studies, NTP elected to pursue a clinical study to see if the effects observed in the animal studies would be observed in humans. A cross-sectional study was designed to measure a variety of endpoints, including metabolomics, reticulocytes, and micronucleated reticulocyte frequencies, in a group of women, age 18 and older, who had been taking black cohosh for at least three months. They would be compared with a reference group of women who have never taken black cohosh. Initially the study specified the use of a certain black cohosh product to standardize the exposures among women, but this limited the ability to recruit participants. The eligibility criteria were changed to permit use of any single-herb black cohosh product. Enrollment is ongoing and has been complicated because many potential participants were found to have used mixed herbal products, rendering them ineligible for the study. Ms. Witt said data compilation and analysis are expected to be completed by late fall 2016.

B. BSC Questions

Dr. Genter asked what endpoints are being evaluated in the metabolomics study. Dr. Rick Paules, DNTP BSB, replied that the study is untargeted. Ms. Witt added that the goal is to identify profiles and patterns in black cohosh users compared to the reference group of non-users.

Dr. Birnbaum asked whether the serum of non-users would be checked to confirm their non-user status. Ms. Witt said biomarkers of black cohosh in serum were not measured, but other hematological parameters are being tested. Dr. Birnbaum asked if the participants' consent forms contain a provision to re-contact them should the study convert into a prospective, longitudinal study. Ms. Witt was unsure, but noted that some participants have been brought back for re-testing if something went wrong with their original sample.

Mr. Kass said it is common that some black cohosh may not actually contain the herb, and asked if that possibility was addressed in the study's power calculations. Ms. Witt said that information would be obtained from the detailed chemical analysis of the samples provided by participants.

Dr. Markowitz asked how many active protocols are in place at the CRU and how long Institutional Review Board (IRB) approval takes. Dr. Shepherd Schurman, CRU, and Dr. Birnbaum explained that the IRB meets only once per month, and a protocol may undergo several rounds of review, which means that approval can take several months. They estimated that there are currently more than 30 protocols in place. Dr. Birnbaum noted that the 7th anniversary of the CRU is approaching, with a dramatic increase in the number of subjects participating in studies.

Dr. Ramos asked why 18-year-old women would take black cohosh. Ms. Witt said specific black cohosh products are marketed directly to pre-menopausal women for relief of menstrual-related

symptoms, as well as to pregnant women for promotion of lactation. Dr. Ramos suggested the study include complete profiling of red blood cells and asked about the recruitment targets.

Ms. Witt said the original target was 25 women per study arm, but the hope was to recruit 50 when the eligibility criteria were changed. The target would be reassessed upon analysis of some of the data, to see whether the study needs to be re-designed or would be sufficiently complete at that point. Dr. Birnbaum said when the eligibility criteria were changed, enrollment jumped dramatically, lending optimism that the desired total would be reached.

Dr. Ramos asked what sort of selection biases were expected in the BPA study, particularly in terms of potential ethnic/racial influences. He felt there is potential for selection bias in the cohort. Dr. Thayer said differences in ethnicity and sex were assessed in the supplemental data and noted that it was a controlled exposure, thus alleviating concern about selection bias. Dr. Ramos said he was thinking of confounders in the area of genetics or pharmacogenetics. Dr. Birnbaum said up to 30 subjects were approved for the study to provide sufficient power to look at genetic differences. She said the study was halted after 14 subjects, because the data were so similar among subjects and the primary research questions had been answered at that point.

Dr. Udasin acknowledged the difficulty of using healthy volunteers in studies like the BPA study. Regarding the black cohosh study, she recommended concentrating recruitment on specific age groups or treatment intent.

Dr. Howard noted that FDA does not recommend or approve black cohosh products, and cautioned against confusing pharmacology with efficacy. He said the National Center for Complementary and Integrative Health is conducting an efficacy study. Ms. Witt confirmed that the NTP study is not evaluating efficacy. Dr. Birnbaum added that the intent of the black cohosh study is to see if any of the outcomes reported in the rodent studies appear in the human population.

C. BSC Discussion

Dr. Udasin congratulated NIEHS on the relevancy of the projects. She lauded the BPA cashier study, since it involved no additional exposures than what people were already receiving, eliminating any ethical issues. She said the black cohosh study is challenging and she asked for more information about the BPA administration.

Dr. Thayer said the cashier study afforded the opportunity to rapidly address some of the exposure questions related to BPA. Dr. Birnbaum said BPA was soaked into cookies to recreate typical human exposure, which is in food. Soaking the test agent in food is a standard method of oral dosing in both humans and rodents.

Dr. Corcoran described the recent actions of the New York state attorney general, against companies selling supplements containing little to none of the alleged principal ingredient. He was concerned that the black cohosh samples were not being DNA barcoded prior to a subject's enrollment in the study. He feared that the information being generated would be contaminated by counterfeit or adulterated products. Ms. Witt noted that it is not a prospective study, that

black cohosh is not being supplied to participants, and that samples would be analyzed at the end of the study.

Dr. Stevens noted that in herbal products, exposure is known to be inconsistent, which could compromise the integrity and usefulness of the data. He said even with a recruitment of 50 subjects, there may not be an ability to get adequate information. Dr. Birnbaum said the reason for the study was concerns raised by the rodent study results, so it would not be appropriate to encourage people to take black cohosh. The study takes advantage of people who are taking it already. Further recruiting might become necessary to ensure having enough subjects that are taking black cohosh, and not adulterated products. Dr. Stevens said measuring exposure is always important, and asked how that would be handled in botanicals, given their complexity. Dr. Walker noted that that question was raised at the April botanicals workshop, a report on which would be presented later in the meeting.

Dr. Peterson summarized the discussion, stating there is much support from the BSC for the direction being taken in this area. She adjourned the meeting for the day at 3:45 PM and Dr. Schurman provided the BSC a tour of the CRU.

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

XI. Report of the NTP Associate Director

Dr. Bucher, Associate Director of NTP, updated the BSC on developments at NTP since the last BSC meeting. He mentioned three workshops: *In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making*; *Shift Work at Night, Artificial Light at Night, and Circadian Disruption*; and *Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety* that were recently held by NTP. He said these workshops are important because they actually deal with problem formulation activities and the ways in which NTP is trying to understand the entirety of the science behind some of these issues.

Dr. Bucher described three recent meetings: *Peer Review of Draft RoC Monographs on Selected Viruses*, *ICCVAM Communities of Practice Webinar: Basic Principles of Quantitative Structure Activity Relationships and Read Across*, and *Peer Review of Draft NTP Technical Reports on Antimony Trioxide and TRIM® VX*. He previewed several upcoming meetings: *Peer Review of the Draft NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate*, *Scientific Advisory Committee on Alternative Toxicological Methods Meeting*, and *Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements*. Dr. Bucher also noted staff changes and several awards recently won by DNTP personnel.

XII. Report on Workshop: In Vitro to In Vivo Extrapolation (IVIVE) for High Throughput Prioritization and Decision Making

A. Presentation

Dr. Warren Casey, NTP Interagency Committee for the Evaluation of Alternative Toxicological Methods, briefed the BSC on the workshop, which was held at the U.S. EPA in Research Triangle Park February 17-18, 2016. He explained that taking *in vitro* data and making *in vivo* predictions is nothing new, but now extrapolation is being done in the context of high throughput screening; that is what makes IVIVE different from the traditional approaches that have been used historically. He noted that it would become more important with Toxic Substances Control Act reform and for rapid responses to environmental incidents. The workshop primarily focused on issues involving toxicokinetics (TK), which address the fate of molecules or chemicals in the body, and absorption, distribution, metabolism, and excretion (ADME) considerations. Dr. Casey described the series of four pre-workshop webinars that were held in preparation for the in-person workshop.

The workshop had roughly 100 participants and followed three themes: TK model considerations, *in silico* and non-animal methods for obtaining TK parameters, and application to prioritization/screening/risk assessment. Goals for the meeting were to (1) review the state of the science, (2) discuss best practices, and (3) identify data gaps. A workshop report manuscript will be submitted for publication this fall.

B. BSC Discussion

Dr. Birnbaum said more attention should be paid to inter-individual variability, not only among humans but among rats as well. Dr. Casey agreed and noted that simulations for population variation are built into some extrapolation models.

Dr. Bucher asked where the information used to set up the workshop had come from. Dr. Casey said much of the *in vitro* information was generated at The Hamner Institutes for Health Sciences. He said NTP Laboratory is also working on some of the key parameters.

Dr. Stevens said he liked the approach to prioritizing chemicals embodied in the workshop. He noted the importance of measuring volume of distribution when trying to extrapolate from *in vitro* to *in vivo*. Dr. Casey acknowledged that volume of distribution needs to be incorporated into IVIVE.

Dr. Afshari said that as the program matures, it will be important to clearly articulate its limitations, including genetic variations, and the one compartment model. She said there is much similarity between pharmaceuticals and environmental chemicals, but the models used in pharmaceuticals are more mature.

She suggested that pharmaceutical researchers should be consulted, including leveraging the partnership with NCTR. She felt it is important for NTP to understand where it needs to lead versus where it just needs to keep up with a field; IVIVE is one area where work is going on in

other places that could be incorporated. Dr. Afshari added that innovation would be aided by recruitment of new, younger scientists.

XIII. Report on Workshop: Shift Work at Night, Artificial Light at Night (LAN), and Circadian Disruption

A. Presentation

Dr. Ruth Lunn, ORoC, briefed the BSC on the workshop, which was held on March 10-11, 2016. She described the steps leading up to the workshop, including the nomination of LAN for evaluation of both cancer and non-cancer outcomes. She noted that work on this nomination is being coordinated by ORoC and OHAT. The purpose of the workshop was to obtain external scientific input on topics important for informing the literature-based health hazard assessments, including strategies for integrating data across evidence streams and exposure scenarios, and to identify data gaps and research needs. Meeting participants provided NTP with input for conducting its health hazard evaluations, identified data gaps and research needs for the field, and discussed studies on interventions. A workshop report is being prepared. OHAT plans to present a concept for an assessment of non-cancer outcomes at the December 2016 BSC meeting. NTP is using input from the workshop to develop protocols for conducting the health hazard evaluations. NTP is also identifying potential interventions by summarizing existing evidence.

B. BSC Questions

Dr. McMartin asked whether there was much discussion at the workshop about controls, particularly in the human studies. Dr. Lunn said there was some discussion about controls.

Dr. Afshari asked about the discussion of biomarkers and molecular endpoints, what information would be needed to develop a protocol, and what question would be addressed. Dr. Lunn replied that methylation studies are an emerging issue; the need for these studies would be emphasized in the workshop report. She said the protocol would cover methods for the literature search strategy.

Dr. Genter asked whether there was discussion of incorporating physiological measurements into the human component of needed research. Dr. Lunn said there was some discussion of that topic.

Dr. Howard commented on the complexity of the task being undertaken. He said the intensity and spectrum of light at night have changed significantly over time, and asked how those changing elements might be incorporated in the evaluation of literature and its publication date. He asked whether a connection with the lighting industry had been considered in order to document when the changes had occurred. Dr. Lunn said the literature evaluation could only assess the data that have been collected, and it is doubtful that information on intensity and spectrum were collected. Dr. Howard suggested reaching out to the lighting industry to gain

knowledge about shifts in lighting. Dr. Lunn said one of the experts involved in the workshop is an expert on lighting, and she would be retained as a technical adviser to the assessment.

Dr. Ramos suggested that the group remain very clear about the difference between shift work and LAN. He added that assessing controls for the different types of studies would be essential. He asked whether the path forward involved studying light pollution. Dr. Lunn said that originally the field had studied shift work at night as a surrogate for LAN, but the field has moved beyond that approach. She explained that NTP is conducting literature-based analysis and preparing recommendations for the field at large, and is not conducting the studies themselves. Dr. Ramos suggested that shift work and disease should be a focus of study. Dr. Lunn noted that NIOSH has conducted some research in that area, which Dr. Elizabeth Whelan confirmed and briefly described.

Dr. Markowitz asked if RoC might come to separate conclusions on shift work at night and LAN. Dr. Lunn said the two are not the same, and studies would not be combined; however, they would likely be included in a single monograph. Dr. Howard added that the issue is not LAN as such, but inappropriate amount and wavelengths of light, such as blue light at night.

C. BSC Discussion

Dr. Udasin served as BSC liaison to the workshop and felt it was especially well organized. She thought, as a clinician, that this is an important public health issue, with potentially modifiable risk factors in terms of cancer causation and some of the other outcomes. She noted that modifications are possible to improve health outcomes for shift workers, those exposed to LAN, nurses, and flight attendants. Dr. Udasin said there is great potential for the evaluation to influence public health.

Dr. McMartin said the lifestyle of night shift workers would be significantly different than day shift workers, making controls important. He said there would be very complicated variables in human studies. He agreed that shift work and LAN should be treated completely separately.

Dr. Udasin agreed, noting that nurses have wide variability in their reasons for working night shifts including family and other jobs. She said this would add complex variables to the evaluation of shift work, but felt that nonetheless it is important to conduct studies.

Dr. Howard said it would likely be the most complicated evaluation undertaken by OHAT. Dr. Bucher concurred and said more workshops would likely be needed. He said the evaluation would be completed in a careful, systematic manner.

Dr. Thayer noted the variety of outcomes, both cancer and non-cancer, being evaluated, and said the initial effort may be to assemble the most direct evidence in each area, without attempting to address everything in one evaluation.

Dr. McMartin suggested examining the literature in behavioral research, where switching light patterns in rodent populations is common.

XIV. Report on Workshop: Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety Workshop

A. Presentation

Dr. Cynthia Rider, DNTP Toxicology Branch, briefed the BSC on the workshop, which was held April 26-27, 2016, at the NIH campus in Bethesda, MD. She noted that NTP held the workshop because of recent public concern over botanical dietary supplement quality and safety, a history of botanical research at NTP that has revealed important data gaps, and the fact that botanicals provide an excellent test case to develop methods for addressing complex mixtures. The key topics for the workshop were identification of active constituents, comparison across botanicals, and understanding of botanicals' ADME. These are important to pursue for hazard characterization, product development, and regulation. The workshop's goal was intended to inform research on botanical safety by communicating current science in key topic areas, obtaining feedback from stakeholders on presented approaches, and identifying data gaps and research needs.

Part of the workshop proceedings was presentation and discussion of three case studies: *Ginkgo biloba* extract, black cohosh extract, and *Echinacea purpurea* extract. They afforded opportunities to explore issues such as comparison across botanicals, test article selection, and knowledge gaps.

The take-home messages from the workshop were: (1) botanical dietary supplements are an important public health concern and an active area of research; (2) botanicals are complex entities that offer unique challenges for research, regulation, and manufacturing; (3) methods to determine sufficient similarity can be applied to botanicals to help with test article selection and relate findings from NTP studies to untested samples; (4) determination of active constituents of botanicals remains a high priority; (5) both whole mixture and active constituent work is needed; and (6) development of best practices for assessing ADME of botanicals is a key area of research. A video of the workshop is available on line at NIH (<https://www.videocast.nih.gov/PastEvents.asp?c=0&s=151>), and a publication is in preparation, as are results of the case studies.

B. BSC Questions and Discussion

Dr. McMartin served as BSC liaison to the workshop. He said it was a well-run workshop with a broad range of speakers and much important information imparted. He was somewhat disappointed that there were not more participants from industry. He said the discussions were excellent, both from the audience and the panels. He noted that the case studies were unique and could be a model for mixture toxicology. He found it interesting that botanicals are subject to wide variation based on time of year and weather conditions. He felt the similarity between the chemical compositions and biological compositions was impressive. In terms of test article selection, it will be a complicated process, and the chemical similarity is a good approach. Regarding the objection about using too high doses, he said that that is simply how toxicology works and it is doubtful the objection will ever be overcome.

Dr. Corcoran said he was impressed by the very systematic approach taken and the high quality of the data. With the exhaustive amount of data, there will be a high level of security in future studies. He felt that the scientific approach has been to understand as much as possible about a small number of questions and to come up with defensible conclusions. He asked how that approach would extend to the public health question, which is much broader. He asked how the thinking and discoveries covered in the workshop could be used to impact other areas. Dr. Rider said there was much effort to prepare the case studies so as to find answers synchronized between the biology and the chemistry.

Dr. Ramos asked about the ability to provide generalizations across the spectrum of botanicals, since it would be impossible to test everything. Dr. Rider said that was the reason behind presenting more than one case study at the workshop. She said that hopefully, as the two case studies beyond black cohosh are developed further, a pattern would emerge, to see whether the approach holds up generally or only in well-defined cases. Dr. Ramos said there would be a lot of value in taking something about which little is known and applying the approach to see how effective it might be. He noted that the safety concern is not limited to active ingredients, but is in the mixtures. He said that the case study on *Echinacea* might be the answer.

Dr. Howard, who clarified that he was not speaking on behalf of the FDA, commented that the workshop was starting to prove a concept that could have tremendous regulatory power. He said that it starts to validate an approach where the chemistry is backed up by the biology, and could have huge public impact.

Dr. Birnbaum said often the biology is what drives the need for the chemistry. Adulteration of botanicals may in some cases not be deliberate, but simply the result of ignorance and/or lack of caring. She said if the biological activity is known, a bioassay could be quicker, cheaper, and faster than a chemical assay. But if the biological activity is unknown, a chemical assay might provide the answer. She said both approaches are valid and may be useful in different circumstances. Dr. Howard agreed, but noted that the assays are not about efficacy, and cautioned against bringing efficacy into the discussion. Dr. Birnbaum replied that efficacy and toxicity are often two sides of the same coin.

Dr. Afshari noted that NTP has an opportunity in this area to consider the impact of its work on the regulatory community. She described the concepts of biosimilars and bioequivalents as areas of pharmaceutical research where some of the same ideas enter in. She said perhaps NTP could borrow some of the terminology used in those areas. She also suggested paying attention to developments in the emerging science of synthetic biology.

XV. Adjournment

Concluding the meeting, Dr. Birnbaum said it had been a great meeting, with much exciting science. She thanked the staff for their participation. She also announced that Dr. Bucher would retire soon, staying on until a new Associate Director of NTP and Director of DNTP is appointed. A search committee has been established, and Dr. Birnbaum asked the BSC for suggestions. She said an advertisement for the position would be placed in about a month.

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Dr. Bucher thanked everyone for participation at the meeting, and noted the great input from the BSC on the wide range of current NTP activities. He thanked Dr. Peterson for chairing the meeting. Dr. White also thanked the BSC members.

Dr. Corcoran called for recognition of Dr. Bucher. The meeting adjourned at 11:00 AM, June 16, 2016.

Dr. Lisa Peterson

Chair, NTP Board of Scientific Counselors

[Signature Redacted]

Date: