

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES**

**MINUTES OF THE ONE HUNDRED FORTY-SEVENTH MEETING OF THE
NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL**

February 23-24, 2016

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred forty-seventh regular meeting on February 23-24, 2016 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. The closed session of the meeting was held February 24, 2016.

The meeting was open to the public on February 23, 2016 from 8:30 a.m. to 4:45 p.m., and on February 24, 2016 from 8:30 a.m. to 9:30 a.m. In accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), the meeting was closed to the public on February 24, 2016 from 9:45 a.m. to 12:00 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Dr. Linda Birnbaum presided as Chair.

Participating Council Members

Habibul Ahsan, MD
Philip Brown, PhD
Vivian Cheung, MD (by telephone)
Jeanne Conry, MD, PhD (by telephone)
Lisa Conti, DVM
David Eaton, PhD
Kevin Elliot, PhD
Kenneth Fasman, PhD (by telephone)
Andrew Feinberg, PhD
Tomás Guilarte, PhD
Della Hann, PhD (*ex officio*)
Howard Hu, MD (by telephone)
James Johnson, Jr., PhD (*ex officio*) (by telephone)
Norbert Kaminski, PhD
Linda McCauley, PhD, RN
Donna Mendrick, PhD (*ex officio*)

Marie Lynn Miranda, PhD
Edward Postlethwait, PhD
Viola Waghiyi
Deborah Winn, PhD (*ex officio*) (by telephone)

NIEHS Staff

Kathy Ahlmark
Janice Allen, PhD
Robin Arnette, PhD
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Bryann Benton
Linda Birnbaum, PhD
John Bucher, PhD
Jed Bullock
Danielle Carlin, PhD
Lisa Chadwick, PhD
Kelly Chandler, PhD
Pamela Clark
Jennifer Collins
Gwen Collman, PhD
Yuxia Cui, PhD
Sally Darney, PhD
Caroline Dilworth, PhD
Christina Drew, PhD
Chris Duncan, PhD
Lisa Edwards
Benny Encarnacion
David Fargo, PhD
Symma Finn, PhD
Christine Flowers
Barbara Gittleman
Kimberly Gray, PhD
Virginia Guidry
Janet Hall, MD
Astrid Haugen
Michelle Heacock, PhD
Jerry Heindel, PhD
Heather Henry, PhD
Jon Hollander, PhD
Stephanie Holmgren
Michael Humble, PhD
Laurie Johnson
Bonnie Joubert, PhD

Helena Kennedy
Annette Kirshner, PhD
Alfonso Latoni, PhD
Cindy Lawler, PhD
Alicia Lawson
Kelly Lenox
Chris Long
Robin Mackar
J. Patrick Mastin, PhD
Kim McAllister, PhD
Steven McCaw
Rose Anne McGee
Mark McLatchy
Liz McNair
Aubrey Miller, MD
Mark Miller, PhD
Sheila Newton, PhD
Aaron Nicholas
Liam O'Fallon
Rick Paules, PhD
Kristi Pettibone, PhD
Jerry Phelps
Nicole Popovich
Molly Puente
Scott Redman
Elizabeth Ruben
Thad Schug, PhD
Daniel Shaughnessy, PhD
Natalie Shaw, MD
Carol Shreffler, PhD
Sadie Smith-Leak
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD
Claudia Thompson, PhD
George Tucker
Fred Tyson, PhD
Michelle Victalino
James Williams
Leroy Worth, PhD
Rick Woychik, PhD
Demia Wright
Darryl Zeldin, MD

Members of the Public Present

Maureen Avakian, MDB, Inc.
Ernie Hood, Bridport Services, LLC
Mike Phillips, RTI International
Joel Van Norman, NIH/EPA
Jennifer Troyer, NHGRI (by telephone)
Fikri Yucel, SSS

I. Call To Order and Opening Remarks

NIEHS/NTP Director and Council Chair Linda Birnbaum, Ph.D., welcomed attendees and called the meeting to order. She noted that Drs. Eskenazi and Kramer were unable to attend. She asked all present in the room to introduce themselves, which they did. She asked the Council members attending by telephone to introduce themselves. Following the introductions, NIEHS Division of Extramural Research and Training (DERT) Director and Council Executive Secretary Dr. Gwen Collman reviewed meeting logistics, including the voting process.

II. Review of Confidentiality and Conflict of Interest

Designated Federal Official, Dr. Gwen Collman, reviewed the Conflict of Interest and Confidentiality procedures, which had been provided earlier to Council members in written form, and reviewed various other administrative matters.

III. Consideration of September 2015 Meeting Minutes

Approval of the September 2015 meeting minutes was moved and seconded, and Council voted unanimously to approve the minutes. Dr. Collman noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, NIEHS

Dr. Birnbaum updated Council on Institute developments since the September 2015 Council meeting.

She began with a report on appropriations, and she observed that "we did get a little bump-up this year," with an approximately \$26 million increase in the NIEHS budget. The NIH budget went up by \$2 billion, but much of that increase was earmarked for specific projects and initiatives, with the remainder split proportionately among the institutes and centers. Thus, the increase was 3.925%, which came out to the \$26 million. She also reviewed the history of NIEHS appropriations, illustrating that fact that

the current appropriation has just now passed the mark for 2010. She presented data showing the reduction in buying power that has occurred. In her Legislative Report, she described several recent congressional briefings, meetings and hearings relevant to NIEHS.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP personnel or grantees. She began with a "One NIEHS" study involving multiple NIEHS divisions that looked at immune effects in people exposed to acetaminophen. She continued with short synopses of recently published studies from DIR, DNTP, and DERT researchers.

She provided an overview of the events planned to celebrate the 50th anniversary of NIEHS, which launched with a kick-off and time capsule event January 21.

Dr. Birnbaum recounted several examples of recent NIEHS news and highlights, including developments related to strategic plan implementation and IT. Staff updates included new hires and promotions. She described recent visits to NIEHS by Representative David Price (D-NC) and Senator Richard Burr (R-NC).

She related considerable background information about the recent lead in water contamination crisis in Flint, Michigan. "It is an environmental tragedy, and a clear example of health disparities," she told Council members. She noted that the Department of Health and Human Services (HHS) was given the lead for the federal response to the public health crisis, and NIEHS was asked to lead the science response, in conjunction with the Science Preparedness Research Interagency Team (SPiRIT), which involves many different federal agencies within HHS. NTP is involved given its expertise in the effects of low-level lead in children, the extramural division is reviewing proposals for studies, and the Worker Training Program is providing training to workers involved in lead pipe removal.

Dr. Birnbaum discussed many recent developments related to children's environmental health research, including the Children's Health Exposure Analysis Resource (CHEAR), Environmental Influences on Child Health Outcomes (ECHO), and several other initiatives, along with upcoming programs and meetings and recent publications in that area.

Dr. Birnbaum recognized the achievement of Dr. Aziz Sancar, a long-time NIEHS grantee at the University of North Carolina, who shared the 2015 Nobel Prize in Chemistry.

Council member Viola Waghiyi compared the Flint lead contamination crisis to the ongoing environmental contamination situation on St. Lawrence Island, Alaska, her home, with far less media attention paid. Dr. Birnbaum noted that Flint was likely to be

“just the tip of the iceberg,” with so many other areas suffering from the environmental injustice bestowed by contaminations, especially in disadvantaged communities such as tribal areas, inner cities, and rural areas.

Dr. Feinberg said that he was also deeply troubled by the issue of environmental injustice due to toxicants, noting that lead contamination is happening in many places. He said that there is a precedent for public health officials mandating actions in public health emergencies, and wondered who would have that authority. Dr. Birnbaum said that too often the public health agencies do not have the funds to be able to act quickly and effectively.

Dr. Miranda said that the media attention to an issue like Flint is wonderful, but it would be even more wonderful if the problem is successfully addressed. She noted that in the past there had been a HUD/CDC program to address childhood lead poisoning, but that eventually the funding evaporated. She said it should become a budget priority again, with an emphasis on behavioral choices. Dr. Birnbaum said that CDC funding for lead is actually up at this point compared to some years in the past. Dr. Miranda said that much of that was devoted to surveillance. Dr. Birnbaum said that they also fund the states to perform public health interventions. Overall, however, the funding is down. “It’s an issue of budget, it’s an issue of will, and it’s an issue of priorities,” she said. She observed that there was great interest when she briefed the other NIH IC leaders recently about the Flint crisis. Dr. Bucher also recently briefed the NIH scientific directors.

Dr. Conry asked about the Zika virus situation. Dr. Birnbaum elaborated on the background of the problem, with the CDC having issued travel warnings for 22 countries related to Zika. She noted that with climate change, there may be more situations like Zika as the territories of mosquitoes carrying infectious agents expand. She said the microcephaly alleged to be associated with Zika has thus far only been seen in a limited area in Brazil, an area with a great deal of pesticide use. She added that she is really concerned about the tremendous use of pesticides going on in areas of Latin and Central America and the Caribbean, many of which are banned in the US. She also noted that the NIH Disaster Response Research (DR2) program has been called into action with the Zika outbreak and the lead contamination situation.

Dr. Conti discussed the unique nature of the mosquito that carries the Zika virus, and is also responsible for Dengue fever. It is more difficult to control with traditional spraying methods, for example. The potential use of bioengineered mosquitoes in Florida is currently being reviewed by the FDA, she added.

V. Superfund Research Program (SRP) Update

Director Dr. William Suk provided Council with an update on the Superfund Research Program, specifically focused on revamping the SRP P42 center review cycle.

He went over background information about the program, including the four mandates upon which it is based. He gave an overview of the various funding mechanisms involved with the SRP, and then turned his attention to the P42 multi-project research centers, where interdisciplinary research activities address complex exposures and disease outcomes to improve public health. He said that the current program cannot be sustained under the present, stagnant budget conditions, necessitating changes to the P42 centers review cycle.

Under the new review cycle, awards will be issued for up to five years for up to 18 P42 centers. They will renew on two asynchronous tracks at 2.5 year intervals, unlike the current annual review of every five years. A period of transition will ultimately result in all current programs with end dates coinciding with one of 2 tracks, through altered grant lengths and cost extensions.

Dr. Postlethwait asked how the change in the review cycle would affect the R01 program. Dr. Suk replied that the P42s are the only aspect of the program that will see the cycle change, although there is planning for how the other mechanisms will fit in. Dr. Postlethwait asked how the decisions would be made about P42s increasing their current length of funding to fit in with the cycle change. Dr. Suk said that in some cases it would be easy, since they would already be coming in for review this year; others that were not as simple were given the option to come in for review early or to delay.

Dr. Guilarte noted that an unintended consequence of the change could be that it would be much more difficult for new centers to apply, having to wait 2.5 years instead of the current one year, thus solidifying the base of the funded programs. Dr. Suk said that that aspect had been considered in detail, and it had been decided that the 2.5-year interval was best to ensure continued programmatic growth, allowing updating of the RFA as well. Availability of funds was also a factor, he said. Dr. Collman added that the review process is very labor-intensive, and the change will allow new science to come into very established programs. She said it is a shift from administrative, everyday work to more programmatic, scientific work for the program.

Dr. Kaminski praised the P42 program, noting that it is "absolutely unique." He asked whether the SRP group had considered eliminating the R01 awards, given the flat budget and importance of transdisciplinary work afforded by the P42s. Dr. Suk said that the R01 budget is approximately \$1.5 million for five years. He noted that attrition had been seen in recent years in non-biomedical research, in areas such as remediation

and engineering. Those elements are best addressed by R01s, and are part of satisfying the SRP mandates.

Dr. Eaton asked if there was any effort in the R01s to encourage investigators who are not affiliated with a center to find such an affiliation. Dr. Suk said that was done, and the investigators are incorporated into the SRP annual meeting to integrate their work into the program.

Dr. Birnbaum noted that not only is the SRP budget flat, but it has never doubled since its inception, unlike the NIH budget.

VI. Report of the Director, DERT

Dr. Collman updated the council on activities and developments within DERT since the last meeting in September. She recognized two retirements within the division, Dr. Annette Kirshner and Mr. Jerry Phelps. She announced personnel changes within the Grants Management Branch. She reported on two “extraordinary international experiences” by DERT employees, James Remington from the Worker Training Program, who worked in Sierra Leone during the Ebola outbreak, and Sri Nadadur from the Exposure Response and Technology Branch, who worked as an Embassy Science Fellow at the US Embassy in New Delhi, India.

Dr. Collman went over the Council Delegated Authorities for FY 2016, which are Council-related actions which Council delegates to NIEHS staff to carry out. She asked for and received a motion to approve the measures, and Council voted unanimously to approve the motion, including the members attending by telephone.

She related final facts and figures for the FY 2015 DERT budget. The payline was at the 10th percentile for R01, R03, and R21 grants, with a 14.7% success rate for all RPGs and 12.5% for R01s. RPGs comprised 74% of the extramural grants. Total funding was \$227 million for 597 non-competing and competing grants, of which \$166 million funded R01s.

Looking ahead to the extramural budget strategy for FY 2016, she said the payline would remain at the 10th percentile, with a total of approximately \$64 million available for RPGs. She noted that there would be 13 FOAs in FY 2016, comprising approximately \$27.9 million.

Dr. Eaton asked Dr. Collman about the perception among many investigators that NIEHS spends much more on RFAs and PARs than on investigator-initiated applications. He asked if the proportion had changed much over the years, and how the proportions roughly break down. She responded that in the past there had been

conversation about how to manage the portfolio in fiscally constraining times, with a variety of strategies discussed. “We are very strategic about choosing RFA topics,” she said, “and we line up things in our portfolio related to the Strategic Plan, looking for opportunities to develop different parts of the field.” She said that the balance in the portfolio is constantly being reviewed. Dr. Eaton said that nothing is wrong, but that it is very important that people understand the rationale behind the decision-making. Dr. Birnbaum added that there is a misconception that NIEHS has much more money at hand than it actually does. Also, she said, due to the transdisciplinary nature of NIEHS interests, it is important to let the community know about those interests.

Dr. Feinberg said it would be interesting to analyze the portfolio during the ARRA funding peak, which he called “a golden couple of years at NIH.” Dr. Collman agreed that ideas were plentiful during that time period, when NIEHS incentivized research on BPA and nanomaterials, among other initiatives.

VII. NIEHS Climate Exposure Challenge

Kimberly Thigpen-Tart, J.D., presented information about the Climate Exposure Challenge. The goal of the challenge is to help decision makers around the country understand and address climate change’s effects on environmental health by creating data visualization tools and maps that connect current science on climate change to the exposure pathways for environmental hazards and risks. Council members heard the first public announcement of the winners of the challenge, which is the first of its kind. Kimberly Thigpen Tart, J.D., from the NIEHS climate change challenge team, revealed the awards made for tools that serve needs in two categories — local and national.

First place, national — PIE Viz, Populations, Infrastructures, and Exposures Visualization Tool, submitted by Julia Gohlke, Ph.D., Samarth Swarup, Ph.D., and Dawen Xie from Virginia Tech. No second place was awarded in this category.

First place, local — Effects of Climate Change on the Future of Local Communities, submitted by Yi Wang, Ph.D., of the Richard M. Fairbanks School of Public Health at Indiana University-Purdue University Indianapolis.

Second place, local (tie) — The San Francisco Climate and Health Profile, submitted by the San Francisco Department of Public Health Climate and Health Program.

Second place, local (tie) — Up With the Waters, submitted by Amanda Koltz from Washington University in St. Louis, and Steve Koltz, NYC web development fellow from the Flatiron School in Brooklyn, New York.

VIII. The Future of Tox21 – Improving on Biological Coverage and Human Relevance

Dr. Rick Paules, acting chief of the Biomolecular Screening Branch, updated the Council on the future of the Tox21 program. He provided background information about the history of the program, which began in 2005. It has been through two phases, with Phase III now beginning.

This phase of the program is designed to improve the biological coverage and human relevance of results by:

- Increasing use of computational models to predict toxicity and metabolism
- Increased focus on human cells with known ability to metabolize chemicals
- Increased focus on genetic variation to understand susceptibilities (toxicogenomics)
- Increased use of stem cells to investigate the effects of chemicals on developmental processes
- Enhanced testing of compounds in lower organisms such as zebrafish and *C. elegans*
- Expansion of understanding of biology by developing and implementing a high-throughput, low-cost approach to measure the entire transcriptome, i.e., high-throughput (HT) transcriptomics

Dr. Paules discussed the hypothesis that the ability to measure alterations in the transcriptome following exposures could provide linkages between chemical exposures and adverse biological outcomes (signatures/biomarkers), between *in vitro* and *in vivo* model systems, and between *in vitro* models and human pathobiology. He noted that at this time, whole transcriptome technologies remain prohibitively expensive for high-throughput applications, necessitating focus on a subset of genes to use in a rapid, low-cost technology suitable for high-throughput studies.

One such subset that has been developed is the so-called Tox21Human S1500+ Gene Set. Several HT transcriptomics platforms are currently being evaluated. The long-term goal is to apply HT transcriptomics to human samples from molecular epidemiological studies and clinical studies.

Dr. Guilarte asked about concordance in the rat liver data. Dr. Paules displayed rat liver data, which showed excellent concordance overall.

Dr. Postlethwait asked how the planned approach would fit in with a paradigm of post-translational modification, so that even if an initiating step in a cascade could not be determined, it could at least be determined that the cascade has impacted the way the cells are regulating their genes. Dr. Paules agreed that some biology would be missed,

with an inability to characterize some of the direct effects, but through altered phenotypes and thus a changed transcriptome, an impact on the cell could be seen. Dr. Postlethwait asked about mitochondrial haplotype. Dr. Paules noted that “there are aspects of biology we won’t capture.” He said the HT transcriptomics is not “the answer,” but one tool.

Dr. Eaton said that a challenge in predictive toxicology is that with a large number of chemicals, toxicity is due to a metabolite, with the ratio of different metabolites especially important. Dr. Paules agreed, and said that Tox21 now has a group using mass spectrometry to characterize cells. Dr. Eaton described organ-on-a-chip work in his group on organ-organ interaction, with much work remaining in that area. Dr. Paules agreed, adding “and then you throw in the microbiome.”

Dr. Feinberg said the concordance was “spectacularly high.” He cited a new area of applied mathematics called network theory, which is being used by researchers involved with single-cell transcriptomics. He said that in addition to what has been done so far, Tox21 should add agnostic, deep RNAseq to discover new cellular modules. Dr. Paules noted that some of the technologies being evaluated are amenable to single cell work, and that Tox21 is very interested in that area, particularly the ability to characterize real networks.

Dr. Kaminski asked if there had been enough comparisons of primary cells across multiple donors to give a sense of the variability across donors. Dr. Paules replied that that is not being done in the liver donor cells, but has been done in lymphoblasts. The variability question is being pursued, but not by looking at the donors. Dr. Kaminski said that moving into primary cells is “a huge step forward.” He noted that the ultimate goal is to move into blood, and asked if human leukocytes had been used in any of the studies conducted to date. Dr. Paules said that they have not yet moved into use of human blood samples.

Dr. Guilarte asked if the comparisons had been done with brain cells. Dr. Paules said that they have IPS cells that are of neuronal origin, and are exploring that area through possible collaborations.

IX. Children’s Health Exposure Analysis Resource (CHEAR) Update

Dr. David Balshaw and Dr. Claudia Thompson provided an update on the CHEAR program and the Environmental Influences on Child Health Outcomes (ECHO) program, respectively.

Dr. Balshaw went over background information on CHEAR, which resulted from the redistribution of funds from the canceled National Children’s Study. He noted that the

program had been put together in record time, with the concept having been approved by Council January 16, 2015 and the first CHEAR awards issued September 24.

"What's normally a multi-year process, we did in nine months," he said. This was accomplished due to the collective efforts of the CHEAR program team, which included not only several members of DERT but also representatives from the Division of the National Toxicology Program, the Office of Science Information Management, and the Division of Intramural Research.

CHEAR will pursue the goals of advancing understanding of the impact of environmental exposures on children's health and development and providing infrastructure for adding or expanding exposure analysis to studies involving research in children's health. CHEAR is comprised of three related components: administrative management, laboratory analysis of environmental exposures in existing biological samples, and data repository and statistical analysis support.

Dr. Balshaw described the National Exposure Assessment Laboratory Network, which has funded six labs, with research centered on targeted and untargeted analysis, indicators of biological response, and a development core. The Data Repository, Analysis and Science Center will be at the Icahn School of Medicine at Mount Sinai. He also delineated the CHEAR Coordinating Center responsibilities. He outlined the project's milestones, including a "friendly opening" later in 2016, and a public opening following that. He also mentioned the CHEAR eligibility requirements.

He emphasized that CHEAR is free to users: "You submit samples, you get data, there's no transfer of money. We've already paid for the analysis."

Dr. Thompson provided an overview of the ECHO Program, which has the overarching goal of investigating the longitudinal influence of pre-, peri-, and postnatal environmental exposures on pediatric development and health outcomes with high public health impact through leveraging existing cohorts and other resources. The core elements include a "synthetic cohort," coalescing existing children's health studies, bringing together those cohorts.

ECHO consists of six FOAs released in December, 2015:

- Extant Pediatric Cohorts
- Coordinating Center (CC)
- Data Analysis Center (DAC)
- PRO Core – leveraging the Validation of Pediatric Patient-Reported Outcomes in Chronic Diseases (PEPR) Consortium (started in FY15 with NCS funds)
- CHEAR Core – leveraging CHEAR (started in FY15 with NCS funds)
- Genetics Core (FY17)

The CHEAR Core is designed to expand CHEAR to meet the needs of the ECHO synthetic cohort.

ECHO awards will be issued September 30, 2016. The program is a trans-NIH initiative, with representatives from 16 NIH ICs and Offices. The NIEHS representatives are Dr. Balshaw, Dr. Thompson, and Dr. Kimberly Gray.

Dr. Birnbaum asked for a round of applause for Dr. Thompson and Dr. Balshaw in recognition of their efforts for CHEAR and ECHO.

Referring to the requirement that CHEAR supports only NIH-funded studies, Dr. Miranda asked about the potential role of state-funded sample collection studies. Dr. Balshaw noted that the NIH peer review process was also important. Dr. Miranda responded that it would be a shame to miss the state-level data collection studies. Dr. Thompson said that in the funding announcement for CHEAR, the first focus was the NIH-funded extramural community, as well as bringing in children's studies that in the past had not looked at environmental issues. In the funding announcement, she added, there was a caveat that could allow for outside groups to participate. So that is "not completely off the table," but the initial focus is the NIH extramural community.

Dr. Miranda asked how the ECHO program would fit in with CHEAR, aside from just the supplements. Dr. Thompson said that the money coming directly from NIEHS is for the supplements. She added that in one respect ECHO is a subset of the universe of what could come into CHEAR. She described several other aspects where ECHO feeds into CHEAR. Dr. Birnbaum added that it is important to remember that CHEAR is a \$49 million program, but that represents four years of funding. \$12 million per year is still a big program, but there are six exposure centers, a data center, and a coordinating center, so the amount is not as large as it may appear at first glance. The hope is that funding will continue for the network of exposure centers as they become indispensable. She noted as well that in its first year ECHO will not use the full \$160 million appropriated. It will use \$90 million in its first year, which is not forward-funded. The remainder will go toward the development of pediatric clinics in IDEA states – that roughly \$60 million is forward-funded, and so starting in FY 2017, the program will have increased funding available, and CHEAR may see some additional funding out of ECHO in 2017. It is a seven-year program, but if it is successful, it may continue beyond that. Dr. Birnbaum said the program is of "very, very high Congressional interest."

Dr. Feinberg urged the group to "beware of batch effects," which could threaten to ruin studies, particularly epigenetic studies, by setting standards for cooperation among laboratories. Dr. Collman assured him that those considerations are already being taken into account.

Dr. McCauley asked how the estimate of existing cohorts numbering approximately 50,000 had been determined. Dr. Thompson explained that it was a target number determined by the group; a goal rather than an assessment of actual, existing numbers. Dr. McCauley asked if there were guidelines about going back to the community for permission to release important pieces of their data to the repository. Dr. Balshaw replied that that is an important piece of what the data center is doing, ensuring the sensitivity of the approach taken by the data center. Dr. McCauley noted that if the cohort has been in existence for a while, getting permission to use samples beyond the original intent might be tricky. She recommended guidelines regarding expectation of turnaround when submitting samples, ensuring that the expectations are realistic. Dr. Balshaw said that would be part of the coordinating center's function, allowing the possibility of seeing where samples are in the workflow at any given time, as well as having an evaluation of facilitation of the process.

X. Program Overview: Breast Cancer and the Environment Research Program (BCERP)

Dr. Caroline Dilworth updated Council on BCERP, the long-standing program jointly funded by NIEHS and NCI. She traced the history of the program, focusing on the importance of community engagement since its inception in the early 2000s, particularly the engagement of the breast cancer advocacy community. She said that the program is currently in its third phase. It started in 2003 with the Centers program, and was renewed in 2010. In the third phase, the recommendations that emerged from the Interagency Breast Cancer and the Environment Research Coordinating Committee (IBCERCC) were quite influential in the design of the phase. The program is slated to become even more transdisciplinary than it had been in the past, with a continued focus on specific windows of susceptibility, expanding beyond the pubertal window that had been the primary focus of the past phases. Also, the program will expand to consider other intermediate markers for breast cancer risk beyond pubertal milestones. With changes in structure and scientific focus, the overarching goals have remained, including the ultimate goal of advancing breast cancer prevention.

The program is progressing with a two-pronged approach that has been pursued since May 2014, when it was presented as a concept to Council. It involves a transdisciplinary research initiative (TRI) and a communication research initiative (CRI), both of which have spawned from two companion RFAs. The TRI, with \$4.1 million per year in funding from NIEHS, will last from FY 2015 until FY 2019. The first awards have been made. It consists of six transdisciplinary research projects and a single coordinating center, which is at the University of Wisconsin, Madison. The CRI, with

funding of \$600,000 per year from NIEHS, will last from FY 2017 through FY 2018, and is currently pending peer review.

Dr. Dilworth provided more details about each of the six TRI research programs, and gave a summary of the windows of susceptibility, chemical exposures, and intermediate endpoints being examined across the projects. She described consortium activities, which include collaboration, data sharing, and attendance of consortium meetings.

The consortium had a virtual introduction via four webinars, and then had an in-person kick-off meeting February 4-5, 2016 at the NCI campus. There, four thematic working groups were identified: Outreach and Translation, Mechanisms, Density, and Protocol Harmonization. The group also worked to develop and approve consortium policies.

Dr. Eaton said he was glad that NIEHS continues to invest in this important area, particularly looking at cohorts of young age. Dr. Birnbaum described the work of a long-standing Child Health and Development Study (CHDS) in California, with two recent significant papers showing strong associations between environmental exposures at young ages and subsequent development of breast cancer. More recently, the program has released data concerning the daughters of those women, where the strongest association was clearly with pre-natal exposure. Dr. Eaton added that a challenging risk message could be presented by studies of oxybenzone, which was a substitute for PABA as a UV screen. Dr. Dilworth agreed that that was a subject of concern, and said that the consortium, with involvement from the community, would be well-qualified to develop good risk communications about it.

Dr. Conti asked that the consortium reach out to veterinary counterparts such as canine cancer researchers.

XI. NIH-EPA Centers of Excellence on Environmental Health Disparities Research

Health Science Administrator, Dr. Symma Finn updated Council on the NIH-EPA Centers of Excellence on Environmental Health Disparities Research. She described how the program aligns with the NIEHS strategic plan goals in particular goals in health disparities, combined exposures, and bi-directional communications. The FOA was issued in 2014 by NIEHS, NIMHD, NICHD, and EPA to encourage basic biological, clinical, epidemiological, behavioral, and social scientific investigations of disease conditions known to be a significant burden among low socioeconomic status and health disparate populations. NIEHS grants were funded in July, 2015. The program's goals are to:

- Promote basic and applied research to assess and mitigate environmentally driven health disparities

- Develop capacity to expand the ability of stakeholders to participate in research
- Develop methods to integrate the multiple factors that contribute to EHDs
- Disseminate knowledge that is culturally appropriate and that will benefit affected communities

Given the complexity of the expected projects, the P-50 grant mechanism was selected. Required elements included a multidisciplinary team, an administrative core, a research projects core with 2-3 R01-type projects and a data sharing plan, and a community engagement core with an evaluation plan. The priorities for the research are:

- Cumulative effects of multi-environmental, physical and social stressors
- Differential exposures
- Land use considerations and health disparities
- Built environment, housing and transportation
- Environmental sustainability and health disparities
- Engagement of affected community members/organizations in the research

Dr. Finn delineated the titles and themes of each center program, their locations and the principal investigators of the five centers, which were funded in FY 2015 at \$4 million. She noted the team members at NIH and EPA who are involved in oversight of the project.

Dr. Brown observed that it was great to hear the last two reports, with so much new work going on involving deep community engagement.

XII. NIEHS and EPA Children's Centers for Environmental Health and Disease Prevention Research

Dr. Kim Gray updated Council on the Children's Centers program, which has been in existence since 1998. She described the history of the program as it has evolved and achieved various milestones through the years. Currently, the program funds 14 centers across the nation. A new RFA was released in 2014. Dr. Gray noted the children's center program goals:

- Better understand environmental factors affecting children's health
- Turn research into real world treatments and interventions
- Establish a national network
- Promote multidisciplinary interactions
- Provide community outreach

The program is set up around a central theme of children's environmental health, with three essential elements: career development of new EHS investigators, fostering community-academic partnerships, and coordination of science across the program by a health specialist. There are three integrated research projects and two cores, an administrative core and a community outreach and translation core (COTC).

Dr. Gray provided an overview of the 2014 RFA, which employs a P50 ("Specialized Centers of Excellence") funding mechanism. The applications were reviewed in May, 2015. NIEHS awards were issued in September, 2015, with EPA awards expected soon. New centers established under the RFA are at Northeastern University and Emory University. Renewed centers are at University of California, Berkeley, Johns Hopkins University, and Columbia/USC. Dr. Gray described the program focus and community engagement activities at each of the centers

She discussed several highlights from the centers' outreach activities, including Dr. Frederica Perera from Columbia University having won the prestigious Heinz Award in 2015. She passed along several examples of press coverage generated by the centers, as well as educational materials produced by the programs. She noted that COTC teams from various centers have been actively involved in policy and legislation as it relates to children's environmental health, and provided examples. She described the most recent Children's Centers Annual Meeting, which took place in October, 2015. The next webinar is scheduled for March 9, 2016, focusing on child care.

Dr. Gray concluded by noting that over the past ten years, NIEHS and EPA have jointly funded Children's Environmental Health Centers with a total funding amount to date of slightly more than \$100 million. Centers receive \$1.5-2 million in total costs per year for five years.

Dr. Eaton asked if any changes are planned to the application cycle for the centers. Dr. Gray said there were currently no plans to change the cycle.

XIII. NIEHS Involvement in Phase II of Human Heredity and Health in Africa (H3Africa) Concept

Dr. Kim McAllister briefed Council on H3Africa, which is an NIH Common Fund program funded jointly with the UK Wellcome Trust. She said the discussion would be an open Council clearance to get the panel's ideas about how NIEHS could be further involved and participate in the second phase of the program.

The overall goal of the program is to enhance capacity for genomics research in Africa by African scientists, to understand the genetic and environmental factors that determine disease susceptibility. Thus, the primary investigators must be African-based

and the majority of the work must be done in Africa. The first phase has focused on building capacity and establishing genomic infrastructure. The second phase, which involves an additional five years of the program, is designed to expand the effort to include many individual NIH IC interests. Dr. McAllister stated that this is the right time for more substantial NIEHS involvement in the program, in terms of incorporating environmental risk factors, expanding the scope to include gene/environment interactions in complex diseases in Africa, and integrating and synchronizing NIEHS grantee and environmental health expertise into the program.

Dr. McAllister noted that H3Africa is trying to address both the present and emerging needs in Africa, which suffers a disproportionate burden of communicable diseases and is experiencing an increasing emergence of non-communicable diseases such as cancer and diabetes, with potentially complex gene/environment components. Studying those components is especially potentially fruitful in Africa, with its high genetic diversity combined with unique exposures and varied environments.

Phase I of the program concentrated on infrastructure development, including a bioinformatics network, three DNA biorepositories, and a strong ELSI component, with an H3Africa genotyping array and the launch of several initial genomic studies. Several of the Phase I projects included environmental factors. Several challenges arose during Phase I, and recommendations emerged for Phase II to address some of those challenges, based on lessons learned from Phase I. They included encouragement of broad consent and re-use of samples and data, as well as establishment of pilot biorepository research projects.

Dr. McAllister listed several of the accomplishments from Phase I of the program and plans for Phase II, which included additional funding opportunities for collaborative centers, research grants, ELSI ("Ethical, Legal, and Social Implications) research grants, BioNet Centers, a coordinating center and training grants. Phase II is also designed to incorporate specific interests of individual NIH ICs and more interaction with other ongoing and planned IC global health initiatives in Africa. She also delineated several parallel NIEHS-funded research efforts in Africa, including examples of landmark NIEHS-funded African research projects such clean cookstove initiatives, indoor spraying of insecticides for malaria control and child neurodevelopment outcomes, and exposure to manganese related to motor and cognitive outcomes. NIEHS also supports two GeoHealth Hubs in Africa. NIEHS has also supported several scientific meetings and conferences on the continent in recent years. She listed some of the possibilities for increased NIEHS investment in H3Africa Phase II:

- Add environment language (metals, toxicants, microbiome, climate change, cookstove, biomonitoring, etc.) related to GxE for FOAs, especially research grants

- Potential for expansion of current H3Africa biorepositories to various biosamples relevant to environmental measurements
- Expansion of BioNet Centers to collect environmental factors and harmonize core phenotypes and environmental measures

She asked Council for its ideas on:

- How can H3Africa best use the expertise of environmental health scientists?
- How can H3Africa best synergize with other global health initiatives in Africa?
- What particular H3Africa programs should NIEHS invest in?

Dr. Hu was the first Council reviewer. He called it “a fantastic initiative,” with the ability to piggy-back on existing investments that have been made by other institutes, leveraging existing samples and populations to address environmental questions. He said that an overall strategic issue involves the question of what the exposure profiles of typical Africans are, which no one really knows. He felt that an ideal solution would be an equivalent to NHANES, with community-based sampling in different parts of sub-Saharan Africa, to be able to characterize exposures not only in rural areas but also in areas of rapid urbanization. He endorsed the gene-environment aspect, but felt that past gene-environment interaction epidemiologic studies had not been done very well, and so wondered what the strategy would be to get such projects through study sections. “This really does get at the overall need and opportunity for NIEHS to have an impact on what we understand about the global impact of pollutants, since this is such an under-studied continent,” he said. He mentioned the WHO long-term study of the global burden of disease, noting that the environmental component of the global burden of disease is “woefully underrepresented.” He said he would encourage NIEHS to support more of those efforts.

Dr. Miranda was the second Council reviewer. She said that although the H3Africa overall mission statement included reference to environment, the Phase I projects Dr. McAllister had shown related to environmental factors were few, and the environmental factor was most often infectious disease or psychosocial factors. Although that is important, that is not necessarily the “E” in environment NIEHS would immediately think of. Thus, the second phase is an opportunity to add more traditional environmental factors to the group’s research. She added that it would also be an opportunity to include more gene-environment studies, although up to now they have not represented major advances. She said the activity would be a good fit for NIEHS due to the emphasis on ELSI issues, which matches well with the NIEHS health disparities portfolio. She recommended that NIEHS further think through its potential participation, and whether it addresses advancing environmental science or works toward better understanding the environmental health landscape in Africa. She urged NIEHS to focus, given the breadth of environmental health issues it has worked on in the past.

With limited resources for this project, it should be decided how to concentrate those resources, as a diffuse pool of investments is unlikely to create the desired synergies. She said she was agnostic as to what the area of concentration should be. She recommended reserving some resources for bringing together the NIEHS-funded awardees, so that they can learn from each other and create synergies. Also, there should be a mechanism for bringing together the NIEHS awardees with other H3Africa awardees working in similar geographic areas. She said the program's focus should be complementary with the domestic NIEHS health disparities portfolio. She noted that good research in this area has the potential to impact development back lending in the medium-to-long term.

Dr. Feinberg called the proposal "fantastic, really incredibly interesting and important." He observed that it would not only be relevant to African health, but would be immediately relevant to US health as well. He noted that beyond genetic diversity, environmental exposures are also much more heterogeneous in Africa. He felt that the opportunity to look at questions of nutrition would be valuable, including nutritional epigenetics. He said that the proposal would fit well with the NIEHS mission.

Dr. Elliott commented about the ELSI aspect of the project, and said that NIEHS could positively influence it, with many relevant issues. He cited the NIEHS strong commitment to community engagement. He felt that there were many rich ELSI questions that could be explored.

Dr. Eaton suggested looking at the interaction between low levels of toxicants such as aflatoxin and infectious disease. He said that aflatoxin has shown a remarkable synergism with hepatitis B virus.

Dr. Brown felt that narrow consent would be preferable to the broad consent emphasis included in Phase II of the project, in that it would be "much more of a democratic, participatory way to go." Dr. McAllister noted that the broad consent would often be instituted on a case-by-case basis, where possible.

Dr. Jennifer Troyer from NHGRI commented by telephone. She is the NHGRI coordinator for the H3Africa program. She said that it would be important to push for broad consent in cases where it would be acceptable so that data could be shared as broadly to the scientific community as possible.

Dr. Conry said that in its meeting last fall, the International Federation of Obstetricians and Gynecologists said that focusing on Africa would be one of its top priorities over the next few years, so the information generated by H3Africa would be important to that effort.

Ms. Waghiyi said it was great that NIEHS is looking to invest in Africa, but wanted to turn the conversation to underserved communities in America, such as her home in Alaska. She described conditions there, where contaminations levels are high and health disparities are severe.

Dr. Collman asked for a motion and vote on the concept. Following a motion and second to approve the concept, all Council members voted in favor with none opposed and no abstentions. Dr. Collman asked Council members to provide further feedback about how NIEHS funding, as a finite resource, could have the most impact.

Dr. Birnbaum noted that NIEHS is interested in nutrition and diet, and their impact on health and relationship to other environmental exposures. She said the opportunity presented by the genetic diversity and diversity of environmental exposures in Africa is substantial. Referring to the H3Africa concept, she said that "The recognition of how the environment impacts our lives is not as great as we would like it to be, so there are opportunities there for us to go further in understanding."

XIV. Concept Clearance: Preconception Exposure and Health Across the Lifespan

Dr. Thad Schug presented the concept regarding preconception exposure and the health of the offspring to Council. The concept aims are to:

- Determine what environmental insults can cause transmissible changes to male and female germ cells
- Identify the mechanistic changes in germ cells resulting from environmental exposures
- Link transmissible germ cell alterations to phenotypic changes in the direct offspring

Ultimately, the question to be addressed is, is the preconception period a vulnerable window of susceptibility?

Dr. Schug provided background information about the scientific basis for the concept, including the Barker Hypothesis from 1989, which posited an inverse relationship between birth weight and death from heart disease in the Dutch Famine Birth Cohort. That idea has evolved into today's DOHaD (developmental origins of health and disease) concept, which now includes both nutrition and environmental exposures and stressors in the womb, and states that early life is a sensitive time for exposure. Dr. Schug observed that NIH has a very broad portfolio looking at the effects of DOHaD and in utero exposure, with many programs looking at early life exposures, but few looking at individuals during their reproductive years, when exposures could result in

changes among their offspring. A central question to look at is, what preconception exposures or windows of exposure to the mother and father can affect germ cells, and can those effects be traced out to effects in the offspring?

Dr. Schug described the preconception window, a period of rapid changes during gametogenesis – rapid cell growth, meiotic division, and metabolic, hormonal, and epigenetic changes. He noted that the period of germ cell development is very different in males and females, occurring both at different time periods and different time durations. He said that it is known that exposures to germ cells and supporting tissues can have lasting effects, such as teratogenic effects, altered germ cell quality and fertility, and lethal DNA damage. The interest is more in subtle changes to germ cells from multiple exposures or exposures during specific windows of susceptibility. These subtle effects are thought to include:

- Altered mitochondria and energy states
- Subtle DNA mutations and copy number variations
- Altered sex-specific gene expression
- Interference with meiosis
- Altered redox states and stress levels
- Altered epigenomes of germ cells

The hypothesis is that some of these subtle changes carry on to the offspring.

Dr. Schug provided examples from the literature of paternal and maternal exposures that have been seen to affect offspring, mainly in the realms of nutrition or stress response. He identified gaps and needs in the state of the science. Data gaps include: 1) evidence clearly linking environmental exposures to parents during the preconception period to health effects in their children and 2) windows of sensitivity, chemicals of concern, mechanisms of action, and health impacts. The scientific need is to build on existing animal models to establish mechanisms of action and linkages to health outcomes. The overall goal of the proposed initiative is to develop a proof-of-principle basic science research program to establish mechanistic links between environmental exposures to germ cells during the preconception period to later-life health outcomes in the first generation offspring. The scope of the research is:

- Work in well-established animal model systems will be considered
- Pre-fertilization exposures, not *in utero* or post-conception
- Research should perform a comprehensive mechanistic analysis on environmentally induced germ cell alterations
- Environmental insults should be non-genotoxic and encourage testing of emerging and under-studied chemicals, such as endocrine disruptors, pesticides, components of air pollution, combined exposures, etc.

- Studies should focus on health outcomes in first generation offspring, not transgenerational inheritance

He provided several examples of potential mechanisms that may be at work in DOHaD, as well as examples of potential disease phenotypes.

The proposed program would consist four-year R01s with a direct cost cap of \$250,000, teaming with NICHD and NCI. The timeline is a summer 2016 release date, review in fall and winter of 2016, and Council review May, 2017. The goal is to fund 6-8 grants with multiple mechanisms and phenotypes, and to encourage multi-PI applications with expertise in both molecular mechanisms and disease endpoints.

Dr. Feinberg was the first Council reviewer. He commented from the genetics point of view, this concept addresses transgenerational inheritance, not Lamarckism. He noted that *in utero* exposures could affect not only that generation, but the second generation as well as the germ cells are formed during that window. He mentioned another area that he thought should be included in the program, the issue of exposure of the germ line, including periconceptionally. He discussed the concept that assisted reproductive technology (ART) may be associated with imprinting defects, citing several papers on that subject. He said it raises enough mechanistic questions to believe that the periconceptional period is important as well. He noted that it is also very important to investigate (but not in the context of this presumed RFA) the issue of *in utero* exposure of the fetus not affecting the germ line, which is completely a separate issue. He said he was very supportive of the concept, and called for inclusion of the periconceptional period. He felt that it was important to adequately fund the idea.

Dr. Conry was the second Council reviewer. She praised the depth, breadth, and impact of the research proposal. She said that her group, the American Congress of Obstetricians and Gynecologists (ACOG), had not started looking at reproductive health and the environment until 2007. She approved of the concept's focus on preconception health, as "that whole time period is absolutely critical." She said that this funding opportunity is particularly powerful, addressing current issues of great interest to ACOG.

Dr. Feinberg added that a key issue is to find some change in the gamete that is also present in either somatic cells of the offspring, or a mechanistic connection can be made.

NICHD representative Dr. Della Hann said that NICHD is "tremendously interested" in the program, at several levels.

Dr. Janet Hall wondered whether the periconception aspect might be the best direction for this particular RFA to take.

Dr. McCauley said she was excited by the concept, calling it "timely and very important." She agreed that the focus should remain on preconception versus periconception. She expressed concern about so little money being devoted to the project. She said that perhaps the intentions are too broad, and that it may be more effective to know a lot about one or two types of chemicals than the "shotgun approach." Dr. Collman noted that the hope is that the funding would be enhanced through participation from the partner institutes.

Dr. Eaton said he hoped that the RFA would emphasize the importance of dose selection, since there has been "way too much toxicology done at such high doses that it is irrelevant," and masks the important, relevant events that happen at lower doses.

Dr. Kaminski asked Dr. Schug to review the RFA timeline, which he did. Dr. Kaminski said he was concerned about short deadlines, in that they could result in poorly prepared applications.

Dr. Guilarte wondered why the program would target emerging chemicals, as opposed to studying well-characterized chemicals with good understanding of mechanisms. Dr. Schug said that would be a challenge, but that investigators would need to have sufficient preliminary data to back their proposals. He noted that many chemicals are well-understood, and that many of the emerging chemicals have similar profiles, so it should not be a huge leap to address them. Dr. Birnbaum said that "most of the emerging chemicals have already emerged," with a significant amount of information already in existence. Dr. Collman added that what is desired is to see a diversity of chemicals being studied.

Dr. Collman called for and received a motion and a second to approve the concept. The vote was unanimous in favor of approving the concept.

XV. Collaborative Research in Environmental Mixtures Concept

Dr. Bonnie Joubert briefed the Council on the concept to support collaborative research in environmental mixtures.

She provided background information about research on environmental mixtures, including the challenges involved. She described the long-standing NIEHS involvement in mixtures research, such as its inclusion in the NIEHS Strategic Plan (Goal #4). There was an RFA in 1998, three workshops held more recently, various seminars and other meetings, invited speakers and visiting scientists, conference symposia, and publications. Past efforts have focused on toxicological studies, with significant challenges to epidemiological studies, including several statistical issues. She noted

that “Understanding and improving statistical approaches and enabling collaborative efforts in epidemiology are crucial for mixtures research to have ultimate public health relevance.”

Dr. Joubert described the 2015 NIEHS mixtures workshop, “Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies.” During the workshop, various statistical approaches were applied to two simulated datasets and one real-world dataset, with comparison of the results across the approaches. The workshop showed that ongoing challenges remain, as no one method outperformed another, which also means that many approaches can be used and considered valid. Greater complexity in the data led to greater variability in the results and less alignment with “truth” in simulated datasets. The workshop showed that a real-world context is needed, as are very large sample size, interdisciplinary research teams, and the development of novel statistical methods. Thus, establishment of a mixtures consortium is proposed.

Dr. Joubert defined consortium-based research, cited several successful consortia, and described the successful output to be gained from consortia. The consortium approach has not been attempted previously in mixtures research due to the challenges involved, one of which is data integration.

The proposed FOA to enable the development of a mixtures consortium would involve an RFA supporting 3-4 U01 applications, with cross-group collaboration expected and with program oversight of mixtures evaluated and key products. Each application would need to have a core group with a lead PI, 3-4 epidemiologists, 2-3 statisticians, and one toxicologist/biologist. An application would also need to include three or more cohorts with related exposures and health outcomes measured at the time of application. New cohorts could join later, if there is appropriate data and expertise. Collaborative work would be expected and encouraged. Initial outcomes from the consortium would focus on methods development:

- Models informed by mechanism and context
 - Incorporation of underlying biology/toxicology
 - Which exposures to evaluate in a mixture
 - Detailed demographic information
 - Large sample size – statistical power
- Examination of heterogeneity
- Meta-analysis vs. pooled analysis

On a broader scale, applications may include:

- Development of a guide for in-depth comparison of results across statistical methods and development of recommendations for epidemiology
- Prioritization of exposures for future research
- Prioritization of mixtures for future research
- Novel methods development
- Software development

Dr. Joubert said that at the earliest, the RFA would be published in the NIH Guide in summer 2016, with applications going to Council in May, 2017. The total cost would be \$2.1 million for up to four awards, with \$350,000 in direct costs per award. The funding would be providing secondary data analysis. Future directions would include growth of the consortium, interaction with other consortia, subgroups with specific focus areas, or broader applications in epidemiology and other fields.

Dr. Ahsan was the first Council reviewer. He said that Dr. Joubert had made a very good case for the concept. He noted that mixtures are too often ignored in studies, which could invalidate findings about chemicals. The aspect is important to address, and it has not been adequately addressed up to now, so the concept is “very timely.” He said the statistical element is the key aspect in need of development. He said that he “overwhelmingly supports” the concept. He felt that there may be merit in restricting the funding applications in disease areas, but that there are pros and cons to that consideration. He felt it would be less important to worry about age and exposure, since the main focus is on methods development.

Dr. Miranda was the second Council reviewer. She approved of the emphasis on statistical development. She called for the concept to go even further, however, since the concept “represents a key opportunity to engage data scientists more broadly, and not just statisticians.” She drew a distinction between data analytics and data analysis. Data analytics involves building the tools and platforms that make it possible for data analysis to be performed. Data analytics is the key missing area to tackle the issue of mixtures, she said, and until that investment is made, the best data analysts will be stymied by a lack of tools and platforms. She recommended focusing the RFA on data scientists and data analytics more broadly. Many huge investments in data science are being made by universities, and NIEHS could leverage these investments, she noted. It is not an early, nascent field, and many mid-career data scientists could likely be recruited into EHS work. She discussed the example of temporal variability being among the major challenges associated with mixtures, adding to the complexity of the enterprise, with issues involving how to architect that type of data, what types of software platforms are available, and how to deal with uncertainty. She said she would argue very strongly to focus the RFA on data scientists, rather than on the traditional team involving toxicologists and epidemiologists. To do so, there would need to be

webinars to attract applications from parties who do not typically apply for NIH funding. Also, review panels would need to be changed to accommodate data scientists. She added that she was not convinced that application to real-world data would result in application to real-world “people data.” She noted that the construction of a synthetic cohort is a huge undertaking, and is challenging statistically. She said that a large NSF award for a data scientist would typically be \$275,000 per year, so the dollars allotted could be stretched to allow 4 or 5 grants instead of just 3 or 4. She said that the concern should not be on disease outcomes or knitting together cohorts, but should focus on priority areas such as how to characterize temporally dynamic, complex mixtures, how to do Bayesian hierarchical modeling for complex mixtures; the big data science questions embedded in the attempt to get on top of mixtures, bringing in the toxicologists, epidemiologists, and human cohort data later.

“I have to admit some skepticism on this,” Dr. Eaton observed. He felt that the mixtures problem is huge and almost intractable. He asked whether the intent is to help design future mixtures studies with robust data collection and statistical approaches, or to pull data sets from existing cohorts to do actual mixtures analysis toward an endpoint. He said it is an important area to address, and agreed that it is mainly a data science issue and should be approached that way. Dr. Joubert described an initial approach using a simulated dataset that would be intended to stimulate methods development. She said one reason there was a desire to include the other experts (e.g., epidemiologists and toxicologists) was that their information might be needed to help develop the models. Dr. Eaton said he was also concerned that the budget is insufficient to pull that many people together.

Dr. Kaminski agreed with Dr. Miranda’s and Dr. Eaton’s assessments. He said the focus should be to develop strategies on how to understand and deal with mixtures, and developing tools to do so. He felt that developing a synthetic cohort or sample dataset would be the correct way to go, in order to start simply.

Dr. Miranda added that with the broad NIH investment in technologies generating huge amounts of complex data, there has been under-investment in the techniques allowing complete leverage of that massive generation of data. While application is important, she said, the field is at a much more fundamental point presently, working to understand how to model complex mixtures. She recommended the inclusion in the RFA of a requirement for an internal scientific advisory committee with toxicologists and epidemiologists involved to get at the biological component, which would take less budget, allowing the funding to be spent on the data scientists who are directly tackling the questions. Perhaps the next RFA would bring the teams together in a more team-based way, she noted.

Dr. Collman asked for and received a motion and second to approve the concept. The Council voted unanimously to approve it, except for Dr. Hu, who abstained because he had been absent from the discussion.

XVI. Adjournment

Dr. Collman thanked the open session presenters and the Council members and staff for their participation in the meeting.

The open portion of the meeting was adjourned at 9:30 a.m., February 24, 2016.

XVII. Consideration of Grant Applications

This portion of the meeting (9:45 a.m. – 12:00 p.m., February 24, 2016) was closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

XVIII. Adjournment

The meeting was officially adjourned at 12:00 p.m., February 24, 2016.

CERTIFICATION:

_____/s/

Linda S. Birnbaum, PhD, DABT, ATS
Chairperson
National Advisory Environmental
Health Sciences Council

_____/s/

Gwen W. Collman, PhD
Executive Secretary
National Advisory Environmental
Health Sciences Council

Attachment:
Council Roster