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

MINUTES OF THE ONE HUNDRED FIFTY-FOURTH MEETING OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

June 4-5, 2018

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred fifty-fourth regular meeting on June 4, 2018 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. The closed session of the meeting was held June 4, 2018.

The meeting was open to the public on June 4, 2018 from 10:30 a.m. to 4:00 p.m. and June 5, 2018 from 8:30 a.m. to 10:00 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 June 4, 2018 from 8:30 a.m. to 10:30 a.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 (via WebEx)
Philip Brown, PhD
William Cibulas, Jr., PhD, MS (*ex officio*) (via WebEx)
José Cordero, MD, MPH
Irasema Coronado, PhD
Brenda Eskenazi, PhD
Della Hann, PhD (*ex officio*)
Shuk-Mei Ho, PhD
Katrina Korfmacher, PhD (ad hoc)
Maureen Lichtveld, MD
José Manautou, PhD
Donna Mendrick, PhD (*ex officio*)
Edith Parker, DrPH (ad hoc)
Brad Racette, MD (ad hoc)
Susan Schantz, PhD
Andy Shih, PhD
Michael Slimak, PhD (*ex officio*)
Patrick Sung, DPhil
Robert Tanguay, PhD (ad hoc)
Deborah Winn, PhD (*ex officio*)
Robert Wright, MD, MPH (ad hoc)

NIEHS Staff

Kathy Ahlmark
Janice Allen, PhD (by phone)
Robin Arnette, PhD
Montserrat Ayala, MD
John Balbus, MD, MPH
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard, MS
Bryann Benton (via WebEx)
Brian Berridge, DVM, PhD
Linda Birnbaum, PhD
Tiffany Bowen
Abee Boyles, PhD
Jed Bullock
Matthew Burr
Danielle Carlin, PhD
Trisha Castranio
Lisa Chadwick, PhD (via WebEx)
Jennifer Collins
Gwen Collman, PhD
Yuxia Cui, PhD
Christie Drew, PhD
Chris Duncan, PhD
Lisa Edwards
Benny Encarnacion
Symma Finn, PhD
Christine Flowers
Amanda Garton
Barbara Gittleman
Kimberly Gray, PhD
Virginia Guidry, PhD
Janet Hall, MD
Astrid Haugen
Michelle Heacock, PhD
Heather Henry, PhD
Jon Hollander, PhD
Chip Hughes
Michael Humble, PhD
Bonnie Joubert, PhD
Helena Kennedy
Heather Knox
Alfonso Latoni, PhD
Cindy Lawler, PhD
Ty Lawson

Robbie Majors
J. Patrick Mastin, PhD
Kim McAllister, PhD
Steven McCaw
Liz McNair
Aubrey Miller, MD, MPH
Sri Nadadur, PhD
Aaron Nicholas
Sheila Newton, PhD
Liam O'Fallon
Kristi Pettibone, PhD
Nicole Popovich
Molly Puente, PhD
Lingamanaidu Ravichandran
Scott Redman
Les Reinlib, PhD
Elizabeth Rubin
Shepherd Schurman, MD
Dan Shaughnessy, PhD
Ashley Singh
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD, MPH
Laura Thomas, PhD
Claudia Thompson, PhD
Brittany Trottier
George Tucker
Steven Tuyishime, PhD
Fred Tyson, PhD
Michelle Victalino
James Williams
Leroy Worth, PhD
Rick Woychik, PhD
Demia Wright, MPH
Humphrey Yao, PhD
Darryl Zeldin, MD

Members of the Public Present

Meena Ananthanarayanan, CSR, NIH (via WebEx)
Ernie Hood, Bridport Services, LLC

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 asked the Council Members attending via WebEx

to introduce themselves, followed by the attendees in the room. Following the introductions, NIEHS Division of Extramural Research and Training (DERT) Director and Council Executive Secretary Dr. Gwen Collman reviewed meeting logistics, including votes to be taken through the Electronic Council Book.

II. Review of Confidentiality and Conflict of Interest

Designated Federal Official Dr. 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 February 2018 Meeting Minutes

Approval of the February 2018 meeting minutes was moved and seconded, and Council voted to approve the minutes, with all in favor. 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 briefed Council on Institute developments since the February 2018 Council meeting.

She began her presentation with a report updating appropriations. She noted that the portion of the NIEHS budget that is tied to the NIH appropriation has increased $36.8 million. The appropriation from the Superfund remained flat, as it has for several years. Much of the recommended $3 billion increase in the NIH budget is devoted to earmarked programs. The question now is whether the budget bills in Congress will be completed by September 30, the end of the current fiscal year. If not, funding would be provided through a Continuing Resolution, as has been the case in recent years.

Dr. Birnbaum described a Congressional Briefing on Neurological Diseases Across the Lifespan, which took place on the Senate side of Capitol Hill on March. She spoke at the briefing, which had more than 60 attendees. She summarized the recent changes in leadership at HHS, and updated progress in the Reimagine HHS and Optimize NIH efforts. The NIH program, which is designed to maximize efficiencies, is expected to take place over the course of 2-3 years.

Dr. Birnbaum described NIEHS endeavors in disaster research, which relate to Goal 5 of the 2012-2017 NIEHS Strategic Plan. Until the NIH Disaster Research Response (DR2) Program was initiated in 2013, many barriers to speedy and efficient disaster research existed. The DR2 program has addressed several of those issues through a variety of initiatives. The efforts have paid off, as NIH researchers were involved within two weeks of Hurricane Harvey in 2017, including several environmental health-related

studies. There was a similar research rapid response to Hurricane Maria. Other time-sensitive research opportunities were funded as well, for phenomena such as wildfires and PFAS contamination.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP personnel or grantees. The first set of publications she described were three papers related to DR2, followed by a One NIEHS paper derived from the Sister Study. She recounted three papers published by DERT grantees, as well as publications from DIR and DNTP researchers.

She shared the new NIEHS public website, which launched April 27, and new developments at *Environmental Health Perspectives*.

She described the recent *Music and Your Health* event, held on Earth Day, and previewed several upcoming events on the NIEHS calendar.

She summarized several recent awards and recognition given to NIEHS personnel and grantees, including the latest group of five Outstanding New Environmental Scientists (ONES) grantees.

Dr. Cordero expressed his appreciation for the rapid research response to recent disasters such as Hurricane Maria.

Dr. Lichtveld noted that her consortium had recently published three papers related to the Gulf Oil Spill. Dr. Birnbaum noted that there is now a huge body of literature emerging from the NIEHS-sponsored work related to the spill, including information about how to counter the adverse effects of such disasters.

V. NIH Budget Process (Budget 101)

Scott Redman from the NIEHS Financial Management Branch reviewed the NIH budget process for the Council.

The process involves three phases: the Administration's (or Formulation) Phase, during which the President's budget is formulated, the Presentation (Congressional) Phase, consisting of presentations, justifications, and hearings, and the Spending / Reconciliation Phase, during which the budget itself is executed. At any given time, he noted, his office is involved in some phase of three different fiscal year budgets. By way of example, he illustrated the many steps in the budget process in progress for FY 2020.

Mr. Redman noted that since FY 2000, NIEHS has operated under Continuing Resolutions (CR) approximately 42 percent of the time. He illustrated where NIEHS funding comes from, and where it goes.

Dr. Birnbaum noted that despite reports that the President had signed a budget, funding cannot be distributed right away, until the money is actually allocated. She praised Mr. Redman for the enormous amount of work he is required to perform every time there is a CR, which presents challenges in funding distribution, including the necessity of issuing partial funding of extramural grants.

Dr. Manautou asked if money could be carried over from one quarter to the next. Dr. Birnbaum replied that that can be done. Mr. Redman said that the quarterly allocations are designed to set limits, but all of the funding need not be used in the quarter. Dr. Collman noted that when a CR comes at the beginning of a year, the institute can ask for the same amount of money that was spent the year before.

Dr. Birnbaum noted that since at least 1999, there has not been a budget by September 30. She asked NIEHS Congressional Liaison Jed Bullock what he had been hearing about whether there is any possibility of having an FY 2019 budget in place by September 30. Mr. Bullock described the current situation, with the process moving more quickly than has been typical in recent years.

Mr. Redman noted that in this election year, odds are against a completed budget emerging by September 30.

VI. Sexual Differentiation and Environmental Health Sciences

Senior Principal Investigator Dr. Humphrey Yao from the Reproductive Developmental Biology Group briefed the Council on his group's research.

He noted that the concept of developmental origins of adult diseases, which was first identified in the cardiovascular system, also applies to the reproductive systems, where formation of most sex organs occurs before birth. Defects in reproductive organ formation manifest as birth defects in severe cases, but minor abnormalities are often left undetected and become a potential cause of fertility problems and neoplasia when the affected individual reaches adulthood.

The major focus of the Reproductive Developmental Biology Group is to understand the basic mechanisms of reproductive organ formation, and to apply that knowledge to investigate the impacts of generic mutations and environmental stressors on fetal sexual development and fertility in adulthood.

To define the process of how reproductive organs form during embryogenesis, the group uses the mouse as its model organism, focusing on molecular and cellular mechanisms underlying the establishment of gonads and reproductive tracts. There has been significant progress in learning how somatic cell lineages are established in

the gonads, in identification of new factors involved in dimorphic development of reproductive tracts, and in investigation of the effects of *in utero* exposure to endocrine disruptors on reproductive systems and lingering impacts on fertility in adulthood.

Dr. Lichtveld asked whether the mice breed earlier given that they are going through puberty earlier. Dr. Yao said that the animals did not show any reproductive differences in terms of measures of fertility such as first litter or litter size. He said it was unclear why, given the early onset of puberty.

Dr. Sung asked how much oxidative stress would be derived from the drinking water containing arsenic in the parts per billion range. He asked if oxidative stress could be ruled out as a mechanism. Dr. Yao said he was unsure, but there was no evidence that such a low level of exposure would be associated with oxidative stress.

Dr. Cordero recognized the significance of Dr. Yao's work in relation to fetal origins of adult disease, and asked if he had looked at any association with cardiovascular disease. Dr. Yao said he had looked at lipid levels, which were higher, but surprisingly, there was no evidence of fatty liver. He said his collaborator is investigating that puzzling outcome.

Dr. Schantz asked whether all of the effects Dr. Yao had seen were in females. Dr. Yao replied that he had focused on presenting the data for females, since the early onset of puberty was so much easier to detect than in the males. He said that the obesity phenotype is also very significant in the males.

Dr. Ho asked whether Dr. Yao had considered using an estrogen receptor α knockout to repeat his experiments. Dr. Yao replied that the estrogen receptor knockout is in a different strain. He said his work uses CD1 animals, and people ask if the results are strain-specific. He uses the CD1 strain as an outbred strain mimicking a human scenario. Dr. Ho noted that he could use a pharmacological antagonist for ERα or β. Dr. Yao agreed that it was possible. Dr. Birnbaum commented that Dr. Waalkes had seen the same tumorigenic responses in three different strains of mice.

Dr. Manautou asked how Dr. Yao would define ectopic in the ectopic activation of hedgehog in the females. Dr. Yao said it is a genetic model, tightly controlled to activate hedgehog in the somatic cells of the fetal ovary. Regarding the absence of fatty liver, Dr. Manautou asked if that was seen in both males and females. Dr. Yao replied that it was, despite the fact that at six months the animals were obese, with higher blood lipid levels. Dr. Manautou asked whether leptin levels were measured. Dr. Yao replied that they were, and were a bit elevated, but not significantly. Dr. Birnbaum said she found the apparent dissociation between the early puberty and obesity surprising. Dr. Yao agreed.

Dr. Manautou asked about lactation, and whether the pups kept with their exposed moms got the same body weight phenotype. Dr. Yao said they had not conducted the experiment, but another group had found that if the pups are kept with the exposed dam, their development is stunted, because the milk content from the exposed mother is so poor that the offspring cannot survive well enough.

VII. Concept Clearance: Functional RNA Modifications Environment and Disease (FRAMED)

Dr. Frederick Tyson, Program Director of the Genes, Environment and Health Branch, presented a concept to support research on the impact of environmental exposures on RNA post-translational modifications, a new field of inquiry called epitranscriptomics.

He provided background information about the flow of genetic information within a biological system, epigenetic regulation of transcription, and the several types of post-translational protein modifications. He defined epitranscriptomics as the study of functional dynamic RNA chemical modifications that regulate translation, describing it as a largely unexplored area where environmental exposures may well have an impact on health and disease. Refinements in existing technologies such as mass spec are facilitating study of RNA modifications.

Dr. Tyson cited the potential to build epitranscriptomics in the NIEHS portfolio:

- Functional studies suggest epitranscriptomics may be associated with multiple biological process and adverse health outcomes such as obesity, cancer, and neurodevelopmental disorders.
- High-fat diets, low-protein diets, UV radiation, and traumatic stress exposures in mammalian models provide evidence that stressors can alter functional activities regulated by RNA modification.

The proposed program would establish an exposure-driven portfolio of mechanistic and biomarker research with proteomic and Next Gen sequencing approaches, and use of model systems with demonstrated relevance to adverse human health outcomes. The program would consist of two RFAs funding R01s and R21s. From a $3 million set-aside, there would be five R01s with $250,000 in direct costs for five years, four R21s with $150,000 in direct costs over three years, as well as an opportunity fund in year 3.

Dr. Ho was the first Council reviewer. She said that the project is very timely, because the whole class of molecules is involved in many disease patterns, including those with transgenerational effects and mitochondrial-related diseases. She noted that even CO^2 content would affect some of the RNA modifications, so many endogenous environmental factors are already affecting this type of processes. With the potential for

so much impact, it will be a wide-open field for exploration, she observed. She said she was highly supportive of the mechanism.

Dr. Sung was the second Council reviewer. He said he was very excited about the proposal, since it has become clear that RNA has much to do with facilitating DNA repair. The phenomenon raises many interesting mechanistic questions. He said it is a great time for NIEHS to get involved in the field and assume a leadership role.

Dr. Ho added that the field offers great opportunities to look at male/female differences in terms of transmittable molecules coming from germ cells. She said that a good question to ask would be whether some of the RNA modifications happen both in the oocytes during oogenesis versus spermatogenesis. She noted that it is "a wide-open field." She cautioned NIEHS to not restrict its offering to paternal inheritance, which could result in a dogmatic fixation on paternal transmittal.

Dr. Tanguay said that the most likely mechanisms from a toxicant would be the readers and writers in terms of a stable signal at concentrations that matter. He felt that the biggest impact would be to understand the intrinsic possibilities at which the key regulators could be modified — their activity or their expression levels — by toxicants. Dr. Birnbaum asked Dr. Tanguay if he felt that way because the modified RNAs would be very short-lived. Dr. Tanguay replied that that was the case. Dr. Tyson added that the modifications could enhance stability, send the molecule down a path toward degradation. He agreed that the priority should be looking at the readers and writers.

Dr. Collman called for a motion to approve the concept. Dr. Sung so moved. Dr. Coronado seconded the motion. The council voted electronically, and once all of the votes were tabulated, approved the concept.

VIII. Human Health Exposure Analysis Resource (HHEAR) Concept

CHEAR program co-director Dr. David Balshaw presented a concept to the council proposing the expansion of CHEAR (the Children's Health Exposure Analysis Resource) to become the Human Health Exposure Analysis Resource, or HHEAR. He described CHEAR, which was established in 2015 with funds redirected from the discontinued National Children's Study. He discussed the structure of CHEAR, and related data concerning its record since it was established. It is now in year 2 of 4.

The proposal is to solicit recompetition of the CHEAR infrastructure to add or expand exposure analysis to advance understanding of the impact of environmental exposures on human health throughout the life course. The goals and scope of the Coordinating Center and the Data Center would be essentially unchanged, with the HHEAR Lab Network being a modification of structure and scope from the network established by

CHEAR. Sometime in the future, there is a desire to add a small grant program for secondary data analysis.

One of the major proposed changes involves HHEAR accepting environmental samples as well as biological samples for analysis, based on interest from several CHEAR clients as well as the ECHO program. This would allow more information on the sources of exposures, analyzing samples such as drinking water, dust, soil, air filters, and more.

Several other aspects are also under consideration, and Dr. Balshaw asked the Council for members' thoughts on the proposed changes:

- Maximizing the client base
    - Support for Intramural Research Projects
    - Expansion to support analyses within defined specific aims and budget of client study
    - Reconsider requirement of "samples in hand" and possibility for supporting prospective/ongoing studies and multiple "waves" of analyses
- "Adding" vs. "Expanding"
    - Original goals of CHEAR were to "Add" (for the first time) and "Expand" (beyond existing) exposure analyses
    - NIEHS remains committed to building IC and program partnerships to support inclusion of exposure
    - Reality that NIEHS grantees currently comprise ~50% of the CHEAR client community

Also, Dr. Balshaw discussed a proposed change to a "pay to play" model for participation by other NIH ICs.

He described the proposed HHEAR structure and NIEHS support:

- Coordinating Center — 1@$1 million annually
- Data Center — 1@$2.5 million annually
- Targeted Analysis labs — 1-2@$2.5 million total annually (~15,000 analyses)
- Untargeted Analysis labs — 1-2@$2.5 million total annually (~10,000 analyses)
- Environmental Monitoring lab — 1@$1 million annually
- Small Grant Program — PAR no set aside

HHEAR funding is anticipated to begin in July 2019, overlapping briefly prior to the expiration of CHEAR funding, and will run through June 2026.

Dr. Schantz was the first Council reviewer. She said she was very supportive of the proposal, particularly broadening the program beyond children to include all age groups. She liked the idea of including a center-focused on environmental analyses. She

approved of the longer funding time frame, as well as the inclusion of the small grant program. She was more hesitant about the idea of accepting proposals from groups who do not have samples in hand. She supported the idea of including people who have specific aims in funded grants to do the analyses, noting that it would be great for the grantees to have access to the resource. She also supported the pay to play provision.

Dr. Ahsan was the second Council reviewer. He said he supported the proposal, including all of the proposed changes. He said the inclusion of the environmental samples was "a no-brainer" and an excellent addition. Regarding the embedding of analysis within new grants, he suggested that it should be limited to new, prospective submissions with existing samples to avoid the issue of overlap. He felt that the decision regarding pay to play should be dependent on the financial situation. He recommended supporting environmental analysis in the All of Us project. He said his only concern about the plans for infrastructure was the possibility of losing an infrastructure in the current program. He felt that if there was sufficient demand, funding statistical analysis as part of the data center would be a good idea, although some labs may prefer to do their own statistical analysis. He supported the small grant idea. He was unsure about the costs involved in the program.

Dr. Balshaw noted that a bit fewer than half of the current clients are using the Data Center's statistical analysis services, with half of them doing their own.

Dr. Eskenazi said she was very interested in the proposal and hopes it will go forward, but expressed some concerns. First, she was worried about laboratory burden, and the potential queue involved. She said she would like to see the pilot studies more beefed up. She liked the idea of entering an arrangement with All of Us and approved of the proposed acceptance of environmental samples. She recommended building in quality control over time. Dr. Balshaw noted that taking a small number of samples to determine ability to analyze was typically done very quickly.

Dr. Wright observed that if there is an issue regarding the number of freeze/thaw cycles or of sample storage, it is routinely suggested that a pilot phase be performed.

Dr. Brown asked if there would be any effort toward combining data. He wondered if PIs would need to add larger sample sizes to their projects if had budgeted to do some analysis on their own, but then have it done at NIEHS. Regarding the issue of other ICs, he recommended asking the PIs to write a memo pledging to add more environmental variables to their research. He also felt that it would be good to have resources available at the Coordinating Center to address ethical, legal, and social implications of the data, and to report data back to individual participants.

Dr. Lichtveld supported broadening the program beyond children. She said that the anticipatory opportunity to be able to project the samples rather than waiting until the samples are in hand should address some of the queueing issues raised by Dr. Eskenazi. She felt that the addition of the environmental samples was key. She supported the provision to not require having samples in hand to apply.

Dr. Winn agreed that piloting would be a good idea. She asked if the approaches had been benchmarked against NHANES and the National Probability Sample. Dr. Balshaw noted that NIEHS does participate in some of the testing programs that CDC performs for NHANES, but that getting access to the NHANES samples is not a trivial exercise. Dr. Birnbaum added that it takes a long time to get any new analytes into the NHANES queue.

Dr. Wright said he liked the idea of adding the environmental samples, but wondered if having the wearables solely in the environmental is the optimal way to go, since many of them use biological fluids like sweat or breath condensate. He suggested that the wearables should possibly be in all three components, the targeted and untargeted labs in additional to the environmental.

Dr. Korfmacher approved of the small grants program. She also encouraged inclusion of some sort of translational or community-based effort.

Dr. Collman called for a motion to approve the concept. Dr. Coronado so moved; Dr. Lichtveld seconded. The council voted electronically, and once all of the votes were tabulated, approved the concept.

IX. Global Environmental Health at NIEHS: Implementation Plan Update

NIEHS Senior Advisor for Public Health Dr. John Balbus briefed the Council on recent institute activities and accomplishments in global environmental health (GEH).

He initially focused on the timeline for the NIEHS GEH program, which got underway in 2008. He related the GEH goals included in the 2012-2017 NIEHS Strategic Plan and showed how those short-term goals had been met as the plan was implemented. He listed the staff members involved with GEH, including the GEH Working Group.

Dr. Balbus described GEH extramural funding, intramural and international activities. He went over the many GEH program products, including webpages, the GEH newsletter and podcasts, and more, including a breakdown of the various GEH activities and media products. He discussed the history of the institute's relationship with the World Health Organization, including the initial designation of NIEHS as the NIEHS-WHO

Collaborating Centre, which took place in 2013 and was renewed in 2017. NIEHS assists the WHO by:

- Promoting international research collaborations
- Raising global awareness of emerging issues
- Supporting education and training in environmental and occupational health sciences

The Collaborating Centre works in four key focus areas:

- Children's Environmental Health
- Environmental Factors and Non-Communicable Diseases
- Health Consequences of Weather and Extreme Climates
- Chemical Risk Assessment Network

The NIEHS GEH program strives to connect researchers and create networks worldwide. Dr. Balbus graphically illustrated those efforts.

X. NIEHS Strategic Plan 2018-2012

Dr. Sheila Newton, director of the NIEHS Office of Policy, Planning, and Evaluation, briefed the Council on the progress and current status of the updated NIEHS Strategic Plan, *Advancing Environmental Health Science, Improving Health*.

The Draft Strategic Plan was posted for comment between February 12 and March 30, 2018. Comments were collected, and a near final draft was created and subjected to further review by NIEHS leadership. Leadership comments have been collected and incorporated, with the text presented to the Council in the Electronic Council Book.

Dr. Newton described the revisions to the earlier draft of the plan. For example, the three main categories are now called "Themes," with the subheads under those categories called "goals." The NIEHS Strategic Plan Cloud has also been updated.

The new plan is scheduled to be launched, released and disseminated in September 2018. Dr. Newton delineated the various plans for the launch. Implementation planning will begin in the summer of 2018, with a variety of tools available to track all of the activities and programs implemented. Results will be posted to the Strategic Plan website.

XI. Report of the Director, Division of Extramural Research and Training

DERT Director Dr. Gwen Collman updated the Council on recent developments in the division.

She began by bidding farewell to George Tucker, Chief of the Grants Management Branch, who has retired. Tucker had 35 years of grants management experience in NIH institutes. Dr. Collman summarized recent DERT-sponsored meetings and workshops.

She spent the remainder of her time presenting a Concept Clearance: International Collaborations in Environmental Health Sciences.

She summarized the global impact of the environment on health, including the Lancet Commission's conclusion that pollution is the leading environmental cause of disease and premature death. She showed the global extent of current NIEHS GEH study locations. She reviewed several elements and issues related to international collaborations for NIEHS in the context of the concept. The collaborations would be partnerships with other countries' research funding organizations to put out joint RFAs.

Dr. Collman said she had been approached by several people across the NIH to join ongoing collaborative activities, raising the question of whether to join NIH-wide activities, or proceed alone with international collaborations. The concept is designed to potentially accommodate both scenarios, depending on what is appropriate in a given situation. To determine participation, NIEHS would engage in portfolio analysis to assess the potential for collaboration, possibly including holding a workshop to explore interest. A workshop is also possible following the establishment of a collaborative program, including sessions within international societies.

The funding announcements are considered to be intramural and extramural collaborations.

Dr. Collman said she would concentrate on collaborative opportunities in Brazil, China, and India, which have legacy relationships with NIH. The review issues for each are slightly different, and as a result each funding announcement will be slightly different. Post-award management of the program, including integration of awardees into the NIEHS family, will present challenges.

She related the history of NIH research collaborations in Brazil, which have focused on infectious diseases research. NIEHS is considering participating in a new FOA with the Brazil Ministry of Health and 4-6 NIH ICs. Funding would take place in FY 2018 or (most likely) 2019. The potential focus of the program would be infectious diseases and neurological/mental health impact, with some focus on related environmental health questions, particularly related to Zika.

The research relationship with China began in 2010, with the signing of a Memorandum of Understanding (MOU) between NIH and the National Natural Science Foundation of China (NSFC). There have since been five rounds of joint research programs with

various NIH ICs. A sixth round is being prepared, and the Chinese collaborators specifically asked the NIH members of their joint working group to invite NIEHS to the table this time, as China wishes to make an investment in environmental health.

Dr. Collman discussed the results of a recent survey of the collaborative grantees. Award length was seen as the largest challenge, as well as the issue of biospecimen transfers.

In the next funding round, NCI would be the lead agency. Dr. Collman related the NSFC research priorities for collaborations with NCI, NIMH and NINDS. For work with NIEHS, the NSFC research priorities would include research on environmental factors and human health, particularly autism, breast cancer, cardiac disease, children's health, neurodegenerative diseases, neurodevelopmental disorders, obesity and diabetes, reproductive system diseases, and autoimmune diseases. Environmental health topics of interest include soil pollution and health water pollution and health, mining occupational diseases, and environmental pollution in public places such as schools and office buildings.

There have been 28 NIEHS-funded grants in China led by U.S. investigators since 2008, with 7 active grants in China in FY 2018.

The NSFC is very interested in holding a workshop at some point, Dr. Collman said, with the timing and content to be determined.

NIEHS has had many activities previously in India, working with different teams, universities, and leaders in government as well as academia. Dr. Collman detailed the various activities, which included Dr. Sri Nadadur as an Embassy Science Fellow in Delhi in 2015. An MOU developed between the Council of Scientific and Industrial Research (CSIR) and NIEHS is pending, awaiting signatures in India. Dr. Collman described the terms of the wide-ranging collaboration.

She delineated many other opportunities for NIEHS collaborations with international partners. There are already several hundred NIH and HHS MOUs in place with countries around the world, creating opportunities for new partnerships. NIEHS is also currently working on an MOU with USAID. There is also interest in participating further in the Embassy Science Fellows Program through the US Department of State, as U.S. embassies in various countries have requested expertise on topics of relevance to NIEHS.

Dr. Eskenazi was the first Council reviewer of the concept. She said it was very exciting, and she enthusiastically endorsed it. She was particularly pleased that the program would be joint money, not just U.S. funds going to another country. Having buy-in from both sides would help to make it work, causing her enthusiasm for the

model. She said that her only concern is that the lower-income countries may not be able to provide funds, and the model may need to be reconsidered as individual countries are dealt with, perhaps arriving at a lower percentage of participation. She felt that the concept is very timely, with the need today to think internationally. She also saw an educational opportunity for both sides. She said that her students were dying to have opportunities for internships abroad working in environmental and public health, and it would be good to include opportunities for students included in the concept. Regarding the question of whether or when to hold a workshop, she said it had been her experience that the relationships necessary for a successful collaboration are not typically fostered in the workshop setting. "It germinates there, but it doesn't really blossom there," she observed. On-site visits would be more valuable, she felt. She approved of the Embassy Science Fellows Program, and recommended working to expand it beyond issues of air pollution. All in all, she felt there was much to be gained within the concept and hoped it would expand to many other countries and grow.

Dr. Shih was the second Council reviewer. He said he shared Dr. Eskenazi's enthusiasm and also wholeheartedly endorsed the concept. His main concern regarding the program was sustainability, in light of the idea of sharing funding. He said the issue of capacity building would be central, even in countries like India and China. He noted that problems with sharing samples are often rooted in capacity building. He suggested that there may be ways to overcome some of those challenges. Regarding award length, he noted that particularly in India and China, there are very valuable population-based cohorts. Regarding the idea of a workshop, he said that in China there may be an opportunity to focus on a wider perspective than just one issue such as air pollution. He endorsed the idea of exploring opportunities to work with other Federal agencies such as the CDC.

Dr. Cordero added his strong endorsement for the program. He noted that several countries such as Brazil already have research efforts related to birth defects that have been in place for many years. He suggested they may be good connection points for exploring the impact of environmental agents. He said that countries such as Mexico and Brazil already have a tradition of funding extramural research through their local agencies, where collaborations may be possible. Regarding funding, he said it was important to look at more than just the dollar figure, but contributions in terms of staffing should also be recognized, particularly in poorer countries.

Dr. Racette was also enthusiastic about the concept. He stressed the importance of personal relationships to build the projects. He encouraged thinking broadly about how to create those opportunities, particularly in-person visits to and from collaborating countries. He suggested care about strong anti-colonial sentiments in African countries, adding to the importance of capacity building, which means different things in different countries.

Dr. Ho noted that many countries would have much in-kind support to offer to collaborations, such as the capacity to analyze many samples. She added that often the barriers would be local cultural and political settings rather than funding per se.

Dr. Manautou supported the recommendation that resources be allocated for developing relationships with collaborating scientists in developing countries. In his experience, he said, productivity is enhanced by collaborators visiting his lab and vice versa. "For this to be successful, there has got to be some degree of exchange and travel," he said.

Dr. Wright asked if the Fulbright program would be involved. Dr. Collman said that the idea was interesting and would be explored.

Dr. Collman called for a motion to approve the concept. Dr. Cordero so moved; Dr. Eskenazi seconded. The council voted electronically, and once all of the votes were tabulated, approved the concept.

XII. Powering Research through Innovative Methods for mixtures in Epidemiology (PRIME) Update

Dr. Bonnie Joubert briefed the Council on progress in mixtures research with the PRIME program. She provided definitions for the designations associated with mixtures, and a history of mixtures research at NIEHS, including a 2015 workshop on statistical methods for assessing health effects of environmental chemical mixtures in epidemiology studies, which called attention to the need for novel methods to address current limitations.

PRIME emerged from an FOA, which resulted in six R01s being awarded in 2018. The program is designed to be ambitious, creative, and to epitomize team science, with an emphasis on cross-disciplinary collaborations.

Dr. Joubert listed the six PRIME R01s and provided details on each project.

Upcoming PRIME activities include in-person meetings and symposia at conferences, and webinars related to statistical methods for environmental mixtures. Dr. Joubert noted that the PRIME webpage should be released soon.

She described the broad, NIEHS-wide effort on mixtures, including colleagues in DERT, NTP, and DIR.

Dr. Slimak asked Dr. Joubert if there were any plans to reach out to other institutes, given the potential applications of mixtures beyond environmental health, such as in nutritional data or social variables. Dr. Joubert replied that she had not specifically

reached out thus far, but that she was considering the possibility of a broader, NIH-wide relationship related to the data science aspect.

XIII. Adjournment

Dr. Collman thanked everyone for a great meeting with thoughtful deliberations. She welcomed the new Council members and offered any additional assistance they might need. Dr. Birnbaum thanked everyone for a very engaging meeting including the NIEHS staff. She said she liked the online voting, but desired to hear the results. Dr. Collman agreed that they would be available during the next meeting.

The meeting was adjourned at 10:00 a.m., June 5, 2018.

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