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

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

September 13, 2016

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred forty-ninth regular meeting on September 13, 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 earlier the same day.

The meeting was open to the public on September 13, 2016 from 10:00 a.m. to 5:00 p.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 September 13, 2016 from 8:30 a.m. to 10:00 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
Philip Brown, PhD (by telephone)
William Cibulas, Jr., PhD (*ex officio*)
Jeanne Conry, MD, PhD
Irasema Coronado, PhD
David Eaton, PhD
Kevin Elliot, PhD (by telephone)
Brenda Eskenazi, PhD (by telephone)
Kenneth Fasman, PhD
Della Hann, PhD (*ex officio*) (by telephone)
James Johnson, Jr., PhD (*ex officio*) (by telephone)
Norbert Kaminski, PhD
Maureen Lichtveld, MD
José Manautou, PhD
Linda McCauley, PhD
Donna Mendrick, PhD (*ex officio*)
Avrum Spira, MD (by telephone)
Viola Waghiyi

Deborah Winn, PhD (*ex officio*)

NIEHS Staff

Kathy Ahlmark
Janice Allen, PhD
Bruce Androphy, JD
Robin Arnette, PhD
John Balbus, MD
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Linda Birnbaum, PhD
Helena Bonner
Tiffany Bowen
John Bucher, PhD
Jed Bullock
Danielle Carlin, PhD
Trisha Castranio
Gwen Collman, PhD
Caroline Dilworth, PhD
Bryan Duran
Lisa Edwards
Katherine Fine
Christine Flowers
Amanda Garton
Kimberly Gray, PhD
Virginia Guidry, PhD
Quaker Harmon, MD, PhD
Michelle Heacock, PhD
Jerry Heindel, PhD
Heather Henry, PhD
Jon Hollander, PhD
Michael Humble, PhD
Bonnie Joubert, PhD
Steve Kleeberger, PhD
Alfonso Latoni, PhD
Cindy Lawler, PhD
Kelly Lenox
Chris Long
Robin Mackar
Robbie Majors
J. Patrick Mastin, PhD
Andy Maynard
Kim McAllister, PhD
Steven McCaw

Rose Anne McGee
Liz McNair
Linette Mines
Sri Nadadur, PhD
Sheila Newton, PhD
Jacqui Niles
Liam O'Fallon
Mitsue Parrish
Kristi Pettibone, PhD
Nicole Popovich
Molly Puente
Lingamanaidu Ravichandran
Scott Redman
Les Reinlib, PhD
Angie Sanders
John Schelp
Thad Schug, PhD
Dan Shaughnessy, PhD
Carol Shreffler, PhD
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD
Laura Thomas, PhD
Claudia Thompson, PhD
Brittany Trottier
George Tucker
Steven Tuyishime
Fred Tyson, PhD
Heather Vellers, PhD
Carmen Williams, MD, PhD
Rick Woychik, PhD
Demia Wright
Michael Wyde, PhD
Darryl Zeldin, MD

Members of the Public Present

Carol Hamilton, PhD, RTI International
Ernie Hood, Bridport Services, LLC
Wayne Huggins, PhD, RTI International
Joyce Keith Hargrove, Keith-Hargrove, Inc.
Michael Lauer, MD, NIH (via video link)
Mike Phillips, RTI International

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 Council members Drs. Feinberg, Guilarte, Miranda, and Zeise 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

Dr. Collman, the Designated Federal Official for the meeting, 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 May 2016 Meeting Minutes

Approval of the May 2016 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 May 2016 Council meeting.

She began with a report on budget matters. She reported that there was still considerable uncertainty regarding the federal budget. She predicted that it would be known by September 30 whether there would be a continuing resolution. She said that the House bill, which proposes a $1.1 billion increase in the NIH budget, would increase the NIEHS appropriation by $16.4 million, while the Senate measure, which proposes a $2 billion increase in the NIH budget, would result in a $28.2 million increase for NIEHS. “We’re currently planning for a flat budget, because that is all we can do at this point,” she said.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP personnel or grantees. She began with a “One NIEHS” paper from several NIEHS researchers and grantees that proposes a framework for systematic review and integrated assessment of endocrine disrupting chemicals. She also provided short synopses of recently published studies from DIR, DNTP, and DERT researchers.

In NIEHS news and highlights, she noted significant staff changes, including the selection of Chris Long to be Executive Office and Associate Director for Management, Janet Hall to be Clinical Director, and the hiring of Rebecca Wiltshire to be Deputy Chief of the Comparative Medicine Branch.

She provided more details to the council about the upcoming events related to the NIEHS 50th anniversary, including the main event at NIEHS November 1. She went over some of the highlights from the five decades of NIEHS and its impact on public health, including current engagement in research on the Zika virus, perfluorinated chemicals, cell phones, lead in drinking water, and many other issues. She recounted recent briefings and forums the institute has held, and summarized several prestigious awards and recognition given to NIEHS personnel and grantees, including the 2016 Dr. Philip L. Smith Award and the Governor's North Carolina Award for Science given to Dr. Birnbaum in recognition of her significant contributions to the state and nation. She also listed several NIEHS winners of NIH Director's Awards and HHS Green Champion Awards.

Dr. Mendrick asked if NIEHS typically offers seminars via WebEx. Dr. Birnbaum replied that it does. Ms. Flowers of the Office of Communications and Public Liaison confirmed that it is the usual practice. Dr. Birnbaum added that with numerous NIEHS people at other locations, it is helpful to webcast events so that they can see them, as well as others. Ms. Flowers noted that the links are available on the NIEHS home page.

Ms. Waghiyi discussed the PDBE (polybrominated diphenyl ethers) flame retardant study Dr. Birnbaum had described. She noted that people on her native St. Lawrence Island in Alaska had very high levels of PDBEs.

Dr. McCauley asked whether real-time protocols would be in place to monitor the impact of the Zika virus. Dr. Birnbaum said an interim protocol had been approved by the IRB, and that others were available on the disaster response website at the National Library of Medicine. Dr. Collman added that there is currently a program announcement for rapid turnaround for grant applications related to Zika research response. Dr. Birnbaum noted that many core centers have used some of their resources to respond quickly in emergency situations.

Dr. Cibulas followed up on Dr. Birnbaum's reference to the CDC reference dose for blood lead in children. He noted that the Lead Poisoning Prevention subcommittee would be meeting shortly to recommend a new reference dose based on data from the NHANES review.

Dr. Lichtveld commented on how much NIEHS has done to support community-based participatory research. Dr. Birnbaum thanked her for the compliment, and reiterated her stance that "you can't do environmental health research unless the communities are

involved from the very beginning." Ms. Waghiyi praised the community-based researchers who have worked in her area.

Dr. Manautou said he was interested to hear that research was to be conducted on potential immune suppression by the Zika infection. Dr. Birnbaum clarified that the question she had raised was more about whether environmental exposures suppress the immune response. Dr. Bucher confirmed that NTP is planning to look at some of the pesticides used for control of mosquitos that carry the Zika virus in immunotoxicological screening tests.

Dr. Elliott asked about the status of the NTP cell phone radiation studies. Dr. Bucher said that the studies continue to be under pathology review, which is taking quite a while as they are enormous studies. He said NTP is still on track for reporting the studies out completely by December 2017. He noted that there had been considerable interest in the recent press release from the scientific and press communities.

Dr. Coronado asked about communication strategies to reach diverse language speakers in the U.S. Dr. Birnbaum said it was an area that could be improved on, and described some encounters she had recently had with community groups. She described some of the communications efforts targeted at lay people. She added that there would be interest in suggestions about how to more effectively communicate with diverse groups. She mentioned several examples of communications with specific community groups. Dr. Lichtveld encouraged showcasing examples of such communication at the upcoming EHS Fest. Dr. Coronado asked if there had ever been surveys of people active in community-based research, asking them to evaluate how the scientist had done. Dr. Birnbaum said it was something that had been done occasionally, but not routinely. Dr. Collman alluded to the Partnerships for Environmental Public Health program, which involves research evaluation and communication as part of its mission, with many resources available. "This theme of community participation and community engagement is really a hallmark of what differentiates us from some of our sister institutes," she said.

V. Evidence-Based Funding: Thoughts about Extramural Research

Via videoconference, NIH Deputy Director for Extramural Research Michael Lauer, MD shared his thoughts on the need to reconsider the metrics used to evaluate biomedical research activity. He noted that while the number of grants funded has remained relatively constant over the past several years, the number of applications from researchers has increased dramatically. Thus, he called for "a new finish line," where the measure used to judge research is not just grants awarded, but a more holistic method taking citations and other factors into account, as well as tracking the number of investigators supported as opposed to the number of grants awarded.

He cited several publications supporting his ideas, including a 2014 paper in JAMA that suggested a "PQRST" approach: productivity, quality, replication, sharing, and translation. He also alluded to a PLOS Biology publication by the NIH Office of Portfolio Analysis that posited a "relative citation ratio" to be a more accurate evaluation method.

He said the efficiency and productivity of the research enterprise has actually declined steadily since the 1950s. Part of the problem is that most of the "low-hanging fruit" has long since been harvested, and the remaining low-hanging fruit is "inherently less valuable and less interesting." Also, some critics think the regulatory environment has become overly complicated and fragments, leading to decreased performance of the overall enterprise.

Dr. Lauer said that one of the goals at NIH over the next 5-10 years is to determine how to make its work more evidence-based, including in its own practices.

Dr. Eaton asked about the presumption that the amount of dollars is not necessarily a good measure of research output. He guessed that comparing that metric to others such as citations and patents would yield a strong correlation. He asked Dr. Lauer if he had done that type of calculation. Dr. Lauer said it was something his group and others had been working on. He said that one emerging concept was diminishing return, in which increasing dollars to an individual researcher did not necessarily translate to a concomitant increase in productivity. He said that Dr. Eaton's point was well taken, raising a very interesting tension. "On the one hand, large institutions benefit from economies of scale…so that is something we would very much like to encourage, but on the other hand, we could also imagine that if all the research was being done in a very small number of places, that probably wouldn't be healthy either."

Dr. Fasman asked if Dr. Lauer had thought about how to measure "softer outputs" such as new regulations, new standards, or new clinical practices. Dr. Lauer said that there is now a dataset measuring citations in the primary results of clinical trials, as well as identification of papers cited in clinical practice guidelines. He said those trends are just the beginning, but other outcomes should be measured as well.

Dr. Mendrick asked whether the situation included baby boomers taking a large share of the funds available. Dr. Lauer acknowledged that aging of the population and the end of mandatory retirement certainly play a role. He also described a phenomenon known as the survival advantage of multiple grants, where losing a single grant is not necessarily a threat to the continuation of a laboratory. If a lab has only one grant and it is not renewed, there is a risk of dropping out of the system. This particularly threatens middle-stage investigators, he noted.

Dr. Manautou asked Dr. Lauer how the current climate and funding trends are affecting training. Dr. Lauer replied said that definite stress is being seen in the world of post-

docs. The number of postdocs has declined, and salaries are substantially lower for PhDs in biomedicine than in other fields. He also cited the recent change in threshold for overtime pay for postdocs.

Dr. Lichtveld inquired about the role of impact factor. Dr. Lauer noted that he had not mentioned impact factor in his presentation. He described some of the problems with impact factor as a measure. "We should not be making decisions about how good a scientist is or whether or not that person is going to be promoted by the impact factor of the journals that they've published," he said. Instead the focus should be on the actual work.

Dr. Eskenazi said academia is on "a collision course," with pressure to increase enrollment while facing loss of state money, with more and more of the base coming from soft money. Dr. Lauer said those fears were well-founded. He said the issues in the field need to be more effectively communicated to students.

Dr. Eaton mentioned a recent publication ranking the innovative universities in the world based on a complex algorithm. He asked Dr. Lauer's opinion on the validity of such an approach. Dr. Lauer said such approaches could signify an effective way to measure success, or could simply confirm biases. He described another approach analyzing innovative phraseology in publications as a metric.

Dr. Ahsan asked if funding from non-health areas had been analyzed. Dr. Lauer said that some of that type of work had been done, in Canada and Australia, for example.

VI. Report of the Director, DERT

Dr. Collman updated the council on activities and developments within DERT since the last meeting in May.

She described DERT staff changes, including the departure of health science administrator Dr. Caroline Dilworth, and the additional of several new staff members.

She recounted several recent DERT highlights, such as inclusion of NIEHS researchers in the NIH Director's Wednesday Afternoon Lecture Series, and Dr. Fred Tyson's July appearance at TEDxDurham.

She reviewed the eligibility requirements and application process to access the Children's Health Exposure Analysis Resource (CHEAR).

She reported on an ongoing DERT workgroup effort to establish an NIEHS framework for translational research. Although there are many such frameworks in existence within NIH, none were seen to speak directly to the NIEHS universe, and the need for a more accurate translational research framework was recognized. The ten-member

workgroup has posted a Request for Information soliciting feedback and a white paper describing its draft translation research framework. The framework consists of a series of concentric circles under the broad categories of fundamental questions, application and synthesis, implementation and adjustment, practice, and health impact. Each circle includes descriptions of the many activities that take place within the category, illustrating the complexity and fluidity of environmental health research. "We don't think that the translational trajectory for work in the environmental health sciences is just from discovery to a product," she said. "There's many steps along the way, and it's bidirectional, or tridirectional." The final version of the translational research framework is expected to be published in summer, 2017.

Dr. Collman also provided details on the Environmental Health Science FEST, which is part of the NIEHS 50th anniversary celebration. The event is planned for downtown Durham, December 6-8, 2016.

Dr. Eaton asked if the CTSAs had been consulted with the draft of the translational research framework, to get their feedback. Dr. Collman said that had not yet been done, but is in the plans.

Dr. Lichtveld said she was excited about the framework. She asked how council members and grantees could be helpful in getting community members to consider it as well. Dr. Collman said it is intended to be shared broadly, and so encouraged all to share it and gain input from their community partners.

Dr. Lichtveld asked how intensive the CHEAR application would be. Dr. Balshaw replied that it is a fair amount of documentation, but the initial request for services is relatively brief. Following that part of the process, more information is requested. The application is roughly 5-6 pages, and the hope is that it will not be too onerous. Dr. Lichtveld asked whether matchmaking would occur, lining up with the appropriate resources. Dr. Balshaw said that would be part of the initial request for services process.

Dr. Mendrick asked about expectations regarding data sharing or meta-analysis related to CHEAR. Dr. Collman said the expectation would be that data generated as part of the CHEAR process would be shared and able to be queried and analyzed in the future.

Dr. Conry commended DERT on the translational framework process, which she said would help write guidelines for clinicians. Dr. Collman asked for that type of feedback in the RFI to help further develop the framework to the benefit of a variety of end users.

VII. NTP Toxicology and Carcinogenicity Studies of Cell Phone Radiofrequency Radiation

Dr. Michael Wyde of the NTP Toxicology Branch briefed the council on 16 years of NTP studies on the health effects of exposure to radiofrequency radiation (RFR).

He described how RFR was originally nominated by the US FDA in 1999. The early years of research through 2005 were spent evaluating existing literature and determining what work was already underway, as well as establishing collaborative research partnerships with the appropriate experts. Designing and constructing an effective exposure system was a challenge, eventually yielding a reverberation chamber exposure system to provide a homogenous electromagnetic environment. The exposure system was completed in 2009, and 21 chambers were installed in Chicago, reflecting the need for separate chambers for each power level. The RFR research program was conducted in rats and mice, and lasted through 2014. It included 5-day pilot studies, 28-day prechronic toxicology studies, and 2-year toxicology and carcinogenicity studies. He added more details about the design and results of each of the studies.

Dr. Wyde noted that NTP pathology review is underway for evaluation of all remaining rat tissues and all mouse tissues. Resources have been shifted to accommodate expeditious review of the chronic RFR studies. Completion of the pathology review is expected in approximately 12-16 months, concurrent with preparation of an NTP Technical Report. The draft Technical Report is anticipated for peer review at a public meeting in late 2017 or early 2018.

Dr. Eaton asked Dr. Wyde if his impression was correct that the tumors found at low incidence were largely benign. Dr. Wyde said that both the gliomas and schwannomas were considered to be malignant.

Dr. Manautou asked about the initial studies looking at body temperature changes. Dr. Wyde said the effects were seen in both males and females, although they were more robust in the males. Dr. Manautou asked what were the critical points used to select a dose range for the subchronic studies. Dr. Wyde said that a measure of one degree Centigrade was used as the cutoff for what was considered to be an excessive increase in temperature. Dr. Manautou noted that the early studies showed no association with cancer, and asked if a potentially protective stress response might be involved. Dr. Wyde said he thought that would be “a pretty big jump.” Dr. Bucher added that cell phone standards allow for a one degree Centigrade increase in temperature, allowing human relevance. Dr. Coronado noted that students are constantly attached to their cell phones, and that much more research is needed. She asked if industry was funding any of the studies and if they have read the NTP report and weighed in on it.

Dr. Bucher said that some of the studies were funded by EU industry, and that NTP has not heard anything official from the cell phone industry. Dr. Birnbaum noted that this was the type of study that could only be done by government, and that as with any good science study, “it raises lots more questions.”

VIII. Regulation of Embryo Development by the Oviductal Environment

NIEHS Science Director Dr. Darryl Zeldin introduced the scientific presentation by Dr. Carmen Williams, who heads the NIEHS Reproductive Medicine Group.

She described a series of experiments conducted by her lab exploring the impact of environmental exposures on a particularly sensitive time window of early development – the very beginning of development of the embryo immediately following fertilization of an egg by sperm. The fertilized embryo spends its first few days in a section called the oviduct, between the ovary and the uterus, which is where implantation eventually occurs.

Her group has found that:

- Estrogenic chemical exposures during oviduct differentiation lead to developmental abnormalities and functional defects, including infertility and alterations in embryo development of the next generation.
- Estrogenic chemical exposures in adults can alter estrogen signaling in the oviduct during preimplantation embryo development and change the developmental program.
- These changes in embryo development can impact offspring health.

Dose and timing were seen as key factors in the effects.

Ms Waghiyi asked Dr. Williams to describe her work in laymen’s terms. Dr. Williams responded, “Environmental impacts can change how the oviduct works, so that it can change the health of the embryo inside the oviduct. Environmental compounds or chemicals that are estrogenic in nature can particularly affect the oviduct, because estrogen is a major regulator of oviduct function, and when [an exposure occurs] it can hurt development of the next generation.”

Dr. Eaton asked if the effects seen with genistein could be reproduced with a low dose of estrogen itself. She said that had not been explored, but that the multi-oocyte follicle phenotype seems to be directly related to the exact potency of the estrogen.

IX. SBIR/STTR Updates and Concept

Dr. Dan Shaughnessy briefed the council on new topics for SBIR funding opportunity announcements.

The four new FOAs are:

- Tools for measuring exposure and responses to engineering nanomaterials
- Organotypic animal models for environmental health research
- Animal and human cells panels to incorporate genetic diversity in toxicity testing
- Educational tools for environmental health science

The new topics are to be phased in gradually over the next six years.

Dr. Eaton was the first Council reviewer. He said he was interested in all four of the areas. He felt that the nanomaterials concept was very timely, as was the organotypic molecules proposal, which would help with the current dearth of comparative toxicology. He noted that the pharmaceutical industry would be very interested in that endeavor. He supported the genetic diversity topic, and agreed with the educational tools opportunities. Overall, he said he was very supportive all four areas.

Dr. McCauley, the second Council reviewer, said that she was also very excited about all four proposals. She suggested development of mechanisms for simple, quick exposure assessment so that communities would not have to wait months to get results. Dr. Shaughnessy agreed that “good enough” information that could be pushed out quickly would be helpful, while communicating the scientific uncertainty around exposure.

Dr. Lichtveld was pleased with the presence of the educational component, particularly in the area of environmental epidemiology. She also looking at risk assessment, especially at the local level.

Dr. Collman called for a motion and second to approve the concept, which she received. The council voted unanimously to approve the concept.

X. Wrapping up the 114th Congress: An Update from Washington

In his first appearance before the council, NIEHS Legislative Liaison Jed Bullock updated the group on the role and responsibilities of the liaison position that he holds, the types and examples of NIEHS-Congress interactions, recent Congressional oversight and U.S. Government Accountability Office (GAO) activity, legislation emerging from the 114th Congress, and a forecast of what may be ahead in terms of decision points by Congress.

He noted that he is a member of the six-person Office of the NIEHS Director in Bethesda, Maryland, and that he is part of the network of 27 legislative contacts across NIH. He succeeded Mary Gant, who had been the NIEHS legislative liaison since 1987, seven months ago. He also serves as the NIEHS liaison to the NIH Office of Legislative Policy and Analysis (OLPA) which is under the NIH Office of the Director (OD), and through OLPA, to the HHS Office of the Assistant Secretary for Legislation (HHS/ASL). Additionally, he liaisons with the "Friends of NIEHS," an outside advocacy organization. His duties include analysis of legislation and facilitation of NIEHS responses to Congressional inquiries.

He described the various types of interactions with Congress, some of which are managed through the Executive Branch, and some of which are direct with Congress. He provided examples of each type of interaction, which include requests for views and review of statements of administration policy about specific legislation pending in Congress, testimony preparation and clearance, questions for the record, inquiries arriving by phone and email, official correspondence, meetings, and technical assistance requests. He also outlined Congressional committee oversight activity affecting NIH and NIEHS, as well as oversight activity being undertaken by the U.S. Government Accountability Office (GAO), which is the investigative arm of Congress.

Mr. Bullock briefly summarized several bills enacted into law to date by the 114th Congress that affects NIEHS, including the *Fiscal Year 2016 Appropriations Act*, the *Frank R. Lautenberg Chemical Safety for the 21st Century Act*, which amended the *Toxic Substances Control Act*, and the *FOIA Improvement Act of 2016*. He also reported on recent legislative activity related to environmental health, and provided a forecast of legislation that may be enacted in the remaining days of the current Congress, including an outlook for a new budget or continuing resolution that would cover Fiscal Year 2017 operations and provide supplemental appropriations to fund the federal response to the Zika virus outbreak.

XI. Adjournment

Dr. Birnbaum and Dr. Collman thanked the presenters, the Council members, and the staff for their participation in the meeting.

The meeting was adjourned at 5:00 p.m., September 13, 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