

September 21, 2015

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Dear Dr. Collins and Dr. Tabak,

The Endocrine Society appreciates the opportunity to provide comments and suggestions on the Environmental influences on Child Health Outcomes (ECHO) Program (the National Children's Study alternative). We submitted comments through the NIH on-line form, but because of the importance of this issue, I also wanted to reach out to you personally to share our recommendations.

The Society applauds the NIH for recognizing that early-life environmental exposures can have long-term impacts. We believe that a better understanding of the developmental origins of health and disease will be critical to long-term efforts to improve public health. The study of hormones will be fundamental to all of the focus areas described in the Request for Information. Many endpoints and biological effects are mediated by hormone action, for example inflammation and oxidative stress, and we urge the ECHO program to evaluate the effects of exposures on hormone action. Further, environmental exposures to chemicals like endocrine disrupting chemicals (EDCs), are risk factors in many diseases. Included among our members are the world's leading experts on hormones and the endocrine effects of environmental chemicals such as endocrine disrupting chemicals (EDCs). Endocrine Society members stand ready to make key contributions to the objectives of the ECHO program.

We urge the NIH to consider chemical exposures, currently the most feasible types of exposure to measure, as a central theme of the ECHO program. These exposures should be prioritized in the early stages of the initiative. We note that the NIEHS has particular expertise in this area, and we recommend that NIEHS maintain a leadership role in the ECHO program and be supplied with sufficient financial and personnel resources to ensure the success of this important endeavor. Below, please find our thoughts and recommendations concerning the following topics: assessing EDC exposures, resources and data management, diversity, and communication.

Assessing EDC Exposures

The Endocrine Society anticipates significant challenges in leveraging existing cohorts to collect standardized data elements as part of the ECHO program. Most existing cohorts are not expected to include all the necessary biospecimen or exposure data sought by the ECHO program, and those that do may not be readily analyzed in aggregate for infrequent outcomes. For EDCs, we anticipate that existing cohorts will have obsolete exposure data that may not be relevant for analysis of newly characterized EDCs or complex mixtures of chemicals. We also note that many EDCs would be expected to have biologically meaningful effects at very low levels. Further, chronic diseases that



have been linked to EDC exposures, such as diabetes, obesity, and cancer, may arise later in life. While we are encouraged by the program's objective to evaluate the maternal "exposome", we note that maternal and paternal exposures are extremely difficult to evaluate. Therefore, active birth cohorts should also be prioritized to ensure that maternal, paternal, and fetal exposures can be synchronously captured. We also question whether certain ongoing birth cohorts can be accurately "retrofitted" to ensure that data can be harmonized with other elements of the ECHO program. RFAs may be required to ensure that cohorts are equipped to appropriately evaluate these exposures.

To systematically address EDC exposures, it will be critical to develop strategies to ensure that the cohorts incorporated within the ECHO program collect data that can be aggregated, compared, and assessed over long periods of time (*i.e.*, many years) with sufficient sensitivity to detect low-dose effects, at least through puberty. At this time, the effects of exposures on developmental biology for individuals younger than 6 years of age is not systematically studied, as this age group is not covered by the National Health and Nutrition Examination Survey. The ECHO Program is well positioned to address this critical gap. By ensuring that environmental exposures are accurately measured in early age cohorts, we can arrive at a better understanding of how exposures affect important developmental endpoints such as neurobehavioral function and IQ.

Resources and Data Management

The Endocrine Society is encouraged that the ECHO program will implement novel data collection and analytic methodologies. Researchers will face significant challenges analyzing complex datasets generated by the ECHO program, including data on multiple types of exposures at different developmental time points. Currently, no robust methods to statistically analyze mixture effects exist. We encourage NIH to issue targeted RFAs to statisticians and epidemiologists to explore approaches to analyzing data generated by the ECHO program. The design and implementation of new analytic techniques to assess mixture effects would have profound implications for toxicology and regulatory decision-making processes.

To efficiently manage resources, we suggest that the ECHO program leverage the President's proposed Precision Medicine Initiative (PMI) cohort. Environmental factors, and in particular EDCs, should be considered in the context of this cohort. We anticipate rapid generation of large amounts of data through the PMI and other ECHO cohorts. Additional synergies can be realized by connecting ECHO and PMI with the NIH Big Data to Knowledge initiative. We also encourage the NIH to engage the Environmental Protection Agency (EPA) to ensure that repositories and data are collected in a systematic way that will be useful to the agency in risk assessments and regulatory decision-making processes. The EPA would be well served by resources that can better link epidemiological data to exposures.

While linking exposure data to human clinical endpoints is of critical importance, we encourage NIH to incorporate data from animal studies to help establish the links between fundamental biology and clinical outcomes from environmental exposures. For example, animal studies can inform epidemiological studies, help researchers develop new or better biomarkers, point to potentially altered pathways, and identify epigenetic changes that explain maternal or paternal exposures that affect children. We are particularly excited by the opportunity to identify and develop new



biomarkers that correlate with increased susceptibility to diseases later in life as a way to identify antecedents of chronic human diseases. Animal studies should collect data from companion animals in addition to laboratory animals. There is a growing literature suggesting that dogs and cats can act as sentinel species for endocrinopathies linked to EDC exposures. To strengthen the program's ability to discover fundamental, causal relationships between exposure and outcome, we recommend that basic scientists with expertise in endocrinology and EDCs be well-represented in the planning, implementation, and evaluation of this program.

Other Important Considerations

The Endocrine Society maintains that ensuring diversity in the ECHO program cohorts is essential to the overall success of the initiative. However, we recommend that NIH consider additional aspects of diversity prior to establishing criteria for IDeA states based on geographic location. By incorporating diverse populations, specifically those populations that are underrepresented in clinical trials, the ECHO program could help advance the science of health disparities. We encourage the NIH to make diversity and inclusion of underrepresented populations a primary consideration for the establishment of IDeA states.

Given the proposed investment of significant resources over multiple years, it will be important to engage the biomedical research community and other stakeholders to ensure long-term support of the ECHO program. Researchers will need to understand the goals of the study and how it may relate to their research programs. Policymakers will need to understand why developmental origins of health and disease are important, and how chemical exposures are linked to human disease. Resources and data generated by the ECHO program should be easily accessible and widely disseminated. For these reasons, we encourage the NIH to develop a communication and community outreach plan associated with the ECHO program.

Summary of Recommendations

The Endocrine Society is encouraged by the opportunities presented by the ECHO program and we look forward to working with the NIH as the program is implemented. In summary, we encourage NIH to adopt the following recommendations in the design of the ECHO program:

- NIEHS should take a leadership role in the ECHO program and be supplied with sufficient resources to ensure success
- Active birth cohorts should be prioritized to ensure that maternal, paternal, and fetal exposures can be captured
- The program should develop strategies to ensure that the cohorts incorporated within the ECHO program collect data that can be aggregated, compared, and assessed over long periods of time
- Environmental exposures to early age cohorts, especially earlier than six years of age, should be prioritized
- NIH should issue targeted RFAs to statisticians and epidemiologists to explore new approaches to analyzing data generated by the ECHO program



- The ECHO program should take advantage of synergies by leveraging the President's proposed Precision Medicine Initiative (PMI) cohort and engaging EPA
- The ECHO program should incorporate data from animal studies to help establish the links between fundamental biology and clinical outcomes from environmental exposures
- Basic scientists with expertise in endocrinology and EDCs should be well-represented in the planning, implementation, and evaluation of the ECHO program
- NIH should make diversity and inclusion of underrepresented populations a primary consideration for the establishment of IDeA states
- NIH should develop a communication and outreach plan for the ECHO program

Thank you for considering the Endocrine Society's comments. If we can be of any assistance in your efforts, please contact Joseph Laakso, Associate Director of Science Policy, at jlaakso@endocrine.org.

Sincerely,

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President
Endocrine Society