Centers for Children's Environmental Health and Disease Prevention Research Program

Review Panel Report
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Table of Contents

ABBREVIATIONS

CBPR	Community-Based Participatory Research
Children's Centers	Centers for Children's Environmental Health and Disease Prevention Research
EPA	U.S. Environmental Protection Agency
NAEHS Council	NIEHS National Advisory Environmental Health Sciences Council
NIEHS	National Institute of Environmental Health Sciences
RFA	Request for Applications

REVIEW PANEL ROSTER

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EXECUTIVE SUMMARY

Over the past 30 years, the NIEHS has invested millions of dollars in children's environmental health research. Since 1998, the Institute has partnered with the EPA to support thirteen research centers devoted exclusively to children's environmental health and disease prevention. These Children's Centers draw upon the resources of community partners and the expertise of top universities and medical centers to focus on the important role that environmental toxicants play in the development of asthma, autism, and other childhood illnesses. As part of a broader effort to evaluate current research approaches used by NIEHS to address children's environmental health research, the Institute in collaboration with the EPA, convened an independent review panel to conduct an evaluation of the Children's Centers as an effective funding mechanism. The panel was asked to provide its opinion on whether the NIEHS should continue the current Children's Centers program, modify it, alter the balance between Center-based and other research approaches, or use a completely different strategy for the next 10 years.

The majority of the panel strongly supported the concept of a Children's Center program to address issues in children's environmental health. The Children's Centers have raised the visibility of children's environmental health nationally and internationally and contributed significantly to the increased awareness in the field of children's health today. Perhaps the greatest strength of the current Children's Center program lies in its use of population-based studies to address questions directly related to children's health. These studies have elevated the visibility of children's environmental health research, and in some cases, have led to successful intervention and prevention programs. Other strengths include the use of community outreach to address research questions in difficult to access vulnerable populations, the promotion of transdisciplinary research, and the training of future researchers in the field (Table 1). However, the panel also identified a number of weaknesses in the program. Primarily, the panel believes the program could be enhanced by strengthening the role of basic science in formulating research questions. In addition, the panel believes the current program overemphasizes a few childhood diseases, is not sufficiently diverse in location and impact, and could better utilize established cohorts and other clinical resources. For these reasons, the panel recommended several modifications to the current Children's Centers program (summarized in Figure 1 and Table 2).

Table 1. Major strengths and weakness of the current Children's Center Program

Strengths	Weaknesses
• Promotes visibility of children's environmental health • Transdisciplinary research • Facilitates access to vulnerable populations • Provide an infrastructure to respond to emerging risk issues (e.g. the World Trade Center) • Successful community outreach • Intervention and prevention actions • Training	• Narrow focus on local concerns • Limited number of health outcomes considered (asthma, autism) • Less than optimal utilization of cohorts and other clinical resources (biorepositories, etc.) by the scientific community • Basic science component not strong in several key emerging areas (e.g., epigenetics, genome-wide analyses) • Limited geographic representation

As shown in Table 2, the panel proposes maintaining an Administrative Core while also providing core funding by way of grants to support new research and initiate pilot projects. A new feature of the recommended model would be the provision of planning grants for up to two years to prepare for full submission of a Children's Center grant. The previous requirement for community-based participatory outreach and translation should be optional; however, supplementary core funding can be made available for community-based participatory research. This approach would afford greater flexibility to investigators to focus on the use of biorepositiories, disease registries, cohorts, clinical samples, etc. to achieve and in some instances expand direct child health linkage. The panel recognizes the importance of community-based participatory research and the need to maintain cohorts that are difficult to cultivate and access. However, the recommended model offers the flexibility of applying for additional funding to support this type of activity while taking advantage of the added benefits afforded using other strategies. Similarly, the emphasis on a new investigator program should become optional and training, as before, remains optional, with supplementary funds available for

Figure 1. Organization of Recommended Children's Centers Program

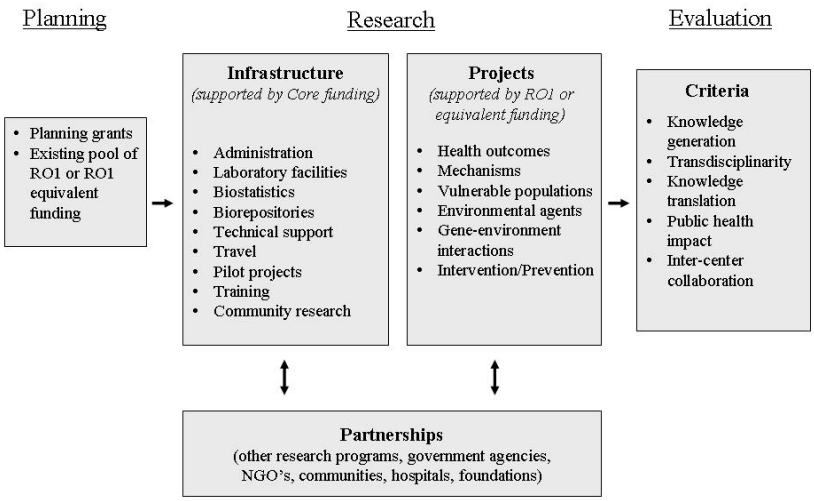


Table 2. Comparison of Current and Recommended Children's Center Funding Models

	Current*	Recommended
Center Structure	Cores + Research Projects (P01)[1]	Cores + Investigator Initiated Funded Grants (e.g. R01/R21[1])
Cores	Administrative Research Support (Optional) Community Outreach &Translation	Administrative Research Support Pilot Projects
Planning Grants	No	Yes (if needed)
Research Projects	Minimum of 3 At least 1 Basic Science Project At least 1 Clinical 1 of the 3 has to utilize CBPR Intervention/prevention****	Minimum of 3 -5 ** Basic Science with a Direct Child Health Linkage*** (no other restrictions)
Center Application Cycle	Varied	Annual
Training		Optional
New Investigator Program	Highly Recommended	Optional

* Current refers to the most recent RFA released on August 24, 2005 (http://www.niehs.nih.gov/dert/past-rfa.htm)
** 3 Research projects would be required initially, but 5 or more would be required for renewal and/or continuation
***Direct child health linkage refers to the use of biorepositiories, disease registries, cohorts, clinical samples, etc.
**** Required in initial RFAs, but not in the most recent

the development of a training program. A critical major difference between the recommended and current model is the requirement of a minimum of 3 **competitively funded research projects** to create a center with the expectation that **a minimum of 2 or more additional competitively funded research projects** will be added to be competitive for renewal and/or continuation. These competitively funded grants must include both basic science and studies with a direct child health linkage. The funding cycle would be annual as opposed to previous intermittent RFAs (which differed each time as to proposal requirements and needs). The competitively funded grants could be from NIEHS, EPA, other NIH institutes or other granting authorities.

In proposing the necessary modifications, the review panel sought to develop a model that would allow the *basic science (broadly defined) to form the foundation for the overall research program* while also retaining research that emphasizes a *direct linkage to child health* (such as through the use of biorepositories, disease registries, clinical specimens, cohorts, case-control studies, or intervention studies, etc.). To accomplish these overall goals, the panel recommends incorporating maximum flexibility in future programs in order to bring in state of the art tools and methods in all areas of children's environmental health research including basic, clinical, and public health.

CHAPTER 1: INTRODUCTION

Background

Children's health has been recognized as a top national priority for many years. Consequently, research and educational programs designed to advance our understanding of the linkages between children's health and the environment have been promoted at multiple levels among the lay and scientific communities. These linkages have served to define the unique susceptibilities of children to environmental exposures as a result of their still developing body systems, and thus higher exposure to foods, drinks and air on the basis of their body size compared to adults, as well as their high risk behaviors that may increase exposure to environmental agents.

In order to maximize the effectiveness of current and future investments of human and financial resources, the NIEHS is conducting a review of its children's environmental health research portfolio. The coverage of the current children's environmental health research portfolio is broad and employs a range of funding mechanisms. The focus areas of this effort include toxicology and behavioral studies, cellular and molecular studies, human research, exposure assessment, public health interventions, and new emerging areas of investigation. The NIEHS and EPA share a common interest in supporting research in children's environmental health, and over the past 30 years, have invested over $150,000,000 in research to address this issue. For the past eight years, the NIEHS has partnered with the EPA to support thirteen research centers devoted to children's environmental health and disease prevention. The Centers for Children's Environmental Health and Disease Prevention Research ("Children's Centers") program draws upon the resources of community partners and the expertise of top universities and medical centers to focus on the important role that environmental toxicants play in the development of asthma, autism, and other childhood illnesses.

For the NIEHS, the Children's Centers program was designed to support basic and population-based research into the biology underlying environmentally-induced diseases in children while at the same time providing a vehicle for community outreach and building scientific capacity in children's environmental health. The 1996 Food Quality Protection Act (FQPA) charged EPA with developing more protective policies for children and promoting the science needed to improve regulatory action. EPA's Human Health Research Multi-Year Plan (2006-2011), which was developed in part due to the FQPA, identifies key science questions for the agency: 1) use of mechanistic data in risk assessment, 2) cumulative risk, 3) susceptible subpopulations, and 4) assessment of risk management decisions. The Children's Centers programs falls predominantly under the issue of susceptible lifestages/subpopulations, and helps address the following questions: What lifestages/subpopulations have differential risk to environmental stressors? What is the basis for the differential risk? What is the risk to each lifestage/subpopulation? How can differential risk be mitigated? From the EPA's perspective, the Children's Centers are addressing these questions by focusing their efforts on developmental toxicology, exposure assessment, biomarkers, epidemiology, and primary intervention.

The Children's Centers program is a prominent component of the research portfolio in children's environmental health at both the NIEHS and EPA. As such, it is necessary to evaluate its effectiveness as a mechanism to stimulate research in this area. In addition, it is important to

determine whether other approaches should be considered to advance the children's environmental health research and educational agenda. Supporting research that shows the greatest promise for rapidly identifying links between environmental exposures and childhood disorders and disease is a primary focus. To aid in this evaluation process, the NIEHS and EPA convened an independent panel to review the Children's Centers program[1].

Scope of the Review[2]

The review panel convened by NIEHS and EPA was charged to review the overall effectiveness of Children Centers as a funding mechanism to address national priorities in children's environmental health research and education (see Review Panel Charge, Appendix 1). The review panel was *not* asked to evaluate the performance of individual Children's Centers. The fundamental question posed to the panel was whether the NIEHS and EPA should continue the current Children's Centers program as is, modify it, alter the balance between Center-based and other research approaches, or use a completely different strategy for the next 10 years. While both the NIEHS and EPA support the current evaluation[3], this report focuses on NIH funding strategies because the existing Children's Centers program utilizes the funding framework of NIH and not the EPA (e.g., R01/P01 versus STAR grants).

[1] The panel is convened as a working group to the NAEHS Council.

[2] This report does not go into significant detail in describing the activities of the Children's Centers. More information on the current program and research activities at individual Children's Centers is available at http://www.niehs.nih.gov/translat/children/grantees/home.cfm.

[3] The EPA is considering a review of known and potential policy impacts of the current and future Children's Centers program, consistent with EPA's Congressional mandates, such as the FQPA, and regional, state and local child health and protection programs. The EPA policy impact evaluation will be convened as a joint ad-hoc committed of EPA's Board of Scientific Counselors and the Agency's Children's Health Protection Advisory Committee.

CHAPTER 2: EVALUATION OF CHILDREN'S CENTERS

Goals of Children's Centers Program

The Children's Centers examine the effect of environmental exposures on children's health. Through a multidisciplinary research approach including basic, applied, and community-based participatory research, the Children's Centers translate and communicate their findings to clinical and public health professionals and policy makers to alleviate the burden of environmentally induced diseases in children. This broad goal has been distilled into the following three specific goals (training expectations have been embedded within each):

1. To stimulate future research on the role of environment in the etiology of disease/dysfunction among children.

2. To develop novel effective intervention and prevention strategies.

3. To promote translation of basic research findings into applied intervention and prevention methods, thereby enhancing awareness among children, their families, and health care practitioners regarding detection, treatment, and prevention of environmentally related diseases and health conditions.

Current Children's Centers Funding Model

The current Children's Center program is funded by 5-year grants under the P01 grant mechanism (Table 3). This support allows for multiple projects, which are multidisciplinary and include the three major pillars of basic, clinical and translational research. The Children's Centers, which are located within major universities and medical centers throughout the country, also collaborate with community partners to address key issues in children's environmental health. Each Children's Center is led by an established investigator, who has assembled a transdisciplinary team of researchers and community partners. The researchers include basic scientists, toxicologists, clinicians, and epidemiologists. Through community outreach, the Children's Centers also serve to build scientific capacity directly with the communities studied. Administrative cores serve to coordinate resources, expertise, infrastructure, current and future collaboration, and cross fertilization with other Children's Centers in order to accomplish designated objectives. By dealing with a wide range of problems within a central research theme, the Children's Centers

Table 3. Current Children's Center Funding Model*

Center Structure	Cores + Research Projects (P01)
Cores	Administrative Research Support (Optional) Community Outreach &Translation
Planning Grants	No
Research Projects	Minimum of 3 At least 1 Basic Science Project At Least 1 Clinical 1 of the 3 has to utilize CBPR Intervention/prevention**
Center Application Cycle	Varied
Training	
New Investigator Program	Highly Recommended

* Current refers to the most recent RFA released on August 24, 2005 (http://www.niehs.nih.gov/dert/past-rfa.htm)
** Required in initial RFAs, but not in the most recent

thus allow for broader-based research programs than those directed toward a targeted problem funded by the traditional R01 mechanism.

To date, thirteen Children's Centers have been supported through the joint NIEHS and EPA funding initiative and eight continue to be funded through this mechanism. The first Children's Center RFA was issued in 1998, and 8 centers were funded. The second RFA was issued two years later, and 4 centers were funded. The third RFA, issued in 2003, funded one new center and enabled 6 centers that had been funded during the first round of funding to be renewed for a second 5-year period. In the fourth RFA in 2005, only one of the centers funded in the year 2000 was funded again for a second 5-year period, and no new centers were added (although one new center was being considered at the time of this writing). In all four RFAs, the requirements set forth were very specific. For example, the first three RFAs required at least three projects to form a center, one of which had to include a community-based participatory research component. In the first RFA, centers also had to include one intervention study; in the second, they had to focus on neurodevelopmental endpoints. In the later RFAs, at least one project had to be a hypothesis-driven study using animal or human specimens to study disease mechanism, effects of exposure, or genetics. These RFAs are available on the NIEHS website at http://www.niehs.nih.gov/dert/past-rfa.htm.

Evaluation Strategy

The overall goal of the evaluation was to assess whether the Children's Centers are achieving the three goals presented above to the maximum extent possible. In order to make this determination, the Children's Centers provided written answers to specific questions focusing on: (1) the greatest achievements from the Center over its lifetime, particularly those that could not have been achieved through individual investigator funding mechanisms (i.e., R01 or R21 grants); (2) direct impacts of the Center on clinical medicine, public health, and public policy related to children's environmental health; (3) high impact publications; (4) faculty expertise within the Center and (5) the Center's training record.

On December 18, 2006, the review panel met in closed session with NIEHS and EPA staff involved in concept development and administration of the existing programs that support children's health research and education as well as with representatives from the Children's Centers. Discussions included agency perspectives, programmatic details and self-assessments of the individual programs and the program as a whole. Additionally, discussions with Children's Center representatives focused mainly on the written responses, as well as an informal dialogue regarding their opinions of: (1) the suitable criteria for evaluation of the relative effectiveness of the Children's Center program for supporting children's environmental health research and training; (2) translation of Children's Center research into tangible community action; (3) unique strengths and capabilities of the Children's Center mechanism leading to improved children's health research and training; (4) strengths and weaknesses of the Children's Center's program; (5) recommendations for changes in RFA requirements that would maximize efficiency and effectiveness; (6) most pressing issues related to children's environmental health, especially within the context of environmental, genetic, social or other factors that may affect children's health; and (7) advances in technology needed to improve global children's environmental health and areas for biggest impact.

Proposed evaluation criteria for the Children's Center program were extensively discussed with Children's Center directors and the agency representatives and in subsequent meetings, a set of criteria to evaluate the success and impact of existing programs and their potential usefulness in the future. The specific criteria for use in this evaluation included:

- Number and quality of publications, extending beyond statistics such as impact factor to include breath of coverage and interdisciplinary activity.
- Contributions to implementation of new policy reflecting scientific data and aimed at prevention in susceptible populations.
- Ability to answer future environmental health questions on the data being collected or deposited in biorepositories.
- Provision of cutting edge training in children's environmental health.
- Evidence for contributions to enhanced children's environmental health status.
- Contributions to understanding of human biology in relation to environmental exposures.
- Translation of basic science to applied science.
- Quality of community intervention components of the Children's Center.
- Leveraging of funds from other sources, including foundations, private sector, community, other government agencies.
- Pursuit of unanticipated research opportunities.

These criteria are not presented in any specific order and may not be inclusive of all the many indicators of program success.

Achievement of Children's Centers Goals

The overall evaluation of the Children's Centers focused on the extent to which the program is achieving the three primary goals listed on page 3. In addressing whether the three goals are being met, the panel identified several strengths and weakness of the Children's Center program that are directly related to the achievement of these goals (Table 4)

1. *The ability to stimulate future research on the role of the environment in the etiology of disease/dysfunction among children.*

   1.1 Successes

Overall, the panel agreed that the Children's Center program has moved in the right direction of stimulating new research and expanding existing research. Due to this program, new frontiers in the field of children's environmental health research have been carved and developed where no other similar efforts have been made. In 1998, little research on children's environmental health existed, especially with a limited amount of preliminary data available. For example, the concept of an environmental cause for autism was just breaking new ground in 1998. Within the short 8-year period from the inception of the initial Children's Centers, research has been conducted in the etiology of environmentally linked respiratory and other diseases, the role of the environment toxicants in pediatric conditions such as autism and attention deficit hyperactivity disorder (ADHD), and the effects of specific exposures on physical and cognitive development. In addition to scientific and medical discovery, the Children's Centers have led to new technological advances in both monitoring daily exposures (e.g., child monitoring devices in backpacks and global information surveillance tracking systems) and measuring specific exposures (e.g., biomarkers in meconium).

Table 4. Major strengths and weakness of the current Children's Center Program

Strengths	Weaknesses
• Promotes visibility of children's environmental health • Transdisciplinary research • Facilitates access to vulnerable populations • Provides an infrastructure to respond to emerging risk issues, (e.g. the World Trade Center) • Successful community outreach • Intervention and prevention actions • Training	• Narrow focus on local concerns • Limited number of health outcomes considered (asthma, autism) • Less than optimal utilization of cohorts and other clinical resources (biorepositories, etc.) by the scientific community • Basic science component not strong in several key emerging areas (e.g., epigenetics, genome-wide analyses) • Limited geographic representation

The successes of the Children's Centers program in this area can be largely attributed to its focus on transdisciplinary research, ability to access vulnerable study populations, and training. Through the transdisciplinary research approach, including basic, applied, and community-based participatory research, genuine efforts have been made by the Children's Centers to alleviate the burden of environmentally induced diseases in children. New knowledge has been gained, for example, on the role of leptins in autism, prenatal exposure susceptibility, sensitivity genes and markers, polychlorinated biphenyls (PCBs) and hearing, the interaction between iron status and smoking on exposure effects, new exposure pathways (e.g., manganese in nose to olfactory bulbs in brain), and immunology links. Environmental linkages to diseases such as asthma now can be better understood and translated to the general public for effective measures to promote increased quality of life. Children's Center research and discovery have led to spin-off grants for supplementing research and outreach funding to conduct new research and ancillary projects. An additional strength of the Children's Center program is the extensive communication and information exchange among Center directors and NIEHS and EPA staff, which includes face-to-face meetings several times per year and regular monthly phone calls. It is evident that the quality of the projects benefited considerably from these information exchanges.

The training of future researchers is also key to stimulating research on the role of the environment in the etiology of disease/dysfunction among children. The Children's Centers have specialized training programs in environmental health and education. This training includes

university courses in environmental health, dedicated research and training projects for graduate students, the training of pediatric and fellows in other medical subspecialties within environmental health issues and childhood disease, as well as continuing education programs on environmental health. In addition, a number of trainees have been hired at the university or medical school hosting the Children's Center or within the Children's Center itself thus allowing new opportunities for current graduates. A new investigator program was highly recommended as part of all RFAs. As many are international trainees, the Children's Centers have had a global impact on environmental health. Programs within high schools and colleges are also serving to educate the next generation of environmental health care workers and community advocates.

1.2 Areas for Improvement

Initial Children's Center RFAs solicited research on a broad array of children's diseases, disorders, and dysfunction. After peer-review, the scientifically meritorious applications primarily fell within the areas of respiratory disease and neurodevelopment, including autism. Successive solicitations attempted to broaden the focus of the program, but were not successful because funding is contingent upon scientifically meritorious scores[4]. The panel agrees that the focus of the Children's Centers has therefore been somewhat limited, and does not address issues such as cancer, endocrine and reproductive disorders, and immune disorders (Table 5). Having multiple Children's Centers working on the same disease is redundant and prevents consideration of other diseases. Similarly, behavioral studies are limited to attention disorders and autism with less emphasis on reading and other learning disabilities as well on other mental health problems. Moreover the scope of inquiry has been relatively broad and on global endpoints (e.g., intelligence) with little examination of the basic biological processes that may be directly perturbed by environmental exposures.

Table 5. Environmental Factors and Health Conditions Not Adequately Addressed

Environmental Factors
- Role of endocrine disruptors and environmental compounds as causal factors
- Role of multiple exposures and mixtures as causal factors
- Role of early development effects on later onset disease
- Role of environmental factors such as nutrition as a causal factor

Clinical and Physiological Considerations
- Childhood cancer focus lacking
- Neurological basis behavior abnormalities focus lacking
- Other areas in immunology besides asthma are lacking
- Birth defects
- Endocrine and reproductive abnormalities

The current program tends to be prescriptive and targeted. Although the initial RFA, which required an intervention, was not restricted to any specific area within children's environmental health, a large proportion of the funded studies focused on asthma, probably because asthma was one of the few endpoints for which an intervention study could readily be designed, given the state-of-the-science at the time. As noted, neurodevelopmental endpoints were explicitly required

[4] In the later RFAs, certain investigators did change their disease focus as the study cohorts aged to include outcomes such as obesity, learning disability, and attention deficit and hyperactivity disorder.

by the second RFA. The requirement of a rigorous community-based participatory research component in most of the RFAs made it necessary to devote a substantial portion of the budget to community relations and outreach, and given that the requirement for at least one project with an at-risk human population was also expensive, relatively little funding was available for the basic science studies. Thus, the relatively narrow range of endpoints that were funded - principally asthma, neurodevelopment, and autism - appear to have been, in large part, due to the constraints built into the structure of the current program. Given these considerations and the need for research on a broader range of topics relating to children's environmental health, the committee concurred that greater flexibility would be highly desirable in any future programs.

1.3 Summary

The review panel agreed there is real value in the cohort studies and interventions provided over the years by the Children's Centers; however, the need for further expansion of the field was also recognized. In addition, the panel recognized that the Children's Centers need to communicate more effectively with basic scientists for the purposes of stimulating integration and interactions. The scope of the basic science in many of the Children's Centers was seen as somewhat limited. Furthermore, the integration of multiple types of technology and research programs to address a specific disease basis requires approaches at a systems biology or genome-wide level to achieve the fastest and most productive discovery. Since few sites can accomplish these approaches alone, large-scale integrative research efforts across multiple sites are required, thereby necessitating collaborations across institutions and beyond immediate geographic regions, including internationally. Presently, the majority of current Children's Centers are in coastal states. Ideally, the Children's Centers would function more as a national network to address collectively the overall program goals. More extensive inter-Center collaborations should be encouraged.

2. The ability to develop novel effective intervention and prevention strategies.

2.1 Successes

From the inception of the Children's Centers program, a central aim has been to translate basic and clinical research findings into novel and effective intervention and prevention strategies that result in tangible public health outcomes. As an integral component of the Children's Centers, intervention and prevention research is expected to meet the same rigorous criteria of basic and clinical research, namely, being hypothesis-driven, appropriately designed, and rigorously evaluated. Since their creation, the Children's Centers have been translating and communicating their research findings to clinical personnel, public health professionals, communities and policy makers. Children's Centers research has led to effective translation of science into policy advocacy, changes in prevention strategies, therapeutics, and clinical management, community-linked outreach and changes in habits and customs (e.g., hand and clothes washing in migrant workers), policy changes (e.g., location of schools and playgrounds), and new laws (e.g., EPA directives on pesticides, changes to New York City bus fleet and ports, reversing the World Health Organization decision on DDT). Since the necessary infrastructure is in place, the Children's Centers have also been able to capitalize on new risk issues as they happen (e.g., contamination from the World Trade Center destruction). The goal ultimately is to enhance individual and community awareness regarding detection, treatment, and prevention of

environmentally-related diseases and health conditions.

2.2 Areas for Improvement

Although the current Center program includes research on causes of disease and prevention/intervention strategies, the panel agreed that the innovativeness of approaches used by the Children's Centers had not necessarily evolved as the science matured. More progress is required in this area, particularly in prevention and therapeutics. The field needs to move beyond exclusive primary prevention (i.e., reducing exposures) toward inclusion of additional prevention strategies as well the development of therapeutics to alleviate the burden of exposure (e.g., iron supplementation and anti-oxidants). Also still needed are the development of therapeutic interventions in therapy and novel methods for early detection. In addition, there seems to be duplication in prevention strategies used by the Children's Centers that may be limiting the field. Significant advances in areas of research that are potentially critical to disease etiology, diagnosis and therapy could be better incorporated into the Children's Center's research. This is in part due to the current structure of the Children's Centers and could be improved through better integration with the basic research supported through the R01 grant program.

2.3 Summary

The focus on intervention and prevention strategies in the current Children's Centers program has led to tangible changes in public health practice and is clearly a major strength of the Centers. However, the panel believes the breadth of strategies employed could be expanded to be more varied and novel.

3. *The ability to promote translation of basic research findings into applied intervention and prevention strategies, thereby enhancing awareness among children, their families, and health care practitioners regarding detection, treatment, and prevention of environmentally related diseases and health conditions.*

3.1 Successes

A critical feature and major strength of the Children's Centers program is its focus on addressing human health directly, for example, by the assembly of unique study populations (i.e., cohorts, case-controls, populations under intervention, etc.) and the formation of biorepositories. The Children's Centers have allowed for the identification and retention of populations of children with distinct exposures during pregnancy and in childhood. The current centers are run by senior investigators who have developed considerable expertise in recruiting and maintaining these high-risk populations. Not only is the information obtained currently on these populations critical for advancing understanding of exposure effects on childhood disease and outcome, the long term follow-up of these populations including into adulthood will also reveal critical information on the prenatal and childhood determinants of adult disease. In many cases, continued access to these populations by Children's Center researchers is due to the emphasis the program places on community outreach. The Children's Centers allow researchers credibility and trust within the community and are thus an important resource for empowering communities by linking them with other professional groups through meetings, conferences, and continuing education programs. In

addition, community-based research expands the capability of the members of the community to participate in planning, implementing and evaluating the effectiveness of interventions and public health strategies. The Children's Centers have also provided critical educational materials for community members and physicians within communities and opportunities for minority students and workers. The panel assessed that effective efforts have been made and resources prioritized to translate research findings into applied intervention. Solid intervention work has been created along with extended links to the communities served. The continuity of this work has proven successful and should be maintained.

3.2 Areas for Improvement

The restricted research foci imposed by NIEHS and EPA on the Children's Centers have limited the scope of the program to a few childhood diseases without imposing limitations on the basic research. In general, due to limited resources and a predominant public health focus of the Children's Centers, the Children's Centers have not met their potential in the basic research of the diseases of interest. Although the applied emphasis has assisted the local communities and enhanced children's health, it does not address novel diagnostic and therapeutic approaches that can be made through better understanding of the basic environmental causes of disease. Examples of specific topics and scientific areas that should be considered in the future include:

-The role of epigenetics and imprinting in disease etiology and as diagnostics.
-The role of micro RNA and Copy Number Variation in disease etiology.
-The molecular basis of environment-genome interactions in disease development.
-The use of genome wide approaches rather than selected genes for discovery
-A systems biology approach to disease etiology for better development of diagnostics and therapeutics

The examples above are only a short list of causal factors, mechanistic elements and clinical considerations not rigorously addressed in the Children's Centers currently.

Future Children's Centers should be innovative in their approach by using new tools and methodologies for research on critical biological pathways.. Attempts should be made to encourage collaboration between Children's Center investigator and basic scientists outside the program. Part of the challenge here may be a lack of awareness of the Children's Centers by the basic research community. While it is acknowledged that there is variability among Children's Centers, overall, the panel identified the need to reinforce the basic science and molecular methods components in order to address new hypotheses that might lead to novel intervention strategies. In many cases, the vital mechanisms strengthening the basic science pieces are currently lacking.

A systems approach, which capitalizes on advances in genetics, epigenetics, genomics, cell biology and physiology, should be considered in order to understand how environmentally-linked diseases develop. It is therefore essential to address how the environment impacts on this process with regard to genome-environment interactions. Thus future research in the children's environmental health research portfolio will need to focus on this area with equal emphasis on the basic research and the clinical management of the disease. Additionally, the research needs to

identify what factors are causative, how these factors alter molecular events that promote the onset of disease, and how this understanding can lead to the development of novel diagnostics and therapeutics.

3.3 Summary

The current Children's Centers have made limited basic research advances into the respective diseases and areas of focus. This is in contrast to the strong research identifying new environmental risk factors for children's environmental health outcomes at the population level and integration into the communities. The strengths of the Children's Centers deal with the implementation of current clinical practices into the communities and providing advances addressing community children needs. However, only limited research discoveries and focus on the molecular and cellular basis of disease etiology associated with the areas of interest has been made.

Overall Summary

In conclusion, the review panel believes a Children's Center program is of value and should be continued in some capacity. However, in order to meet the goals discussed above, the program needs to be modified in order to strengthen the connection with researchers in the basic sciences. An altered Children's Center model would likely prove more effective than trying to pair up additional grant opportunities. In addition to the long-range goals of this program identified above, training and career development have also become important objectives. The Children's Centers create synergism among investigators with diverse backgrounds and expertise. In addition, a major strength of the Centers model has been the community-based participatory research component because this has promoted respect and trust of the community being served as well as health partnership with community members. However, the review panel believes the community-based research requirements reduced the Center's ability to emphasize better translation of the basic research into the Children's Centers.

CHAPTER 3: FUTURE RESEARCH IN CHILDREN'S ENVIRONMENTAL HEALTH

Overall Goals

Proposed Children's Environmental Health Program Goals:

1. **Scope:** Address a broad range of important children's environmental health issues
2. **Knowledge generation:** Identify the etiology and fundamental biological mechanisms of environmental determinants of children's health outcomes
3. **Transdisciplinarity:** Recruit investigators from different disciplines, working in a synergistic transdisciplinary manner
4. **Knowledge translation:** Promote translation of basic research findings into applied intervention and prevention methods
5. **Training:** Increase the pool of highly qualified personnel to address children's environmental health issues

As part of its evaluation strategy, the review panel identified key components of a successful overall research program in children's environmental health. From this list, the panel focused on the elements that could best be achieved within a Children's Centers program versus those that could be accommodated via other funding mechanisms. Thus, a discussion of features that should be included in the entire research portfolio of children's environmental health provides a basis for understanding the recommended changes discussed below.

Scope. The research program should cover a wide range of topics in children's environmental health.

Knowledge generation: To understand the best therapy and diagnostics for disease requires the molecular basis of the disease to be elucidated in regards to the potential causal factors, molecular and cellular abnormalities developed, and subsequent disease etiology. Since future research will also need to take advantage of the current advances in science that address these elements of the molecular basis of disease, this may require interdisciplinary and integrated research efforts outside the single site of a specific Children's Center.

Transdisciplinarity. As noted above, recent advances in basic science, particularly in genomic, molecular, and cellular biology, hold considerable promise for improving our understanding of the role of the environment in the etiology of disease/dysfunction in children, potentially leading to the design of interventions for prevention and treatment based on the disruption of exposure-endpoint biological pathways. The cost of applying these methodologies to humans exceeds what could be covered within the current Children's Center program project framework. A new research program focused on stimulating studies initiated jointly by center-based epidemiologists and laboratory-based basic scientists could lead to important advances in the field.

Knowledge translation. Efforts to communicate the latest sound science to community participants has been a major feature of the Children's Centers from their inception and should continue. An additional strength has been the active advisory role that members of participating communities have played in the design and implementation of previous studies.

Training. Recruitment and development of young and mid-career scientists to the field of children's environmental health featured prominently in the previous Children's Centers and should be an important component of future children's environmental research program as well.

Scientific Data Needs

The scientific data needs for children's environmental health are wide-ranging due to the biological and societal complexity of this life stage. During development, major changes occur in basic molecular and cellular processes thereby enhancing the possibility that chemical exposures can have markedly different outcomes on an embryo, fetus, infant, child, or adolescent. The cultural and societal modifiers of exposure are also diverse and life-stage dependent. The complexity of these issues therefore requires a highly integrated scientific approach, which maximizes both the opportunity for transdisciplinary research and the translation of basic research results into plausible interventions and public health outcomes. The panel viewed the following scientific issues as particularly relevant to children's environmental health:

- The etiology of children's environmentally-induced disease at the cellular and molecular level
- How life stage modifies the effects of a chemical exposure
- Genetic and other biomarkers of individual susceptibility
- The multiple effects of the same pollutant
- The risks associated with exposures to mixtures of chemicals
- The effects of life stresses on chemical exposures
- Biomarkers of exposure
- Gene-environment interactions
- New technologies to measure:
    - exposures in the field to both chemical and biological agents
    - locations of exposed individuals
- Animal models that reflect human disease

Recommendations

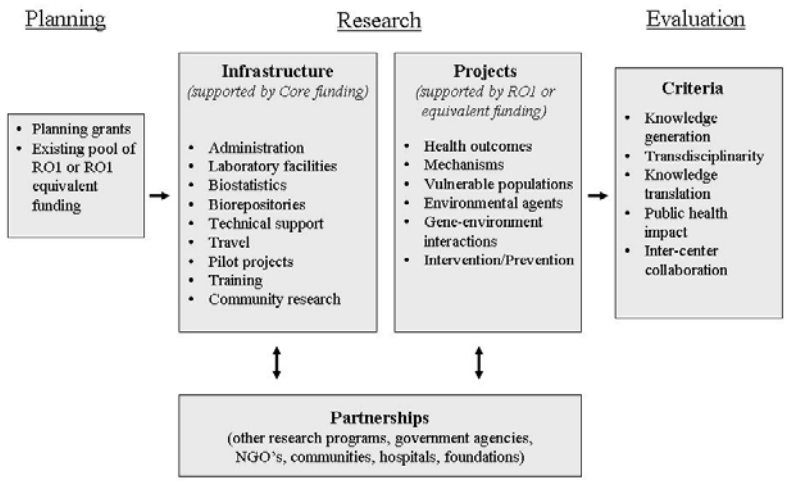
Overall, the review panel recommends the NIEHS and EPA retain a Children's Center program, although one that is modified from its current form. In proposing modifications to the current Children's Centers program, the review panel sought to develop a model that would allow the *basic science (broadly defined) to form the foundation for the overall research program* while also retaining research that emphasizes a *direct linkage to child health* (i.e., through the use of biorepositories, disease registries, clinical specimens, cohorts, etc). To accomplish these overall goals, the panel considered it important to *minimize the number of prescribed elements* in a Children's Center program and therefore recommend the required and optional components listed below.

Core Center Program:

Required	Optional
• Administrative core • Research support cores, such as laboratory facilities, cohorts, biorespositories, biostatistics support, technical support, subject recruitment • Strong basic science program with results directly linked to child health • Three or more externally funded research projects initially and five or more after three years (to be eligible for renewal) in addition to Core infrastructure support • Transdisciplinary pilot projects	• Community-based participatory research • Training • Intervention/prevention programs

The review panel maintains the quality of the basic science in the Children's Center program will likely be enhanced by a program whereby competitively funded grants (i.e., R01 or peer-reviewed equivalent) form the basis for a Center application. Such a program would provide both the clinical resources and samples to allow the basic research to advance, while also via independently funded R01 grants bring the state of the art research in large scale to address the problem. Also, to understand certain diseases better and provide effective therapy for them, broader scale efforts will be required to integrate diverse research programs into specific clinical areas and sites in the future than currently available. A new unique component of the recommended model is for the provision of planning grants that will allow the development of research vision, collaboration, and projects required to be competitive in a Center application. Initially, three competitively funded grants would be required to start a Center but would be expected to increase to a minimum of 5 during the Center's existence. Also, to encourage transdisciplinary research, the panel is recommending that some fraction of the Center funding (perhaps on the order of 10%) should be designated for pilot projects in order to stimulate further collaboration and a transdisciplinary approach. The organization of a Children's Center program is represented schematically in Figure 2. The primary elements of the funding strategy include:

Figure 2. Organization of Recommended Children's Centers Program



- Provide support for **planning and developing** applications to build collaborations that lead to the development of a new Children's Center.
- Require minimum of 3 **competitively funded research projects** to create a center with the expectation that a minimum of **2 or more**

additional competitively funded research projects will be added to be competitive for renewal and/or continuation.

- Centers are funded for up to five years (renewable upon favorable review).
- **Annual competitions** for funding to provide an ongoing opportunity for investigators to initiate new children's environmental health research programs.
    - Designate funds for transdisciplinary R01/R21 grants focusing on the application of leading edge basic science to new issues in children's environmental health. The goal is to add to the pool of grants that directly tie mechanistic approaches to children's health, and to help established and nascent Children's Centers meet the requirements for R01 or peer-reviewed equivalent projects.
    - Core funding should be available to support **infrastructure**, such as administration, laboratory facilities, biostatistics and bioinformatics, technical support, biorepositories, and travel.
- A portion of the core funding (on the order of 10%) should be designated for **pilot projects** to encourage transdisciplinary research.
- Additional funds may be provided to support **training**.
- Additional funds may also be provided to support **community-based participatory research**.
- **Review criteria** should include: knowledge generation, transdisciplinarity, knowledge translation, public health impact and inter-center collaboration.

Example 1. Two investigators are studying the impact of a class of pesticides on DNA methylation rates and a common childhood disease. They have funding to study different aspects of the problem using cell-based and animal models. They have reached a point in their research where they wish to pursue testing the methylation of a specific set of genes in humans that have this disease and compare this against exposure to pesticides during pregnancy. They know of another funded researcher who has such a population and would be willing to pursue evaluating the hypothesis with them. To achieve this goal, the investigators bring together their expertise to propose a Children's Environmental Health Research Center aimed at studying environmental causes of this disease. They would use the Center mechanism to build a services core for obtaining and tracking the use of tissue samples, data management and analysis of both the human data and the animal data and overall administration of the research effort.

The recommended elements could be implemented in many ways and two examples are presented. These examples are simply illustrations of the possible types of Children's Centers that could be developed; these are not intended as an indication of the types of research that should receive priority.

Because it is not clear at this point which specific opportunities are best suited for transdisciplinary collaborations the committee views that the recommended research program should encourage basic scientists and epidemiologists initially to apply jointly for

Example 2. Three investigators at the same university are studying different childhood diseases through funded grants for case-control studies. Recent publications indicate that a collection of different genes, all affecting lipid metabolism, seem to be related to the three diseases. The investigators wish to further explore the role that alterations in lipid metabolism may be playing in these childhood diseases as a potential common linkage. They apply for planning grant funding to develop a Center application to use the Center mechanism to establish a structure allowing them to broadly address this concept over the three disease groups. Eventually, the investigators will need to bring in additional researchers who will be seeking new funds to address specific hypotheses regarding environmental exposures that might alter expressions of these genes using animal models. The core of the Center would be a genomics/proteomics facility supported with a systems biology group to address the complex analyses of the signaling pathways associated with lipid metabolism.

exploratory R21-type grants in order to conduct relatively "high risk" pilot studies to explore proposed applications of basic science that will allow them to study at-risk populations and/or their biological specimens. An added advantage of starting with a relatively small-scale pilot study is that such a study will provide an opportunity for the investigators to determine how well they can work together across traditional disciplinary boundaries.

Leveraging Scientific and Other Resources:

At the same time, the review panel recognizes that a major strength of the current Children's Centers program is its focus on addressing environmental health issues in children, primarily through population-based studies. These studies have led to successful public health intervention and prevention programs and raised the visibility of Children's Centers. For this reason, the review panel proposes to maintain a program that *directly* addresses children's health. However, the panel strongly affirms that the Children's Center investigators should have maximum flexibility in determining the specifics of this direct human linkage. Whereas the current program requires community-based participatory research as an essential element, the recommended model makes this an optional component and affords greater flexibility by allowing use of biorepositiories, disease registries, cohorts, clinical samples, etc. to achieve and in some instances expand direct child health linkage. A significant concern of the panel was that the previous elements of community-based participatory research and prevention/intervention may have unintentionally limited the impact of Center research by focusing the Center on questions of primarily regional relevance. This concern does not discount the importance of community-based participatory research and the need to maintain cohorts that are difficult to cultivate and access. Instead, the recommended model allows investigators the flexibility of applying for additional funding to support this type of activity while taking advantage of the added benefits afforded using other strategies. **The panel therefore recommends that NIEHS allow flexibility in future programs in order to bring in state of the art tools and methods in all areas of children's environmental health research including basic, clinical, and public health.**

In addition to the limited number of populations studied in the current Centers, many at risk populations have been recruited under NIH-funded grants (including the NIEHS Superfund Basic Research Program). These populations could also be involved in this new phase of transdisciplinary children's environmental health research. The major investment that has already been made in identifying, recruiting, and winning the trust of the current populations identified in the Centers makes them and their biorepositories unique resources for this type of research. **The panel recommends the NIEHS leverage to the maximum extent possible these resources in building future Centers.**

One of the review panel's major criticisms of the current program was the relatively narrow range of issues covered (i.e., asthma and respiratory disease, air pollution, neurodevelopment, pesticides, metals, and polychlorinated biphenyls) and duplication of research focus at several of the Children's Centers. **The review panel recommends that the NIEHS and EPA explore methods to expand the breadth of topics covered while maintaining the highest quality science and not dictating the issues to be covered.** Perhaps one approach would be to develop focused Children's Centers on additional diseases and use all possible partnerships to create an integrated clinical and basic research programs involving multiple stakeholders and funding

agencies. Another approach would be to significantly strengthen and expand communication with centers of developmental biologists. Currently, Children's Centers themes tend to be focused on disease or exposure and the expansion recommended by the panel could focus on broader themes; the panel's priorities are listed below:

- Children's diseases and health outcomes
- Biological mechanisms of children's diseases
- Identification of vulnerable populations (including genetic susceptibility and lifestyle)
- Environmental agents (including classes of agents such as endocrine toxicants)
- Gene-environment interactions
- Intervention and prevention

The review panel was especially impressed with the current Children's Centers that were successful in partnering with other organizations and encouraged any future Centers to continue and expand on this practice. Such partnerships can greatly increase the public health impact, visibility, and national/international relevance of a Center. Attention needs to be devoted to mechanisms that will encourage and facilitate the leveraging of increasingly limited federal government research funds with funding from other agencies, private foundations, etc. For example, pilot project funding by NIEHS and EPA might be made contingent on a matching contribution by the investigator's institution. Certain partnerships can lead to additional funding opportunities that promote the expansion and longevity of an individual Center. There are a number of other resources which have developed and need to be both incorporated into the current Centers and used to promote future partnerships and collaborations. These include the National Children's Study that will be a critical partner in the future. Numerous Children's Hospitals also have major programs nation wide in areas of similar interest could also be more effectively included as partners. Some of the partnerships discussed by the panel include:

- Other child health research programs, both in the U.S. and abroad
- Major child health research initiatives, such as the National Children's Study and the National Birth Defects Prevention Study
- Hospitals and clinical facilities
- Government agencies such as the Center for Disease Control and Prevention (CDC)
- Non-governmental organizations (NGOs)
- Public health associations
- Parent and child health advocacy groups
- Private foundations
- Community organizations
- International organizations such as the World Health Organization (WHO)

The panel believes the modified approach recommended above will enable the NIEHS and EPA to continue its support of basic and applied research that shows the greatest promise for rapidly identifying links between environmental exposures and childhood illnesses. This is a vital component to the detection, prevention and treatment of environmentally-related diseases in children.

APPENDIX 1: REVIEW PANEL CHARGE

Title: Future Research Models for Children's Environmental Health Research

Background:

NIEHS has traditionally played a pivotal role in funding research on children's health. Many of the innovative new programs developed recently by the NIEHS will help to address key issues in children's environmental health. In addition, for the past eight years, the Institute has partnered with the U.S. Environmental Protection Agency (EPA) to support thirteen research centers devoted exclusively to children's environmental health and disease prevention. These centers draw upon the resources of community partners and the expertise of top universities and medical centers to focus on the important role that environmental toxicants play in the development of asthma, autism, and other childhood illnesses. The major goals of this program include:

1. stimulate future research on the role of environment in the etiology of disease/dysfunction among children,
2. to develop novel effective intervention and prevention strategies, and
3. to promote translation of basic research findings into applied intervention and prevention methods, thereby enhancing awareness among children, their families, and health care practitioners regarding detection, treatment, and prevention of environmentally related diseases and health conditions.

In addition, the Children's Centers, like many of the other centers funded by the NIEHS and EPA, had a number of goals related to community outreach and building scientific capacity in the communities being studied.

Children's health is a top priority, and both the NIEHS and the EPA are committed to making the most of every research dollar. To achieve this goal, the NIEHS and EPA are conducting a review of the many ways of funding research on children's environmental health. The Children's Centers Program is a prominent component of the research portfolio in children's environmental health at both the NIEHS and EPA. However, one needs to consider whether this is the most effective method to stimulate research in children's environmental health and whether other approaches should be considered. Supporting research that shows the greatest promise for rapidly identifying links between environmental exposures and childhood disease is a primary focus.

Review Structure:

An independent review panel, convened by the Office of Risk Assessment Research of the NIEHS, will review the Children's Centers program and the associated portfolio of investigator initiated research on Children's Health to address the four questions listed below. The Children's Centers Review Panel ("the Panel") will consist of 11 senior scientists with diverse expertise pertaining to children's health and the environment. This panel will be

convened as a working group to the NIEHS National Advisory Environmental Health Sciences Council.

Charge:

The main questions with respect to evaluating the Children's Centers are:

1. To what degree have the Children's Centers met the three goals?
2. Does the Center mechanism provide sufficient flexibility to capture the current and future needs for research in children's environmental health?
3. Are there other types of research and funding approaches that should be developed to better achieve our goals in children's environmental health?
4. Given the advantages and disadvantages identified through answering the first three questions, should the NIEHS continue the current Children's Centers program, modify it, alter the balance between Center-based and other research approaches, or use a completely different strategy for the next 10 years?

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Elwood Linney, PhD, Duke
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