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**Department of
Preventive Medicine**

**RE: Centers for Children's Environmental Health and Disease Prevention
Research Program Evaluation**

Dear Dr. Thayer:

I have some comments on the "Review Panel Report" of April 6, 2007. Our research
group has been conducting research on children's environmental health with NIEHS
support for several years in the form of Center and Program Project grants.

We believe these forms of research support have allowed us to make several major
contributions that could not have been made otherwise. A brief summary follows:

Effects of ambient air pollutants on respiratory health:
- Current levels of air pollution have chronic, adverse effects on lung
  development in children from the age of 10 to 18 years, leading to clinically
  significant deficits in attained FEV_1 as children reach adulthood.(1)
- Respiratory health in children is adversely affected by local exposures to
  outdoor NO_2 or other freeway-related pollutants.(2)
- Organic carbon (OC) and nitrogen dioxide (NO_2) are potential causes of the
  chronic symptoms of bronchitis in children with asthma. Previous cross-
  sectional studies may have underestimated the risks associated with air
  pollution.(3)
- Residential traffic exposure is associated with increased school absenteeism,
  especially among children with asthma.(4)
- Residential traffic exposure is associated with prevalent asthma, lifetime
  asthma and wheeze.(5)
- Traffic exposure is associated with slow lung growth independent of regional
  pollution.(6)

Genetic and other host susceptibility:
- The TNF-308 GG genotype may have a protective role in asthma pathogenesis
  depending on airway oxidative stress levels.(7)
- In children possessing at least one copy of the TNF-308 A variant, exposure to
  two or more household smokers was associated with a twofold risk of a school
  absence due to respiratory illness and a fourfold risk of lower respiratory

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illness-related school absence compared with unexposed children homozygous for the common TNF-308 G allele.(8)

- Gluthathione-S-transferase M1 and P1 (GSTM1 and GSTP1) variants affect asthma occurrence, lung function growth, and school absenteeism.(9-14)
- GSTM1 and GSTP1 modify the adjuvant effect of diesel exhaust particles on allergic inflammation.(12)
- Certain variants in intercellular adhesion molecule-1 (ICAM-1) are associated with reduced risk for asthma. Differences in associations of asthma risk with ICAM-1 were found between African-Americans and non-Hispanic and Hispanic whites.(15)
- High microsomal epoxide hydrolase (mEH) activity is associated with increased asthma risk and children with both high mEH activity and GSTP1 105Val are at the greatest risk.(16)
- The clara cell secretory protein gene (CC16) variant allele at position 38 was associated with susceptibility to asthma and wheezing in African-Americans. This allele was also associated with the risk of early onset asthma among non-Hispanic Whites with a family history of asthma.(17)
- Decreased airway flows predict new onset asthma in preadolescent and adolescent children.(18)

Novel statistical methods and approaches:
- Statistical methods have been developed related to the general multi-level modeling paradigm, with a focus on flexible modeling techniques for nonlinear lung function trajectories in children and their relationship to air pollution. The models address many issues that arise in Children's Health Study (CHS) data, including ecologic inference, multi-pollutant and subgroup analysis, simultaneous modeling of several outcomes, and exposure measurement error.(19)
- A testing strategy called the "focused interaction testing framework" (FITF) was developed to identify susceptibility genes involved in epistatic interactions for case-control studies of candidate genes. In CHS data, FITF identified a significant multilocus effect between NQO1, MPO, and CAT, three genes involved in the oxidative stress pathway. In an independent data set, these three genes also showed a significant association with asthma status.(20)
- For analysis of a single candidate gene, the SNP interaction model with phase information (SIMPle) model can be used to identify important SNPs and underlying haplotype structures across a variety of causal models and genetic architectures.(21)In the context of pathway analysis, two statistical alternatives to traditional approaches were developed to take advantage of prior knowledge about genes that potentially lead to disease.(22)
- A new statistical procedure that utilizes measurement error models was developed to estimate missing exposure data in health effects assessment.(23)

Effects of exposure to tobacco smoke on health:
- Exposure to environmental tobacco smoke is associated with increased respiratory-related school absenteeism among children, especially those with asthma.(9)
- Maternal and grandmaternal smoking during pregnancy may increase the risk of childhood asthma.(15)

- Regular cigarette smoking increases the risk for new onset asthma among adolescents, especially among those who were exposed to maternal smoking during the *in utero* period.(24)

Exposure assessment methodology:
- The development of models to assess air pollution exposures within cities for assignment to subjects in health studies has augmented the field of exposure assessment and may help to reduce scientific uncertainties that now impede policy intervention aimed at protecting public health.(25)
- Methods were developed to optimally locate a dense network of monitoring stations representing land use, transportation infrastructure, and the distribution of at-risk populations which has widespread applicability for the design of pollution monitoring networks, particularly for measuring traffic pollutants with fine-scale spatial variability.(26)
- Local traffic patterns influence ambient ozone levels and are potentially useful for assessing within-community variability in ozone exposure.(27)

Effects of the 2003 Southern California wildfires:
- GSTM1 status modified the effects of wildfire smoke during the southern California 2003 wildfire season on asthma symptoms.(28)
- Exposure to wildfire smoke during the southern California 2003 wildfire season was associated with increased eye and respiratory symptoms, medication use and physician visits in Children's Health Study participants.(29)

Linkages of population-based research with basic science research:
- Second hand smoke exposure has adjuvant effects on allergen induced nasal allergic responses that is 10- fold larger in children than adults.(30)
- Nasal allergic responses to diesel exhaust particles are reproducible and identify a subpopulation of children with enhanced allergic responses from DEP.(31, 32)
- *GSTM1* and *GSTP1* modify the adjuvant effect of diesel exhaust particles on allergic inflammation.(12)
- *GSTM1* and *GSTP1*are important cytoprotective factors that reduce SHS and DEP exacerbation of allergic responses.(33)
- Expression of phase II enzymes through induction of antioxidant response elements is a natural protective mechanism from oxidant pollutants such as diesel particles. Overexpression of these enzymes is a potential future chemopreventive strategy.(34)
- Sulforaphane can mitigate the effect of diesel exhaust particles in respiratory epithelial cells, demonstrating the chemopreventive potential of phase II enzyme enhancement.(35)

We simply could not have done this multidisciplinary research if R01 type grants were the only means of research support even if somehow we could link them.

In my opinion, the "Review Panel Report" of April 16, 2007 misses the mark. Although the review panel is a distinguished group, population scientists were underrepresented and the Environmental part of NIEHS got too little attention.

It is not surprising to see a largely basic science panel come up with a recommendation that "basic science (broadly defined) to form the foundation for the overall research program …". While I am in favor of basic research, this recommendation seems too restrictive (if not self-serving to the interests of panel members).

There are other inconsistencies that make the report lack full coherence. The "scientific data needs" listed on page 13 are more suited to population approaches than to basic science approaches. Indeed, our recent research efforts cover most of these needs.

I also take issue with the implication that too much money is being spent on asthma. NIEHS should be encouraged to raise research support for studying other childhood diseases rather than decreasing support for the most important chronic disease of children.

In summary I believe it is extremely unwise to set up research guidelines that essentially restrict the types of multidisciplinary population research that provide directly relevant results for understanding etiology and therefore prevention strategies. While basic science should be encouraged, impeding or restricting population research is a serious mistake.

Thank you for the opportunity to express my opinion. I will be happy to engage in further discussion of these issues.

Sincerely,

John M. Peters, MD, ScD
Hastings Professor of Preventive Medicine
Co-Director Division of Environmental Health

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