

August 5, 2002

**National Children's Study**

**Proposed Core Hypothesis**

Submitted by

**Health Disparities and Environmental Justice Working Group**

**I. Proposed Core Hypothesis:** Psychosocial stressors in combination with chemical/physical toxicants and genetic predispositions have a cumulative influence on the disease burden of children.

We propose to demonstrate how variations in the physical and social environments are associated with *differential exposure* of children to toxicants (such as pollutants, allergens, etc.) and *differential susceptibility* to the harmful effects of these exposures, leading to systematic disparities in child health and development. Key to this hypothesis is the notion that both physical toxicants and social adversities are unevenly distributed in our society, and that social conditions may modify the impact of environmental toxicants on specific child health outcomes. This hypothesis is based on a broad definition of "environmental toxicity" that includes chemical/physical toxicants as well as social toxicants, such as community-level risk factors or socioeconomic disadvantage, which can adversely affect the health of populations {Fullilove 1991 #33820}.

This is a crosscutting core hypothesis, laying out a framework for testing the interaction of physical and social exposures on a range of child health outcomes and will demonstrate why a large prospective multi-level strategy is needed. Examples of child outcomes discussed here include childhood asthma, birth outcomes, and impaired development; additional or other outcomes can be assessed using this framework.

**Secondary Hypotheses:**

1. Maternal antenatal exposures to chemical/physical and social toxicants can be associated with birth and other child health outcomes. Such exposures can be validated by maternal, fetal and neonatal biomarkers of exposure.
2. Postnatal and early childhood exposures to chemical/physical and social toxicants can be associated with measures of child development and child respiratory health. Such effects will be accompanied by measurable physiological processes (i.e., autonomic regulation, response to challenge/stress, information processing) and biomarkers of exposure.
3. Measures of maternal and family functioning during early childhood can moderate the impact of social and physical toxicants on child health and development. These include measures of the care-taking environment.
4. Prenatal and postnatal exposures can have additive or interactive effects on the child outcomes.
5. Individual-level effects of exposures to physical and social toxicants can be moderated by the impact of social context. That is, individual risk can be conditioned by community characteristics.
6. Genetic polymorphisms can moderate the effect of toxic exposures on, for example, the risk of asthma as measured by sensitization, biomarkers for allergy, asthma symptoms and diagnosis. Specific to asthma outcomes, we hypothesize that polymorphisms in the IL-4, IL-13, CD 14, and SOCS-1 (Suppressor of Cytokine Signaling-1) genes can be associated with risk of asthma as measured by sensitization, IgE levels, TH-1 vs. TH-2 cytokine levels, asthma symptoms, and asthma diagnosis in early childhood. Also consider assessing the effect of polymorphisms in metabolic activation and detoxification genes (CYP1A1, GSTM1, and GSTP1) on the relationship between exposure (i.e., airborne toxicants) and PAH/aromatic adducts at various child ages. To our knowledge, no study has examined IL-13 or CD14 polymorphisms in relation to the risk for asthma or allergy in an African American or Hispanic population.

Genetic susceptibility may also take the form of common polymorphisms that can affect metabolism, hence toxicity and carcinogenicity in the individual. The P450 (CYP1A1) gene plays a role in activation of PAH to DNA-binding intermediates. The glutathione-S-transferase genes are involved in detoxification of PAH and other environmental carcinogens. The prevalence of certain of these polymorphisms ranges from 10-50%.

## **II. Workgroups (collaboration across workgroups is encouraged):**

This hypothesis will be shared with the following workgroups before it is submitted in its final format:

Study Design

Ethics

Community Outreach

Social Environment

Health Outcomes

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## **IV. Public Health Significance**

We have selected asthma as an example of a childhood illness with large race/ethnic, social, and geographic disparities that determined by multiple social and physical exposures, in concert with susceptibilities.

Briefly, pediatric asthma is a serious and growing public health problem in the United States {Beasley R, Crane J, et al. 2000 #40840}, having increased by 58% since 1980, with the burden of disease most acute in urban areas and among race/ethnic minorities (Clark et al. 1999; Nelson et al. 1997; Weiss et al. 1993). Asthma is currently recognized as a chronic inflammatory disorder with a complex cellular and molecular basis (e.g., Holgate 1997), but the etiologic factors that predict asthma development and group differences in rates of childhood asthma remain elusive. Recent studies show a disproportionate distribution of asthma across populations (e.g., Claudio et al. 1999) suggesting that prenatal exposure to different types of environmental toxicants and social stressors may be important for the development of early childhood asthma.

An association of asthma prevalence with low-income, inner-city residence is established {Newacheck PW & Halfon N. 2000 #40990}, yet interaction of socioeconomic, ethnicity and place of residence factors has not been explained (Mielck et al. 1996; Strachan et al. 1990; Kaur et al. 1998). A number of studies suggest that more severe forms of asthma are related to poverty (Townsend 1988; Littlejohns and Macdonald 1993), and these findings are generally consistent with the hospitalization and mortality studies. A recent study of geographic variations in pediatric asthma rates, sampled by ethnicity and socioeconomic level, show considerable variation in

prevalence of severe asthma (persistent wheeze) by ethnicity, socioeconomic level *and* geography (Duran-Tauleria and Rona 1999). After adjusting for level of community disadvantage (overcrowding, % unemployed, % without a car, and % over 65), ethnic differences in prevalence of severe asthma disappear, but some geographic variation remains. While the persistent geographic variation in severe asthma rates may be due, in part, to the poor management of asthma in poorer areas, it is also possible that material and behavioral characteristics associated with poverty, such as parental smoking, air pollution, housing conditions, and allergens, may contribute to the disparities. To date, virtually no studies have applied state-of-the-art geographic methods to study the structural aspects of the asthma problem in different geographical regions (rural or urban). Although residential variation has been observed, spatial statistics have not been used to explore the concentration, unevenness and clustering of asthma in the urban environment.

## V. Justification for a Large, Prospective, Longitudinal Study

Testing this hypothesis requires examination of biological processes and biomarkers of exposure in social context, permitting the study of individual etiologic risk factors as well as the study of factors contributing to health disparities or group differences in rates of childhood health outcomes. The hypothesis links social and physical environmental conditions to child health outcomes, and requires the following elements: (1) well-defined social and physical/chemical exposures; (2) validated biomarkers of exposure (e.g., cotinine, blood lead concentrations, etc.) and measures of biological response to exposure (e.g., immunologic, neuroendocrine parameters); and (3) multi-level analysis of both exposures and outcomes. All exposures must be assessed over time, beginning during the prenatal period, so that issues pertaining to timing and total burden of exposure can be assessed, including various combinations of pre- and postnatal exposures. There is evidence that some physical and social exposures have cascading effects via the triggering of other effects, while other effects show a lag and do not become manifest until a later point in time. Furthermore, exposures may change over time; therefore, it is important to identify critical periods of greatest vulnerability and to quantify the cumulative burden of exposure over time. All exposures must be assessed at multiple levels of experience, including individual (micro) and community-level (macro) measures. For example, exposure to poverty or substandard housing may be measured at the individual level (personal income, number of homeless episodes) and the community level (average income in the neighborhood, amount of concentrated poverty, proportion of imminently dangerous buildings in the neighborhood). The mechanisms operating at the individual level cannot be adequately understood without reference to group-level data. This permits the testing of cross-level questions in which the impact of individual exposure to toxicants may depend upon or be conditioned by community-level conditions and social processes. Although biological mechanisms reside at the individual level, we are ultimately concerned with explaining disparities in the health status of populations. Populations with different levels of exposures (both physical and social) must be included, as well as populations with different prevalence of morbidity/mortality. This allows us to study “dose-response” relationships, as well as community impacts on individual outcomes, all of which require large sample sizes and representation from multiple population groups. Large sample sizes will also be required to assess a range of exposures *within* specific populations. For example, African American children (a high asthma prevalence group) with different exposures to social and physical toxicants will need to be identified.

Exposures to social adversities are rarely singular (e.g., Guillette 2000), and tend to co-occur with hazardous physical exposures, giving rise to environmental inequities whereby the most vulnerable members of society bear the greatest ‘toxic’ burden (Krieger et al. 1993; Zapata et al. 1992). Chronic social adversity may directly affect child health and may moderate or exacerbate the harmful effects of physical toxicants, altering individual as well as population effects in systematic ways (e.g., Bellinger 2000; O’Campo et al. 1997; Collins and Hammond 1996). To date, few child health studies have been designed to explore such interactions, resulting in possible underestimates of psychological and biological effect sizes. To address this issue, it is necessary to assess social context.

It is also important to address cumulative or ongoing exposures using a longitudinal repeated measures approach. As noted by Weiss (2000), the total burden of toxic exposures may be a more powerful determinant of child health and well-being than any specific exposure (Bellinger and Stiles 1993). The accumulation of multiple social stressors has been shown to predict child intellectual functioning and social competence better than any single risk

factor (Sameroff et al. 1997). Needleman et al. (1996) have also demonstrated this point in evaluating the impact of early lead exposure on child IQ and behavior, in the context of multiple social stressors. Indeed, the co-occurrence of hazardous exposures and social adversities in this society is a tragic example of environmental injustice, in which the greatest toxic burden is carried by those who can least afford the adverse consequences. There is considerable evidence to suggest that low-income, minority children carry a disproportionate risk, both because of differential exposure and possible differential susceptibility. In the United States, 60% of Hispanics and 50% of African Americans, compared to 33% of Caucasians, live in areas failing to meet two or more of the national ambient air quality standards (Wernette and Nieves, 1992; Metzger et al., 1995), but the variability in exposure across communities is not well documented.

The notion that community-level conditions can produce profound effects on host susceptibility to disease derives from the longstanding existence of strong social class gradients in health (Cassel 1976; Black 1982). Recent studies show that children born to women who live in violent, crime ridden, physically decaying neighborhoods are more likely to experience growth and developmental problems (Zapata et al. 1992; Kleigman 1992). Other studies suggest that the stresses of racism and community segregation are associated with lower birth weights (David & Collins, Jr. 1997; Wise 1993; Krieger 1993). However, the question of whether community-level adversity has a deleterious impact on child health and well-being, independent of individual level risk factors, and whether the predictive power of these individual level factors depends upon community-level conditions, has only recently been put to empirical test (O'Campo et al. 1997; Rauh et al. 2001). Furthermore, studies have shown considerable heterogeneity in living conditions among low-income families, despite generally high rates of social and material hardship (e.g., (Reeb et al. 1987; Mendoza et al. 1992; Manfredi et al. 1992; Mayer & Jencks 1988).

The large sample will also permit study of the *joint* influence of race and social class. The rationale is that race and poverty are both accompanied by social-structural inequality in the U.S. This includes the notion of relative deprivation, which may be at least as important an influence on child health outcomes as absolute deprivation (e.g., Wilkinson 1997; Kennedy et al. 1998). One argument views relative poverty as a form of social exclusion, suggesting that the racial discrimination underlying this exclusion (including residential segregation) contributes directly to general health (Krieger and Sidney 1996), as well as child health outcomes. There is a substantial literature on the negative health effects of perceived discrimination (Williams et al. 1997), but it is unclear whether these risks operate primarily at the level of individual experiences, or whether additional risk is conferred by exposure to institutionalized racism (Stafford and Ladner 1990; Krieger 1999).

The need for extensive follow-up through childhood is further supported by the literature suggesting that the sub-clinical developmental effects of fetal and early postnatal exposures to environmental toxicants may become manifest over time, as children attain higher developmental stages or experience additional environmental challenges. For example, toxic exposures can trigger a cascade in which neurotoxic effects initially appear as cognitive deficits that in turn may lead to behavioral disruptions such as ADHD and other functional disorders. Continued monitoring of toxicant exposure in the first few years of life allows assessment of the cumulative impact of exposures on the developing brain.

Decisions regarding inclusion of groups with different exposures, different susceptibilities and different outcomes, and the comparisons planned within this framework, depend upon the choice of health disparities to be studied; for example, emphasis would be placed on those that are most salient, most serious, and/or most persistent in the U.S.

## **VI. Scientific Merit:**

### ***What theory supports the hypothesis?***

The theoretical basis for most studies seeking to explain socioeconomic disparities/gradients in child health rests heavily on a 'poverty paradigm', suggesting that impoverished groups are among the most vulnerable members of our society. While children in poverty *are* disproportionately exposed to many environmental health risks {Olden & Poje 1995 #23820}; {Heritage 1992 #27860}; {Wernette & Nieves 1992 #27760}; {Metzger, Delgado, et al. 1995

#27830}), not all poor children have adverse health outcomes. As reviewed below, there are a number of systematic group differences in child health indicators, including childhood asthma and impaired development, which are not explained by economic disadvantage alone. The poverty paradigm simply does not seem to be an adequate explanation for many infant and child health problems of African American and other minority communities (e.g., Rowley et al. 1993). Furthermore, there is considerable variability in child health outcomes *within* racial/ethnic groups, suggesting that health gradients are at least partly determined by where children reside, how long their families have lived there, and a complex array of psychosocial, behavioral, and cultural factors characterizing the lifestyles of American families.

Possible sources of additional variability include length of residence in the U.S., and exposure to all of the social and physical conditions that accompany residence in the U.S. In fact, studies of the health effects of nativity and acculturation generally support the argument that degree of racial/ethnic identification is a better predictor of fetal and child health outcomes than race/ethnicity alone. For example, birth weight appears to be more strongly affected by place of residence and social factors than by race. African American and Mexican American women who reside in, but were born outside of, the U.S. are less likely to have a low birth weight (LBW) infant than their U.S.-born counterparts {Cabral, Fried, et al. 1990 #27900} {Williams, Binkin, et al. 1986 #27880} {David & Collins Jr. 1997 #33930}, despite lower educational levels and higher rates of poverty (Balcazar et al. 1993). This advantage for foreign-born women has been called an epidemiologic paradox; that is, despite current economic disadvantage, there appears to be something protective about the life experiences of foreign-born individuals {Alder-Storthz, Matson, et al. 1983 #130} {Zambrana et al. 1997}. Birth weight differences, however, may disappear with subsequent pregnancies {Cabral, Fried, et al. 1990 #27900}, suggesting the influence may be due to place of residence and not place of mother's birth.

Recent studies show that women who live in violent, crime ridden, physically decayed communities are more likely to experience pregnancy complications and adverse birth outcomes, after adjusting for a range of individual level sociodemographic attributes and health behaviors {Zapata, Rebollo, et al. 1992 #33040} {Kleigman 1992 #32970}. Others have suggested that the stresses of racism and segregation are associated with lower birth weights {David & Collins Jr. 1997 #33930} {Wise 1993 #32790}. The effects of individual poverty on birth outcomes are exacerbated by residence in disadvantaged neighborhoods {O'Campo, Xiaonan, et al. 1997 #34020}; Rauh et al. 2001).

In addition to better birth outcomes, first generation immigrants have fewer acute and chronic childhood diseases and fewer health-related school absences in adolescence (Institute of Medicine 1998). The social, economic, material, and cultural factors responsible for providing this protection are largely unexplored, nor do we understand why increased exposure and acculturation to mainstream U.S. life is so often accompanied by worsening health outcomes. Furthermore, it is not clear if acculturation effects are consistent across all geographic areas. It is not clear if child health disparities, observed so frequently to fall along economic and ethnic lines, are exacerbated by exposure to environmental conditions or to an increase in susceptibility to these conditions, possibly brought about by the breakdown of traditional behaviors and social supports. Ethnographic as well as epidemiologic approaches are needed to identify individual as well as group factors associated with health outcomes among minority Americans (Runyan et al. 1998; Rogers et al. 1996). Implicit in these findings is the view of race as a social rather than a biological construct, underscoring the need to consider the complex array of social conditions and physical exposures that accompany racial/ethnic identification. To date, none of these studies has included detailed information on residential history, including stability, geographical movement patterns, and toxic exposures associated with place of residence as possible determinants of child outcomes.

## **VII. Potential for Innovative Research**

### ***Application of Geographic Information System Technology:***

Geographic information system (GIS) technology is a relatively new tool in the field of epidemiology and has been used to understand the complex spatio-temporal relationships between environmental pollution and disease and for identifying exposures. GIS is a powerful computer mapping and analysis tool that allows large quantities of

information to be viewed and analyzed within a geographic context. Data from multiple sources, geographic (spatial) as well as non-geographic (demographics, median income, racial distribution, location of toxic release inventory sites) can be integrated and modeled using several functions like automated address matching (residential sites of subjects), distance function (proximity to roadways, toxic release inventory sites and bus depots), and buffer analysis. These methods have been used to estimate relationships between environmental contaminants and adverse health effects (Craun et al. 1985; Cohen et al. 1991). Guthe and colleagues (Guthe et al. 1992) assigned lead exposures in the Newark, NJ area to predict populations of children at high risk of exposure. Glass and colleagues (Glass et al. 1995) used GIS to investigate residential environmental risk factors for lyme disease in Baltimore county MD. Recently, Kohli and colleagues (Kohli et al. 1997) used GIS methods to identify individuals living in areas with high background concentrations of radon in Sweden. The Centers for Disease Control has developed a mapping program, Epi-Map, describing the spatial distribution of disease occurrence (Dean et al. 1992). These reports indicate that the GIS approach can be an effective tool for quantifying exposures of individuals to environmental agents.

A number of recent studies have drawn attention to the phenomenon of spatial autocorrelation (SA) in area-level analyses of associations between environmental conditions and health outcomes {Culhane DP, Lee C, et al. 1996 #41980}. Positive SA means that observations from places next to each other may be influenced by each other—a lack of independence that may apply to housing conditions. SA is useful as an analytic tool to identify clustering or links between spatial patterns and causal processes (Meade et al. 1988). Because we are interested in the degree to which toxic exposures are spatially distributed and how they are associated with housing and other community conditions, we propose using SA statistics to determine the scale(s) to which exposures cluster (i.e., apartment buildings, blocks, tracts, etc.). Such information is useful for the study of dispersion as well as determining the most appropriate scale(s) for the targeting of interventions (Millar and Gruenewald 1997).

The monitoring and modeling studies we propose here will begin to fill important gaps in our current understanding of the levels and distributions of air pollution exposures among children living in diverse neighborhoods. In addition to contributing information on the differential prevalence of exposures by residential area and type of building, we propose using estimates of exposure information to test longitudinal hypotheses regarding the etiology of asthma and impaired development.

## **VIII. Feasibility**

*Critical Period for Exposure and Outcomes:* Critical periods will be identified in relation to selected child health outcomes. Here we make the point that both antenatal (exposure at multiple points during gestation) and postnatal assessments (repeatedly throughout childhood) are necessary.

*Sampling Needs:* The specific race/ethnic groups in which child health disparities have been documented will need to be reviewed and populations selected on the basis of scope, seriousness, and persistence of the health disparity. Some populations will need to be over-sampled because they are relatively small minority groups with excess/disproportionate morbidity/mortality in the child health problem of interest (for example, SIDS among Native Americans, asthma among some Latino groups, etc.). Special strategies for sampling and recruitment will be needed to ensure adequate rates of participation and sample maintenance among minority groups in which cultural values may not be consistent with research study participation. Special attention should be directed to adequate sampling from hard-to-reach populations such as homeless, incarcerated, and migrant families.

*Measurement Tools:* Multi-level techniques for assessing community conditions will be needed (see use of innovative techniques—above). To assess economic conditions, we suggest operational definitions of the material correlates of poverty in order to better assess the actual living conditions. Material hardships are defined as unmet basic needs in the areas of food, housing, and medical care (adapted from {Mayer & Jencks 1988 #33730}); these three domains were selected because they define the basic need areas in which non-cash benefits are provided by the United States government (e.g., food stamps and WIC, public housing, Medicaid). Mayer and Jencks have noted that material hardship at the individual family level reflects more than the distribution of wealth (actual

income), and may be a useful indicator of the degree of socioeconomic disadvantage experienced by individuals in the proposed study. For example, studies have shown that there is tremendous heterogeneity in living conditions (and health behaviors) among low-income women (e.g., {Reeb, Grahan, et al. 1987 #33740}; {Mendoza, Ventura, et al. 1992 #33010} {Manfredi, Lacey, et al. 1992 #32990}).

Biomarkers of exposure to a variety of physical and chemical environmental toxicants are available. Biomarkers of exposure to social stressors have received less attention. We suggest both antenatal and postnatal measures of maternal immune system and neuroendocrine system function.

Biological samples will be needed including tissue samples (placenta, saliva, blood, urine, and vaginal fluid (for infection in pregnancy). We suggest an innovative technique for quantifying exposure to pesticides and other toxicants in pregnancy—meconium sampling (see papers by Barr, Whyatt and others).

*Data Analytic Tools:* The addition of contextual level data to individual data requires accounting for the effects of clustering, as women who live in the same area will be similar since they share a number of unobserved characteristics defined at the community level. As a result, the usual assumptions of independence will be untenable. Previous work has shown that ignoring clustering with limited dependent variables may lead to over-optimistic estimates of standard errors and biased estimates of regression coefficients. To account for intra-cluster correlation, we suggest taking advantage of recent developments in multi-level modeling (Bryk and Raudenbush 1992; Rodriguez and Goldman 1995). This will also permits the testing of cross-level hypotheses, involving both individual- and aggregate-level variables. In addition, we suggest using spatial-effects models, where the random effects representing unobserved characteristics of a cluster are correlated with those of adjacent clusters. Such models have been applied in the context of disease mapping by Clayton and Kaldor (1987).

Communities will be characterized with respect to social conditions (i.e., violent crime rates, school drop-out rates, presence of local tenant organizations, social capital) and material conditions (i.e., overcrowding, location of diesel bus depots, waste transfer stations, transportation routes, sewage treatment plants, adequacy of garbage removal, abandoned buildings). Social scientists will make use of U.S. Census and other administrative databases. Additionally, they will obtain detailed ethnographic information from each community for the purpose of understanding residents' perceptions of, and relationships to, their social and material environments. These data will be linked to the macro social influences of the communities, including housing dimensions, to the individual-level findings generated by the intensive psychosocial, behavioral and biological study of the cohort, for the purpose of exploring the underpinnings of child health disparities. This exploratory aim involves the testing of analytic models in which macro characteristics of the residential environment are included along with individual-level factors (including biomarkers of exposure) in contextual analytical models to predict child health and developmental morbidity at three years of age. Because multi-level statistical techniques require sufficient variability of study factors within each of the target communities, cross-level effects will be tested (in which toxic exposure-disease relationships are conditioned by community context) only after careful scrutiny of the individual-level findings.

*Community Involvement:* As mentioned above, special strategies for sampling and recruitment will be needed to ensure adequate rates of participation and sample maintenance among minority groups. Additionally, participation by community leaders and community-based organizations is necessary in order gain entrée into many minority and ethnic communities, to adequately assess community characteristics, in the development of culturally sensitive instruments where none exist, in the evaluation and dissemination of findings to diverse audiences, and in the development of appropriate intervention strategies using study findings.