The Green Housing Study

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United States Centers for Disease Control and Prevention (CDC)
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LIST OF ABBREVIATIONS (for Green Housing Study protocol)

AE = Adverse effect
AER = Air Exchange Rates
ASCII = American Standard Code for Information Interchange
ATS = American Thoracic Society
Bla g 2 = Major allergen from German cockroach (*Blatella gernamica*)
BNBAS = Brazelton Neonatal Behavioral Assessment Scale
BSID-II = Bayley Scales of Infant Development, Version II
CAMP = Childhood Asthma Management Program
CBA = Cost-benefit analysis
CCR = Cost/Charge Ratio Files
CEA = Cost-effectiveness analysis
CER = Cost-effectiveness ratio
CDC = Centers for Disease Control and Prevention
CI = Confidence interval
CPI = Consumer Protection Index
DAD = Diode array detection
DDE = Dichlorodiphenyldichloroethylene
DDT= Dichlorodiphenyltrichloroethane
Der f 1 = Major allergen from dust mite (*Dermatophagoides farinae*)
Der p 1= Major allergen from dust mite (*Dermatophagoides pteronyssinus*)
DNPH = dinitrophenylhydrazine
ECD = Electron capture detector
ED = Emergency department
eNO = Exhaled Nitric Oxide
EPA = Environmental Protection Agency
ETS = Environmental Tobacco Smoke
FDA = United States Food and Drug Administration
$FEF_{25-75\%}$ = The ratio of FEV_1/FVC, forced expiratory flow between 25-75% of vital capacity
Fel d 1 = Major allergen from cats (*Felis domesticus*)
FEV_1 = Forced Expiratory Volume in 1 Second
FVC = Forced Vital Capacity
GC/MS = Gas chromatography/mass spectrometry
GIS = Global information system
GM = Geometric mean
GPS = Global positioning system
GSD = Geometric Standard Deviation
HEPA = High-efficiency particulate air
HCUP = Healthcare Cost and Utilization and Project
HPLC = High Performance Liquid Chromatography
HUD = U.S. Department of Housing and Urban Development
HVAC = Heating, ventilation, and air-conditioning
ICAS = Inner-City Asthma Study
ICER = incremental cost-effectiveness ratio
IgE = Immunoglobulin E
IQ = Intelligence quotient
IOM = Institute of Medicine
IPM = Integrated pest management
IRB = Institutional review board
MEPS-HC = Medical Expenditure Panel Survey Healthcare Component
M2M = Mark-to-Market
Mus m 1 = = Major allergen from mouse (*Mus musculus*)
NAMCS = National Ambulatory Medical Care Survey
NBAS = Neonatal Behavioral Assessment Scale
NCICAS = National Cooperative Inner City Asthma Study
NHAMCS = National Hospital Ambulatory Medical Care Survey
NHANES = National Health and Nutrition Examination Study
NHIS = National Health Interview Survey
NIEHS = National Institute for Environmental Health Sciences
NIH = National Institutes of Health
NIS = Nationwide Inpatient Sample
NPV = Net present value
OAHP = HUD's Office of Affordable Housing
OR = Odds ratio
PAE = Participating Administrative Entity
PCA = Physical condition assessment
PEF = Peak expiratory flow
PFT = Pulmonary function testing
PTFE = Polytetrafluorethylene
PI = Principal investigator
PIR = Poverty income ratio
PM = Particulate matter
$PM_{2.5}$ = Particulate matter ≤ 2.5 in aerodynamic diameter
PMCH = perfluorinated methylcyclohexane
PPM = Parts per million
PV = Present value
Rat n 1 = = Major allergen from Norwegian rats (*Rattus norwegicus*)
RR = Rate Ratio
SAE = Serious adverse effect
SAS® = Statistical analysis software
SES = Socioeconomic status
SOP = Standard operating procedure
UV = Ultraviolet
VOC = Volatile organic compound

Table of Contents

I. SPECIFIC AIMS

Overall goals

Two main goals of this study are: 1) to compare levels of certain environmental chemical and biological agents in green vs. control, multi-family, low-income housing; and 2) to ascertain differences in the health of the residents in these homes. These goals will be accomplished in an ongoing building renovation programs including but not limited to public housing and "Mark-to-Market" (M2M), sponsored by United States Department of Housing and Urban Development (HUD). Thus, the residents of these homes are similar in terms of socioeconomic status. Briefly, the M2M program is a nationwide initiative that encourages landlords of multi-family properties to use green building principles. In partnership with HUD, the CDC will leverage this opportunity to collect survey and biomarker data from residents and to take environmental measurements in their homes. The results of this study will provide data that will allow CDC and the HUD to identify housing factors that are not only energy-efficient, but have the potential to improve the health outcomes of one of the most sensitive populations, low-income children with asthma.

Specific Aims

The proposed study (*The Green Housing Study: Environmental health impacts on women and children in low-income multifamily housing*) will address several of the research gaps that were mentioned above. The specific aims of this study are as follows:

1. To conduct an exposure assessment of chemical and biological contaminants, pesticides, volatile organic compounds (VOCs), fungi, indoor allergens (in terms of variety and concentration) in green vs. control housing.
   a. We will measure interior levels of pesticides in surface wipe samples; fungi and indoor allergens in dust samples; and VOCs in air samples.
   b. We will also compare biomarkers of VOCs and pesticides (in terms of variety and concentration) in the residents of green and control housing.

2. To examine the relationship between living in green vs. control housing and asthma morbidity (e.g, symptoms, ED visits, use of medications, lost school/work days) of children with doctor-diagnosed asthma (ages 7-12 years). We will adjust for allergic sensitization and ETS.

   2.1 To examine the relationship between living in green vs. control housing and respiratory morbidity of the mothers/primary caregivers of the enrolled children.

Figure 1. Hypothesized relationships among green housing rehabilitation strategies, environmental exposures, and asthma-related health outcomes.

Hypotheses

1. Green housing utilizes different strategies to reduce environmental contaminants. We hypothesize that these strategies will lead to 1) lower levels of environmental contaminants compared with those of control housing, and 2) lower levels of related biomarkers in the residents of green vs. control housing.

    a. Integrated pest management (IPM) is a method to reduce pests such as cockroaches and mice by eliminating entry points in the home and harborage areas.
        i. We hypothesize that IPM will result in lower cockroach and mouse allergen levels while at the same time lowering the concentrations and array of pesticides in the green vs. control homes.
        ii. We hypothesize that concentrations of pesticide metabolites in sera of children living in green housing will be lower than those living in control homes.

    b. The use of low VOC paints, carpeting, and other building materials should lead to lower concentrations of aldehydes, ketones, and alcohols.
        i. We hypothesize that the levels of VOCs will be lower at baseline in green-renovated vs. control homes.
        ii. We hypothesize that concentrations of VOCs in urine of children with asthma (ages 7-12 years) living in green housing will be lower than those living in control homes.

    c. Insulation can reduce sources of moisture, specifically condensation. We hypothesize that green housing will have more and possibly better insulation (e.g., higher R-value) than control housing. We hypothesize that insulation (e.g., dual-paned windows, insulated cold water pipes, and rigid insulation above concrete floors and in exterior walls) will result in lower concentrations of dust mite (and therefore their allergens) and fungi.

    d. Another aspect of green housing is improved ventilation which can reduce moisture and decrease indoor concentration of VOCs. For example, improved exterior wall insulation can reduce condensation and a properly-sized and maintained central heating, ventilating, and air-conditioning unit (HVAC) can help buildings keep dry and at the same time, exhaust environmental contaminants to the outside.

        i. We hypothesize that green housing will have a higher percentage of units with the recommended air exchange rates than control housing.
        ii. We hypothesize that green housing units will have lower VOCs than control homes.
        iii. We hypothesize that green housing units will have lower levels of fungi and dust mite allergen than control homes.

2. If irritants and allergens are lower in green vs. control housing, residents of green housing should experience decreased asthma morbidity. Specifically, we hypothesize that children with asthma (ages 7-12 years) in green housing will have lower asthma morbidity, adjusting for environmental tobacco smoke (ETS) exposure.

    2.1 Furthermore, we hypothesize a lower level of respiratory morbidity among mothers/primary caregivers of the enrolled children who live in green housing vs. control housing.

II. BACKGROUND

Rationale

The efficacy of green building design features in reducing allergens and toxic substances within the home has been assumed based on conventional wisdom. A better understanding is needed of the extent to which green-

built, low-income housing actually reduces exposures to these compounds when compared to standard-built, low-income housing. In addition, this study may provide insight into how specific green building practices (e.g., use of low chemical-emitting paints and carpets) may influence levels of substances in the home (such as volatile organic compounds (VOCs). A study investigating these topics would provide a solid foundation upon which to explore green affordable housing's potential to promote healthy homes principles. This investigation is consistent with the Centers for Disease Control and Prevention's (CDC) health protection research agenda, which calls for research to identify the major environmental causes of disease and disability and related risk factors. In addition, this study directly supports several of the United States Health and Human Services' (HHS) Healthy People 2010 objectives and the proposed 2020 objectives (proposed objectives available at www.healthypeople.gov/HP2020/Objectives/TopicAreas.aspx):

Goal: Promote health for all through a healthy environment.
8-16 Indoor allergens
8-24 Exposure to pesticides
8-25 Exposure to heavy metals and other toxic chemicals
8-27 Monitoring environmentally related diseases

Goal: Promote respiratory health through better prevention, detection, treatment, and education efforts.
24-2 Hospitalizations for asthma
24-3 Hospital emergency department visits for asthma
24-4 Activity limitations
24-5 School or work days lost

Many studies exist that examine the indoor environment in relation to health outcomes such as asthma. Table 1 lists contaminants in homes that have been shown to exacerbate pulmonary conditions.

Table 1. Contaminants in homes that are known to exacerbate pulmonary conditions.

Factor	References
Moisture	Bornehag 2004, Franchi 2006, Gunnbjörnsdóttir 2006, Savilahti 2000, Skorge 2005
Poor ventilation and heating	Franchi 2006
Environmental tobacco smoke	Franchi 2006
Wall-to-wall carpeting	Franchi 2006
Pet allergens	Custovic 2003, Munir 2003, Skorge 2005
Dust mites	Gotzsche 2004
Cockroach allergens	Rosenstreich 1997
Rodent allergens	Matsui 2006, Phipatanakul 2002
Pesticides	Senthilselvan 1992
Plastic materials	Jaakkola 2000
Nitrogen dioxide	Zota 2005
Combinations of the above	Salam 2004, Platts-Mills 2000, Sobottka 1996, Spengler 2004

Green building principles and occupant health

Green building principles and indoor air quality: Few studies have explored how green building practices affect occupant health. Ramachandran et al. (2005) measured airborne fungi, carpet loadings of dust mite allergens, cockroach allergens, cat allergens, and carpet fungi in a newer school building designed to optimize indoor air quality (Ramachandran et al., 2005). Researchers found that levels of all measured parameters were comparable for the new school versus an older school. In Australia, indoor air quality was measured in a low-allergen school and three standard schools (Zhang, Spickett, Rumchev, Lee, & Stick, 2006). They found non-statistically significant reductions in dust mite and cat allergens in the low-allergen school, as well as significant

reductions in formaldehyde and moisture levels. Swedish researchers sampled allergen levels using four different methods in conventional and allergy prevention classrooms (Karlsson, Renstrom, Hedren, & Larsson, 2002). They noted a poor correlation between sampling methods and no significant difference between low-allergen classrooms and conventional classrooms. Finally, in a small study in Finland lower levels of indoor air pollutants in hypoallergenic versus conventional housing was found (Tuomainen, Tuomainen, Liesivuori, & Pasanen, 2003). Asthmatics in the hypoallergenic building reported non-statistically significant improvements in respiratory symptoms versus those in the conventional building.

HUD Guidelines for Green Housing: In the HUD green renovation projects, several rehabilitation components could affect health. Some of these components are listed below. CDC and HUD will work together to document which of these occurred in the individual study homes.

-Window replacement
-Integrated pest management (IPM)* vs. traditional pest management
-Insulation
-Individual water heaters
-Heating and cooling equipment (appropriately sized)
-Central heating and cooling systems (appropriately sized and joints sealed in air distribution system)
-Cleaning products and materials
-Kitchen and bath exhaust fan
-Carbon monoxide alarms
-Smooth-surfaced floors
-Low VOC carpet
-Low or no VOC paint, primers, adhesives, caulk, and sealants
-Rubber walk-off mats
-Rubber stair tread
-Cementitious siding
-Changes to facilitate household waste recycling
-Green management of construction/rehabilitation debris
-Combined heat and power system
-Roofing replacement
-Landscaping replacement/modification
-Thermostat
-Air and thermal barriers

*Integrated Pest Management (IPM) – Comprehensive IPM involves reducing a variety of pests (e.g., rodents, cockroaches, termites, ants). Some IPM strategies are relatively easy to implement, while others are more difficult. For example, rodent- and cockroach-focused IPM can involve sealing food in containers, decreasing access to pet food sources, caulking cracks, and repairing holes in floors and walls. On the other hand, termite treatments can be more extensive. Optimally, IPM measures should be implemented with the advice of a professional trained in IPM. IPM has been shown to reduce cockroach and mouse allergen levels in homes (Arbes, Sever et al., 2003; Phipatanakul et al., 2004; Sever et al., 2007). The energy efficient design of green housing may incorporate many IPM principles, reducing the need for pesticides in these homes (Williams et al., 2006).

Evidence for associations between indoor agents and health effects

Cockroach allergens: Low-income inner city homes often have high levels of cockroach infestation. Both home and building-level characteristics can be related to high pest exposure (Chew et al., 2006; Rauh, Chew, &

Garfinkel, 2002). Inner-city children were more likely to be allergic and exposed to high levels cockroach allergen than to dust mite or cat allergen (Rosenstreich et al., 1997). The children in the study who were allergic to cockroach allergen had three times the rate of hospitalizations and nearly twice as many unscheduled medical visits compared to non-allergic children or those allergic to dust mites or cat dander. Asthma severity has been linked to cockroach specific immunoglobulin E (IgE) in the sera of patients with mild, moderate, and severe asthma (Henderson, Ownby, Trumble, DerSimonian, & Kellner, 2000).

In 2000, the Institute of Medicine (IOM) concluded that:

1) There is sufficient evidence of a causal relationship between cockroach allergen exposure and exacerbation of asthma in sensitized individuals.

2) There is suggestive evidence of an association between cockroach allergen exposure and the development of asthma in preschool-age children.

3) There is insufficient information to determine whether or not associations exist between cockroach reduction, symptom improvement, and lung function in sensitized asthmatics (IOM, 2000).

Rodent allergens: The National Survey of Lead and Allergens in Housing estimated that detectable levels of mouse allergen existed in 82% of the nation's homes, and homes with low-income residents and older homes were likely to have increased concentrations of this allergen (Cohn, Arbes, Yin, Jaramillo, & Zeldin, 2004). Ninety-five percent of homes in the National Cooperative Inner-City Asthma Study contained Mus m 1 allergen in the settled dust (W. Phipatanakul, Eggleston, Wright, Wood, & Study, 2000a). The mouse allergen concentrations in many of these inner-city homes were similar to those found in animal facilities and were sufficiently high to elicit symptoms in sensitized individuals. However, the true source of a biologically relevant exposure in the home environment remains unknown. Many researchers have assumed that the bedroom would be the most significant source of exposure for many indoor allergens (Phipatanakul 2006). In New York, the mouse allergen levels in beds and kitchens were significantly correlated ($r= 0.63$, $p < 0.001$); however, kitchen levels tended to be higher ($p < 0.001$) and more variable (Chew, Perzanowski et al. 2003). Less is known about residential rat allergen exposure, although 33% of the homes of inner city children had detectable rat allergen, Rat n 1 (Perry, Matsui, Merriman, Duong, & Eggleston, 2003). The number of hospitalizations and unscheduled medical visits because of asthma were significantly higher in those children who were both exposed and sensitive to rat allergen.

Dust mite allergens: Most houses in temperate climates have several characteristics necessary for maintaining populations of mites. These include multiple nest sites for mites (e.g., carpets, upholstered furniture, and bedding); a food supply in the form of human skin scales; and temperature and humidity levels that are optimal for mite growth (IOM, 2000). Dust mites can produce an array of proteins, many of which have been shown to be allergenic to humans. Some of the most common taxa of dust mites include *Dermatophagoides farinae, D. pteronyssinus, Euroglyphus maynei* (Platts-Mills, Vervloet, Thomas, Aalberse, & Chapman, 1997; Voorhorst & Spieksma, 1969). In sensitized individuals, inhalation of Der p 1, an allergen from the dust mite *Dermatophagoides pteronyssinus*, causes an immediate drop in forced expiratory volume and may produce asthma-related late responses that persist for up to 2 weeks. In a study of 4 year olds, an independent effect of allergen sensitization on asthma was observed only with house dust mites, odds ratio 8.07 (95% CI 4.60–14.14) (Arshad, Tariq, Matthews, & Hakim, 2001). Other studies have demonstrated that moving asthmatic children and adults into mite-free environments was associated with improvement of asthma symptoms (Platts-Mills, Vaughan, Carter, & Woodfolk, 2000).

Allergens in the urban environment: At least two studies found that low-income African American children were neither sensitized nor exposed to high levels of cat allergen (Call, Smith, Morris, Chapman, & Platts-Mills, 1992; Huss et al., 2001). Several studies have demonstrated that in homes where exposure to multiple allergens is likely, exposure to cockroach allergen or exposure to the combination of cockroach and dust mite allergen is the most significant predictor of sensitization and that these exposures are major risk factors for asthma (Alp, Yu, Grant, Rao, & Moy, 2001; Call et al., 1992; Gruchalla et al., 2005; Huss et al., 2001; Rosenstreich et al., 1997; Turyk et al., 2006). Dust mite concentrations greater than 2 μg/g have been associated with a greater risk of allergic sensitization (Sporik, Holgate, Platts-Mills, & Cogswell, 1990). Indoor allergen concentrations in excess of 8 U/g (cockroach) and 1.6μg/g (mouse) have been associated with higher frequencies of medication use and medical provider visits (W. Phipatanakul, Eggleston, Wright, Wood, & Study, 2000b; Rosenstreich et al., 1997). Dust sample concentrations for rat allergen between 4 to 1413ng/g were noted to be significantly higher in sensitized asthmatic children versus those without asthma (Perry et al., 2003). Average levels of allergens in the National Survey of Lead and Allergens in Housing were: 1.40 μg/g (dust mite), 0.292 – 1.376 U/g (cockroach), and 0.38 – 0.52 μg/g (mouse) (Arbes, Cohn et al., 2003; Cohn, Arbes, Jaramillo, Reid, & Zeldin, 2006; Cohn et al., 2004) . Simultaneous exposure to fungi, indoor allergens (e.g., from cats, dogs, dust mites, cockroaches, mice and rats), and outdoor allergens (e.g., from grass, tree, and weed pollens) is common. Exacerbation of asthma in low-income populations is likely to be multifactorial, and no single exposure dominates (Brugge et al., 2003).

Because of different housing stock across the country, some home characteristics are not consistently associated with dust mite, mouse or cockroach allergen (Chew, Burge et al. 1998; Chew, Higgins et al. 1999; Phipatanakul, Eggleston et al. 2000; Rauh, Chew et al. 2002; Chew, Perzanowski et al. 2003; Cohn, Arbes et al. 2004; Matsui, Simons et al. 2005; Cho, Reponen et al. 2006). For example, the U.S. national housing survey which included information from buildings in 75 locations found that mouse allergen was higher in high-rise buildings (≥ 5 floors) compared low-rise apartments (1-4 floors) (Cohn et al. 2004). This finding is not directly applicable to some cities such as New York where a majority of the housing in low-income neighborhoods is greater than 5 floors. In fact, shorter apartment buildings (i.e., fewer than 8 stories in New York) had 10-fold and 6.25-fold greater odds (compared with taller high-rise buildings) of having high mouse allergen levels in the kitchen and bed, respectively (Chew et al. 2003). This highlights the importance of considering the geographic factors that influence allergen levels within the home.

Fungi: There has been a substantial amount of research examining the impact of fungi and moisture on occupant health. Up to 40% of United States homes are reported to have problems with fungi (Brunekreef et al., 1989). Skin test results indicate that between 3 and 10% of persons worldwide demonstrate hypersensitivity to common airborne fungi (Horner, Helbling, Salvaggio, & Lehrer, 1995). Sensitization to allergens early in life increases the risk of developing asthma (Peat, Salome, & Woolcock, 1990). Specifically, sensitization to fungi is associated with the existence and severity of asthma (Bush & Prochnau, 2004; Jaakkola, Hwang, & Jaakkola, 2005; Maurya, Gugnani, Sarma, Madan, & Shah, 2005); inner-city children are especially affected (Crain et al., 2002; Kattan et al., 1997) . Infants with a maternal history of asthma were significantly more likely to exhibit persistent cough and wheeze when exposed to increased concentrations of indoor fungi (Belanger et al., 2003; Gent et al., 2002). Furthermore, a Boston prospective birth cohort study found a significantly increased risk of developing lower respiratory tract illness among infants exposed to high indoor fungi levels (Stark, Burge, Ryan, Milton, & Gold, 2003) and a greater risk of allergic sensitization by age 5 (P.C. Stark et al., 2005). The presence of a “mold odor” in a home, while controlling for confounding variables, has been shown to be an independent risk factor for the development of asthma with an incidence rate ratio of 2.4 (95% CI 1.1–5.6) (Jaakkola et al., 2005).

Homes with damp indoor spaces and high concentrations of fungi can aggravate pre-existing respiratory conditions such as asthma (Institute of Medicine, 2004). The Inner-City Asthma study looked at homes demonstrating an increased concentration of fungi in the home compared to the outdoor air concentration

measured on the same day (O'Connor et al., 2004). Residents of homes with higher concentrations of airborne fungi indoors than outdoors were significantly more likely to report dampness or leaks in any room, evidence of moisture and leaks, musty smell, and evidence of cockroaches. Modern building practices, such as increased use of synthetic building materials and inadequate ventilation or drainage, can promote fungal growth (NIH, 2005). Further research is needed regarding the efficacy of green building practices in preventing the growth of, or reducing the burden of, indoor fungi.

Volatile Organic Compounds (VOCs): A number of VOCs that can cause adverse respiratory effects are commonly found in the home environment. These include formaldehyde, benzene, toluene, xylene, ethylbenzene, styrene among others (IOM, 2000; Sunesson, Rosen, Stenberg, & Sjostrom, 2006). In 2000, the Institute of Medicine concluded that there was insufficient evidence to determine whether or not an association exists between indoor residential VOC exposures and the development or exacerbation of asthma. The report recommends that indoor exposures to VOCs be limited where practical by source removal, source avoidance and increased ventilation. The IOM called for prospective cohort studies to characterize exposure (IOM, 2000).

Associations between VOCs and asthma: Following the IOM report, a few studies have provided preliminary evidence for an association between elevated VOC levels and adverse health effects, including asthma. Young Australian children with asthma were exposed to significantly higher VOC levels than controls (Rumchev, Spickett, Bulsara, Phillips, & Stick, 2004). Among the VOCs observed in this study; benzene, ethylbenzene, and toluene were most strongly associated with a primary diagnosis of asthma. The study also found that for each 10 $\mu g/m^3$ increase in concentration, the risk of having asthma increased by nearly two and three times for toluene and benzene respectively. In one study, asthmatic children in public housing were exposed to benzene levels that exceeded the cancer risk level in 32% of samples, chloroform levels that exceeded the cancer risk level in 38% of samples. Of all VOCs measured, toluene and 1,4-dichlorobenzene had the overall highest mean and maximum levels (Brugge et al., 2003) . A recent review article noted that although observational studies have identified an association between VOC and asthma indicators, further studies are needed to confirm this finding, characterize effect size, and determine the biologically relevant duration of exposure (Dales & Raizenne, 2004).

Pesticides: While health effects associated with pesticide exposure are myriad and range from mucus membrane irritation to neuropathies, cancer, and death (Amdur et al., 1991), we will focus on one main health outcome, asthma exacerbation. Similar to the case of VOCs, assessment of the biologically relevant time period of exposure can be difficult for pesticides. For example, a population-based school study in California found that children with pesticide exposure in the first year of life were more likely to have early persistent wheezing than those not exposed during the first year of life (OR=3.6, 95%CI (1.6-8.1) (Salam, Li, Langholz, & Gilliland, 2004). In the same study, pesticide exposure at any other time (other than the first year of life) was negatively associated with early persistent wheezing (OR=0.7, 95%CI (0.3-2.0), but this did not reach statistical significance.

In the past, organochlorine, organophosphate, carbamate and pyrethroid pesticides could be found in most U. S. homes (Quandt et al., 2004). However, recent bans on residential use of chlorpyrifos (2002) and diazinon (in 2004) have led to lower exposures of these pesticides in the homes, particularly of inner-city apartments (Whyatt et al., 2004). Several housing characteristics have been found to predict indoor pesticide levels. For example, housing dilapidation has been associated with cockroach infestation, cockroach allergen and multiple pest eradication efforts (including use of pesticides) (Rauh et al., 2002). Based upon studies of pesticide exposure in children's homes, researchers concluded that household pesticides are best measured via dust sampling (Bradman et al., 2005). Many pesticides have low volatility and if not exposed to UV light, they can persist in indoor environments at high concentrations, although levels vary substantially depending on use level (Rudel, Camann, Spengler, Korn, & Brody, 2003).

Pesticides and asthma: There are considerable data indicating that dysregulation of both parasympathetic (cholinergic) and sympathetic autonomic control of airways, such as by pesticide exposure, may be important in the occurrence of asthma and its severity (P. J. Barnes, 1995). Dysregulation of parasympathetic function predicts the onset of wheezing in adults. (Sparrow, O'Connor, Basner, Rosner, & Weiss, 1993) Although there are few direct studies of the effects of organophosphate and carbamate pesticide exposure on asthma risk, farm workers' exposure to carbamate pesticides has been associated with the occurrence of asthma after adjustment for other relevant factors (Senthilselvan, McDuffie, & Dosman, 1992). Professional fumigators have an increased occurrence of allergy and asthma in parallel with a greater than 20% decrease in red blood cell levels of acetylcholinesterase (Garry, Kelly, Sprafka, Edwards, & Griffith, 1994). Exposure to chlorpyrifos has also been associated with an increase in the occurrence of atopic conditions (Thrasher, Madison, & Broughton, 1993). These studies suggest that pesticide exposures could be important etiologic and morbidity-modifying factors in the occurrence of childhood asthma. Nonetheless, only two major studies of childhood exposures (not exclusively set in an agricultural environment) have shown associations between pesticides and asthma prevalence (Salam et al., 2004; Sunyer et al., 2006). In the school-based California study, exposure to herbicides or pesticides in the home during the first year of life was associated with a greater odds of children presenting with early persistent wheeze (OR=3.8, (1.7-8.40)) (Salam et al., 2004). In the Spanish study, diagnosed asthma and persistent wheezing were associated with the organochlorine and DDE at birth (for each 1 ng/ml increase, OR=1.18 [1.01-1.39] and OR=1.13 [0.98-1.30], respectively), but not with DDE at age 4 years (Sunyer et al., 2006).

New methodologies for exposure assessment: In 2006, the NIH established the Genes, Environment and Health Initiative (GEI) with the long range goal of providing a foundation of technology and knowledge to enable population scale studies on the interaction of genetic and environmental factors in human disease. At the outset of the GEI it was determined that large scale, broadly focused Gene-Environment interaction studies would require an improved capacity in exposure assessment. Specifically two aspects were identified, the first being the need for improved definition of exposure at the level of the individual and the second being an comprehensive view of the environment integrating an assessment of exposures and lifestyle factors.

The Exposure Biology Program is divided into four component areas: sensors for assessment of chemical exposures (SACE), diet and physical activity, psychosocial stress and addictive substances, and biological response indicators to each of these environmental agents. Each of these programs is working individually, with opportunities for cross-program collaboration, to develop a new set of tools which will address the most common limitations of the current technologies used for exposure assessment: indirect measurement, lack of temporal or spatial resolution, limitation to single endpoints and a high degree of obtrusiveness. Each of the programs is product oriented with a goal of delivering prototype devices and biomarker panels for field testing and validation at the end of the four year granting period. The Sensors for Analysis of Chemical Exposures (SACE) program within the Exposure Biology Program of GEI was developed to build a next generation of sensors for defining real-time exposure with the expectation that this will increase the power of environmental epidemiology and gene-environment interaction studies.

Through SACE, the NIEHS and NIH have funded eight projects to develop integrated sensor devices which include not only the capability to detect multiple analytes of interest in a highly time resolved manner, but also integrate on board data handling, GPS based localization and in a few cases activity pattern analysis as well. The projects are detecting a wide range of analytes including particulate matter (PM 10, 2.5 and 1), allergens (dust mite, cat, cockroach and more), pesticides, oxidants, molecular gases (O_3, COx, SOx, NOx), and volatile organic compounds (benzene, toluene, xylene, and high priority industrial pollutants). In summer 2010, CDC established an interagency agreement with NIEHS to use three type of these devices in each of the home visits in order to improve exposure assessment in the Green Housing Study. The details of the devices are described later in this section.

Outdoor air pollution: In laboratory studies, investigators often have the ability to carefully control exposures that might be related to health effects. Because this study is tethered to HUD's green renovations programs, randomization is not a feasible option for study site selection. Nonetheless, there are some factors such as outdoor air pollution which we can control by the use of GIS in matching the green buildings to the control buildings. The reason for the matching is that conceivably, the greenest building located in a heavily polluted neighborhood (i.e., proximity to major roadways, airports, and bus depots) might have outdoor exposures that outweigh any potential health benefit of the green attributes. Proximity to major roadways has been associated with high concentrations of particulate matter (PM) less than 10μm (PM_{10}) which is from coarse grinding activities and also with high concentrations of particles less than 2.5 μm ($PM_{2.5}$) which is associated with combustion sources (Liao et al., 2006). Moreover, proximity to major roadways is associated with emergency department (ED) visits (Tolbert, Klein, Peel, Sarnat, & Sarnat, 2007; Tolbert et al., 2000), asthma prevalence (van Vliet et al., 1997) and morbidity (e.g, lung function and bronchial hyperreactivity) (Brunekreef et al., 1997; Janssen et al., 2003), and allergy (Morgenstern et al., 2008). Specifically, the diesel exhaust particulates within the $PM_{2.5}$ fraction augment the allergenicity of the particles (Diaz-Sanchez, 1997). Thus, proximity to sources of PM should be adjusted not only in site selection (and matching) but also in statistical analysis.

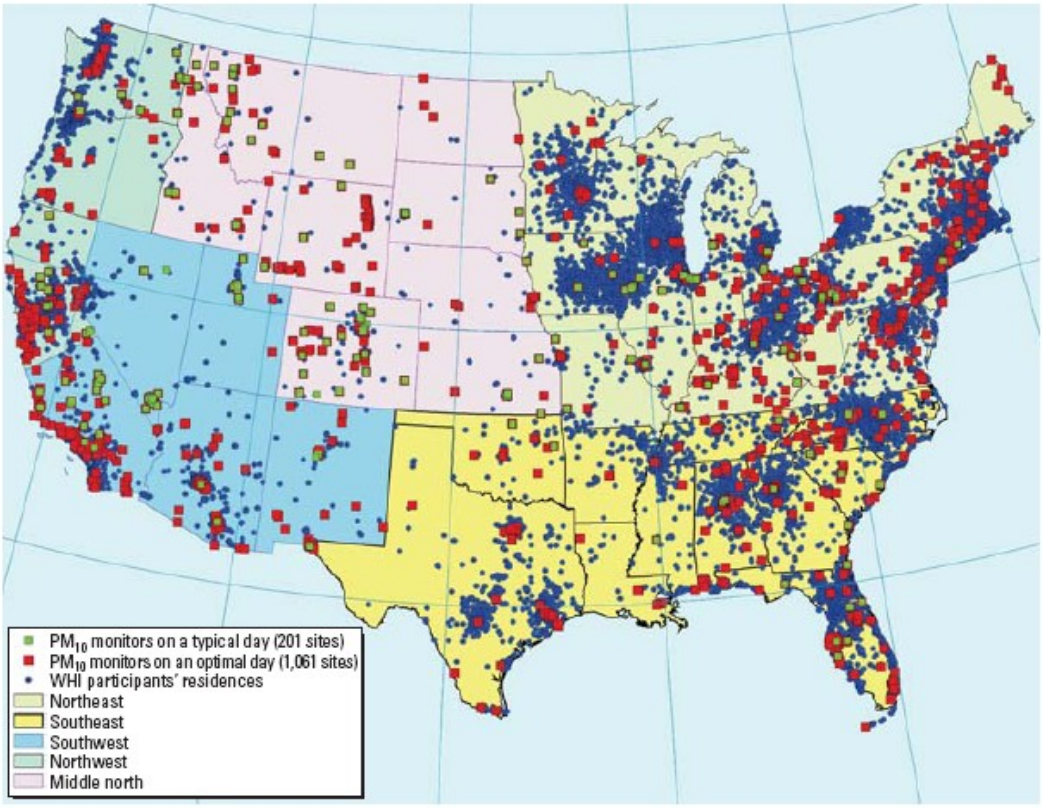


Figure 2. Spatial relationships between residential locations in a study by Liao et al (2006) and EPA monitoring sites for $PM_{2.5}$ and PM_{10}.

III. PRELIMINARY STUDIES

In Atlanta, GA, a pilot study was conducted to assess levels of VOCs, pesticides, fungi, and allergens in 31 apartments with green characteristics (e.g., low VOC paints and carpets) and in 34 apartments located in a traditionally-built/maintained housing complex. While the study was able to provide informative baseline exposure data for the two types of housing, some limitations could affect the generalizability of the study including region of the country (South), age of buildings (post 1980s), and population (elderly). Preliminary results are shown below.

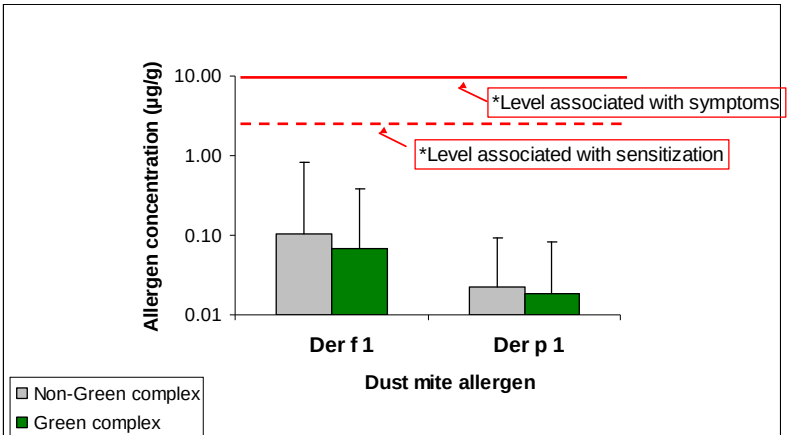


Figure 3. Comparison of dust mite allergens in green vs. traditional buildings.

Dust mite allergen concentrations were low in both green and traditional apartments which may account for inability to detect significant differences. In addition, cockroach and mouse allergens were also rarely detected, 2/65 (3%) and 9/65 (14%), respectively. Again, we were not able to detect a significant difference between green and traditional housing with these rarely detected allergens. Given that both housing complexes were comprised of elderly residents, these findings will not likely be generalizable to housing with children.

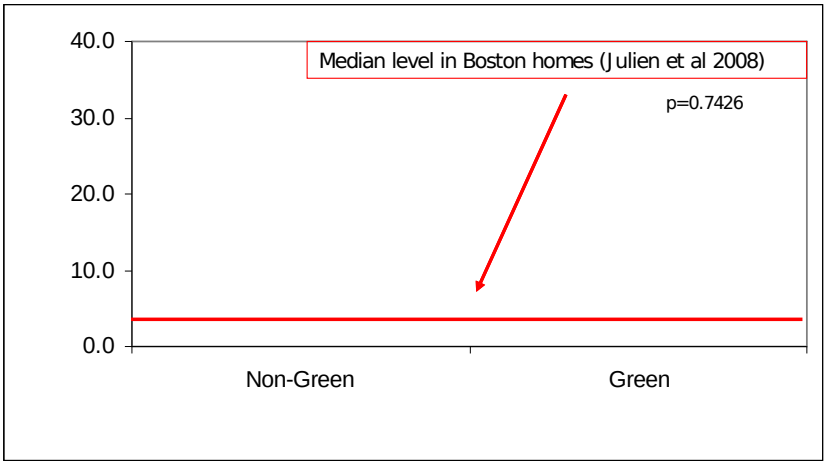


Figure 4. Comparison of pesticides in green vs. traditional buildings.

Pesticide levels were much higher than those reported in a Boston Study (Julien et al., 2008). Nonetheless, we were not able to detect a difference between the two types of housing. We speculate that resident use of pesticides was a factor that could have overwhelmed any difference due to building-wide pesticide application practices. In addition, generalizability to other regions of the country could be a factor due to different pesticide application habits and availability.

Based upon preliminary formaldehyde data (n=26 traditional units and n= 24 green units), formaldehyde levels were significantly higher in the green units (0.02 ppm vs. 0.05 ppm). However, no adjustment for ETS exposure or open windows has been conducted. With this small sample size, adjustments might not reach statistical significance, but could help in understand source contributions.

IV. METHODS

Overview

The United States Department of Housing and Urban Development (HUD) subsidizes both publicly- and privately-owned housing across the country, notably in urban areas. HUD requires that these subsidized properties be rehabilitated to maintain a certain level of habitability. CDC will leverage the opportunity to study rehabilitated properties in thirteen (13) study locations (large metropolitan areas that are located in different climactic regions of the United States). The selection criteria are described below:

1. City must have one or more housing developments which are receiving a HUD-subsidized green-renovation.

a. These renovations must occur within the timeline of our study period (5 years, although, we will ask OMB for a continuation prior to the expiration of the initial 3-year OMB approval)
b. Housing developments should have many apartments which will undergo the green renovations. Smaller housing developments would severely hamper recruitment of our targeted sample size in each city. However, we will consider cities which have several housing developments with a smaller number of apartments, given that the housing developments will undergo renovations within 6 months of each other.
c. Green renovations must meet inclusion criteria: Low VOC materials and Integrated Pest management (IPM).

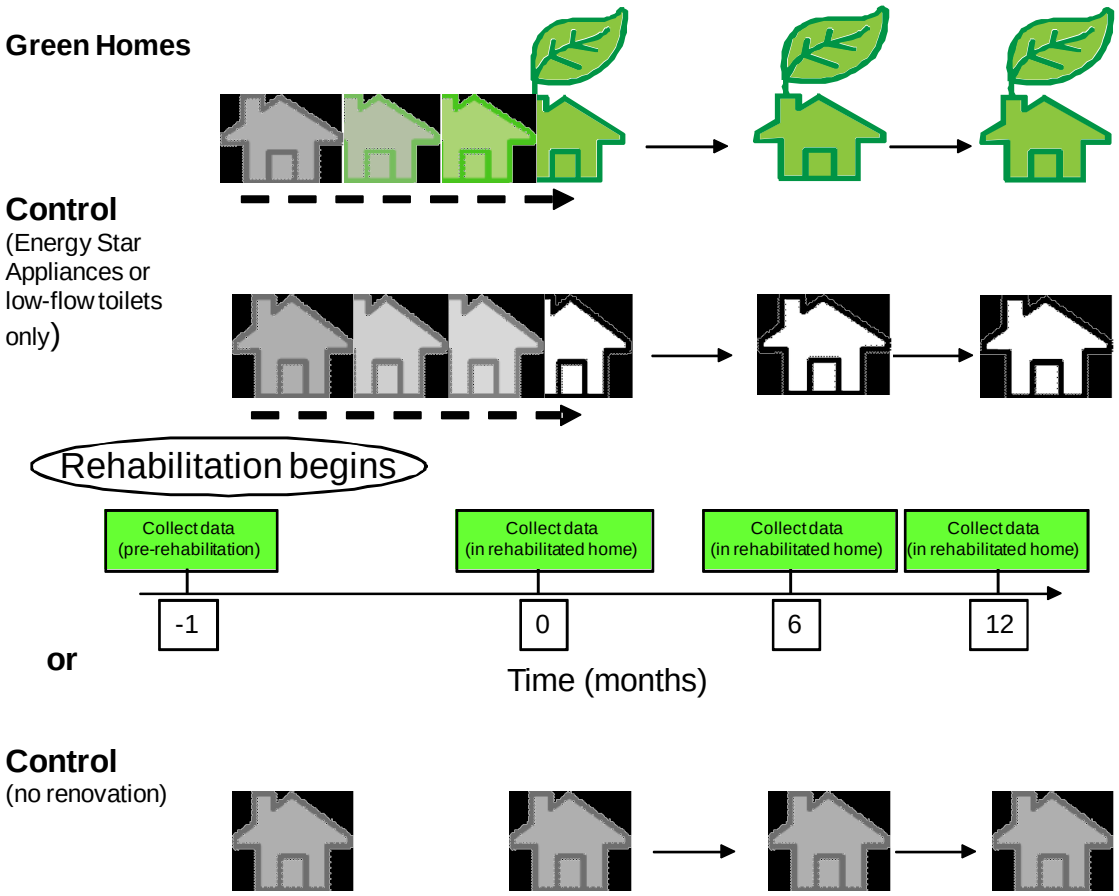
2. The housing renovations within the city must occur in areas with high prevalence (i.e., greater than the national average which is 9.1%) of childhood asthma (based upon National Health Interview Survey data, (Akinbami et al. 2009)). This is to enhance the potential pool of study participants. Areas of lower asthma prevalence would severely hamper recruitment of our targeted sample size in each city.
3. Cities are located in different regions of the country and/or represent different types of housing stock.

From each of these geographically-stratified study sites, 32 green intervention homes and 32 control homes (total = 64 homes * 13 study sites = 832 homes) will be included. Within each study site (i.e., city), both the green intervention and control homes will be from the same housing development or neighborhoods to ensure homogeneity with regard to housing type and other socioeconomic factors. Changes in environmental measurements (pesticides, VOCs, particulate matter (i.e., PM 2.5 and 1.0), indoor allergens, and fungi) over the 1-year follow-up in both types of housing (green intervention and control) will be compared, thus each home's follow-up measurements will be compared with its own baseline exposure level. This two-group pre-post within-group and between-group comparison will increase ability to detect differences in exposure levels and asthma outcomes that might result from the green renovations in our study. In addition, we will compare environmental measurements and health outcome data with national surveillance data (i.e., National Health and Nutrition Examination Survey (NHANES) and the National Lead and Allergen survey) or other relevant populations (e.g., National Cooperative Inner City Asthma Study (NCICAS), Inner City Asthma Study (ICAS). At this time, these sites have not been determined by HUD and CDC. When the study sites are selected, the data collection partners will include: 1) CDC; 2) HUD, and 3) the contracted research institutions (to be determined).

An overview of the study implementation is described below. Briefly, study sites will be selected, participants will be recruited at each study site, survey, clinical, and environmental sample collection will occur at repeated time points, samples will be analyzed in selected laboratories, statistical analysis will be conducted, and results will be translated to participants and the community in general. All study consent forms and questionnaires will be available in both English and Spanish (by certified translators). Reading level will be maintained at an 8th grade level (Flesh-Kinkaid assessment available through Microsoft Word).

In Figure 5, we describe a scenario of how measurements collected in green-renovated homes would be compared to: 1) those of the baseline, 2) those of homes where the renovation is comprised of only Energy Star appliances or low-flow-toilets, or those of homes without any renovation at all. Residents will participate for 1 month prior to rehabilitation, the time required for rehabilitation of their home (usually just a few days), and 12 months after completion of the rehabilitation. More details of the study design are provided in Part B of this information request.

Figure 5. Diagram of renovation schedule (green intervention vs. control)



Recruitment and eligibility criteria

The opportunities for obtaining respondent consent will occur during town meetings at each participating Green Housing Study site. At the housing complex, CDC investigators will describe the study to residents (including intended uses of information collection and publication of results in aggregate form rather than at the individual-level), answer questions, and invite their participation. Residents who express interest in the study can contact the site projector coordinator either at the town hall meetings or by telephone. Subsequently, contracted staff (trained by CDC study investigators) will schedule a home visit with the residents. During this home visit, bilingual (English/Spanish or English/Chinese) study staff will describe the study again to the potential study participant. During this home visit, each resident's eligibility will be assessed (i.e. the Screening Form will be filled out by the aforementioned staff based on responses from the mother/ primary caregiver). If a resident is eligible and is willing to participate, then the consent (or assent) form will be reviewed with the study participant in language (English, Spanish, or Chinese) appropriate to participant. If the resident agrees to participate, the consent form will be signed by both the participant and the interviewer obtaining consent. The consent form describes the purpose of the study, what is expected of the participant during the study, intended uses of the data, study duration, alternatives to participation, data security and data sharing, compensation, and potential risks and benefits of the study. During the consent process, potential subjects are encouraged to ask questions. Participation in the study is voluntary, and withdrawal from the study has no influence on future healthcare. Assent will be obtained from children age 7-12. The assent form is a simplified version of the consent form that is written at a level that a child (age 7-12) can understand and they are encouraged to ask any questions they might have about the study. The children ages 7-12 will be assenting to providing blood and urine samples for the study; they will <u>not</u> be asked to respond to survey questions—their mothers/ primary caregivers will be providing that information. Copies of the consent and/or assent forms will be provided to the study participants. Participants will receive monetary compensation for participation as outlined in the consent form.

Inclusion criteria:

1. Children (age 7-12 years with asthma)
   - Child's mother/primary caregiver has been ever told by a physician that the child had asthma and hild's mother/primary caregiver reports that child has experienced asthma-related symptoms (wheezing, slow play or night awakening) during the past 6 months.
2. Mothers/primary caregivers (≥ 18 years) of the children listed above.
   - No clinical markers will be collected, but we will ask questions regarding their home environment that might be related to health outcomes of interest and also regarding their health and that of their children.
3. Green homes will be renovated using low VOC materials and integrated pest management (IPM) principles

Exclusion criteria:

1. Health condition (e.g. Cystic Fibrosis or Diabetes Mellitus) that would make it difficult to participate.
2. Does not live in housing complex on average 7 days per week.
3. Plans to move before the 1-year follow-up of study is completed.
4. Mother/ primary caregiver does not speak English, Spanish, or Chinese

Health and Environmental Assessments

Summaries of the clinical and environmental measurements are shown in Tables 2 and 3. The baseline measurement will occur up to one (1) month prior to commencement of rehabilitation activities. Baseline part 2) will be collected in the home one (1) week after completion of rehabilitation activities (or if this is a control home, this measurement will occur at the same time period as the matched group of renovated homes). Total time of study participation is approximately 1 year, although the exact time will vary depending upon the rehabilitation scenario. Residents will participate for 1 month prior to rehabilitation (or if this is a control home, this measurement will occur at the same time as the matched group of renovated homes), the time required for rehabilitation of their home, and 12 months after completion of the rehabilitation. Estimated time for rehabilitation activities (e.g., new paint, carpeting, Energy Star appliances, IPM) should be only a few days.

Table 2. Summary of clinical measurements

Factor	Mother/ primary caregiver	Child with asthma (Age 7-12)
Blood		
Baseline	—	✓
Urine		
Baseline	—	✓
Baseline (part 2 occurs after renovation is completed)	—	✓
6-mo. follow-up	—	✓
12-mo. follow-up	—	✓
Pulmonary Function Test		
Baseline	—	✓
Baseline (part 2 occurs after renovation is completed)	—	✓
6-mo. follow-up	—	✓
12-mo. follow-up	—	✓
Exhaled Nitric Oxide		
Baseline	—	✓
Baseline (part 2 occurs after renovation is completed)	—	✓
6-mo. follow-up	—	✓

12-mo. follow-up	—	
Respiratory Symptoms Questionnaire		
Baseline	✓	✓
Baseline (part 2 occurs after renovation is completed)	✓	✓
6-mo. follow-up	✓	✓
12-mo. follow-up	✓	✓

*Blood will be used for assessment of allergy status (IgE)
** Urine will be used for assessment of cotinine (marker of ETS exposure), pesticides, and VOC metabolites

Table 3. Summary of environmental measurements in homes*

Type of assessment	Baseline	Baseline part 2 (after renovation is completed)	6-Month follow-up	12-Month follow-up
Allergens	✓	✓	✓	✓
Fungi	✓	✓	✓	✓
Pesticides	✓	✓	✓	✓
VOCs	✓	✓	✓	✓
Particulate Matter ($PM_{2.5}$)	✓	✓	✓	✓
Temperature	✓	✓	✓	✓
Relative Humidity	✓	✓	✓	✓
Air Exchange Rate	✓	✓	✓	✓

* The mother/ primary caregiver's home is the same as that of the child. Dust sampling will occur in the children's beds as well as those of the mother/ primary caregiver. Except for the pesticide measurements in the kitchen, all other measurements will be limited to the child's bedroom.

Assessments for children: Upon enrollment, the technicians (with training provided by CDC) will collect all of the study baseline information from the primary caregiver during the initial visit. This includes: a home characteristics questionnaire, an environmental exposure assessment, and health questionnaire. For those children (age 7-12) who meet asthma inclusion criteria, we will also collect urine samples, a blood sample, nasal and throat swabs for assessment of acute respiratory illness (ARI), exhaled nitric oxide (eNO), and conduct pulmonary function testing by spirometry. Details regarding these assessments are provided below.

Questionnaires: Information will be collected on frequency and duration of asthma-related symptoms, healthcare utilization, school and work absences, and medication use. The home characteristics questionnaires will inquire about the type of building, heating and cooling of the home, furnishings, cleaning regimens, the presence of pets and pests, environmental smoke, and reports of dampness. The methods of data collection will include written survey data collected through personal telephone, and text messaging interviews of enrolled mothers/ primary caregivers (Table 4). Trained staff will visit each enrolled woman's home four times (including the initial visit to obtain consent and baseline measurements) during a 1-year period to administer a battery of questionnaires. Each of the surveys will be administered in-person to the enrolled mothers/ primary caregivers in the study by bilingual (English and Spanish or English and Chinese) interviewers. In addition, brief text messages will to inquire about respiratory infections will be sent at the end of months 1, 2, 4, 5, 7, 8, 10, and 11. All enrolled mothers/ primary caregivers will also be contacted by phone at two time points during the same 1-year period just to update contact information and inquire about respiratory morbidity. Enrolled children (ages 7-12 years) will not be interviewed; however, their mothers/ primary caregivers will provide information about their children's exposures and health outcomes.

Table 4. Surveys administered during a 1-year period

Type of Survey/ Form		Responses of the Mother/ Primary caregiver (of child with asthma age 7-12 years)
Screening		10 minutes
Baseline Questionnaire	Home Characteristics	15 minutes
	Mother/ primary caregiver	15 minutes
	Children with asthma 7-12 years	15 minutes
Monthly Texts about child's respiratory symptoms (occurs during months when phone or home visit not conducted)		1 minute (eight timepoints) = 8 minutes
3 and 9-month Phone contact		5 minutes (two timepoints) = 10 minutes
6 and 12-month Follow-up Questionnaire	Environment	10 minutes (two timepoints) = 20 minutes
	Mother/ primary caregiver	10 minutes (two timepoints) = 20 minutes
	Children with asthma 7-12 years	10 minutes (two timepoints) = 20 minutes
Time/Activity	Mother/ primary caregiver	5 minutes (four timepoints) = 20 minutes
	Children with asthma 7-12 years	5 minutes (four timepoints) = 20 minutes
Estimated response time during a 1-yr period		163 minutes

Temperature and Relative Humidity Measurements: Temperature and relative humidity measurements for each home will be obtained during each home visit. A HOBO® continuous data logger (Onset Computer Corporation, Bourne, MA) will be placed on the floor in each home's living room for one week, and continuous measurements (every 5 minutes) of temperature and relative humidity will be recorded.

Dust sampling: Sampling for allergens and fungi will be carried out by technicians using a standardized protocol developed by CDC. All field staff will be trained by CDC in the proper methods for sample collection and handling. Dust samples will be collected separately from kitchens and beds by using a canister vacuum cleaner. One dust sample will be collected from the kitchen, focusing on the baseboard area and perimeter of the oven and refrigerator, for a duration of 3 minutes. Another dust sample will be collected from the index child's bed. Finally, a third dust sample will be collected from the bed of the mother/ primary caregiver. The mattress and pillows associated with the upper half of the bed will be vacuumed for 3 minutes. After sampling, each filter will be sealed in a sterile plastic tube and stored at -20^{o}C until analysis for indoor allergens and fungi.

Indoor allergen analysis: Frozen dust samples will be transported to the laboratory at CDC. Samples will be analyzed dust mite (Der f 1 and Der p 1), cockroach, (Bla g 2), cat (Fel d 1), and mouse allergens (Mus m 1) using commercially available multiplex immunoassays (Indoor Biotechnologies, Charlottesville, VA).

Fungi analysis: Dust samples from the beds will also be analyzed for a total biomass marker of fungi, ergosterol, by GC/MS.

Volatile organic chemicals (VOCs): Continuous air monitoring will be conducted using passive diffusion dosimeters for VOCs (one for solvents and one for aldehydes). The passive dosimeters will be placed in each participating home for 5 days. Total VOCs will be quantified using GC/MS. Aldehydes will be desorbed from passive 2,4-dinitrophenylhydrazine (DNPH) treated media, and the derivatized aldehydes are to be analyzed by high-performance liquid chromatography (HPLC).

Pesticides: Dust samples will be collected by wiping a measured 12-inch square section of the floor along the baseboard in the kitchens. Samples will be gathered on gauze squares wetted with isopropanol and will be analyzed using gas chromatograph/mass spectrometry (GC/MS) and HPLC (High-performance liquid chromatography/ mass spectrometry (Table 5). Common pyrethroid (*cis* and *trans* permethrin, cyfluthrin), organophosphate, and carbamate pesticides will be analyzed in addition to a synergist that is used uniquely in pyrethroid pesticides (piperonyl butoxide).

Table 5. A list of pesticides that EPA can measure in environmental samples.

Organochlorines	Pyrethroids/Pyrethrins
α- and γ- Chlordane	Allerthrin
Heptachlor	Bifenthrin
P,p=DDT	Cyfluthrin I, II/III, IV
P,p=DDE	Cypermethrin I, II/III, IV
Organophosphates	Deltamethrin
Chlorpyrifos	Esfenvalerate
Diazinon	Fenpropathrin
Malathion	Imiprothrin
Phenyl-Pyrazole	Λ-cyhalothrin
Fipronil	*Cis*- and *trans*-Permethrin
Other	Pyrethrin I, II
Piperonyl Butoxide	Prallethrin
	Resmethrin
	Sumithrin
	Tetramethrin I, II

Air Exchange Rates (AER): Air exchange rates can be quantified using non-toxic tracer gases such as SF_6 and perfluorinated methylcyclohexane (PMCH). The method to be employed in this study will use the perfluorocarbon, PMCH. In brief, the method is accomplished using by releasing the tracer gas inside the home and allowing it to reach steady state. With passive air sampling for a period of 12 hours up to one week, the PMCH is collected and then analyzed by gas chromatography and electron capture detector (GC/ECD). The

range of quantification is 0.10 to 2.5 air changes per hour (ACH), and the upper limit of detection is about 3.0 ACH.

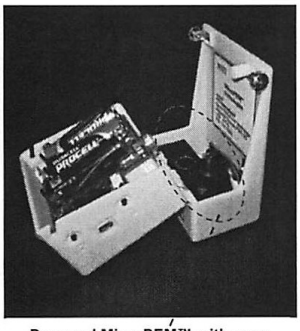
Particulate ($PM_{2.5}$) Monitoring: Monitoring for particulate matter ≤ 2.5 µm ($PM_{2.5}$) will be conducted in the living room (at a height of 1.5 meter) using integrated sampling for a one week period during each home visit in order to enable for adjustment of seasonal variation. Integrated samples will be collected using constant airflow portable sampling pumps designed for quiet indoor operation. Samples for $PM_{2.5}$ will be collected on 37 mm, 2.0 µm pore-size PTFE membrane filters using single-stage Personal Modular Impactors (SKC, Inc.). The pump flow-rate will be calibrated at a flow rate equal to 3 L/min in the laboratory prior to the start of sampling and checked at the end of sampling with a BIOS DryCal DC-2 flow meter.

Outdoor air sampling: To obtain an estimate of outdoor PM and VOC exposure for each of the housing developments, we will conduct 1-week air sampling on rooftops under protected cover during winter, spring, summer and fall. These measurements will be repeated throughout the entire study period for a given city. These repeated measures should yield a better estimate of the average outdoor PM and VOC exposure and reduce the influence of local events that might give rise to extreme values.

Opportunity for real-time exposure assessment of VOCs and PM: The CDC has an interagency agreement NIEHS to provide field-deployable units that measure particulate matter with an aerodynamic cutpoint of 2.5 µm ($PM_{2.5}$), 1.0 µm ($PM_{1.0}$), and VOCs to be used for field validation in a study of the potential environmental and health benefits associated green eco-friendly construction and maintenance practice in the Green Housing Study. These devices were developed as part of the NIH's Gene- Environment Initiative (GEI), specifically the Sensors for Assessing Chemical Exposures (SACE program). NIH will provide up to five (5) field-deployable units from <u>each</u> of the selected SACE investigators that have developed sensors which are both 1) field-deployable and 2) capable of measuring analytes relevant to the Green Housing Study. These devices will collect measurement side-by-side with the traditional air sampling devices during each of the home visits. The advantage of these devices is that they can measure peaks of exposure that might not be captured with traditional integrated air sampling equipment. The peaks might be more closely related to the biomarkers that will be collected (e.g., VOC metabolites in urine and exhaled nitric oxide). Figures 6,7, and 8 below describe the three devices that will be used in the Green Housing Study.

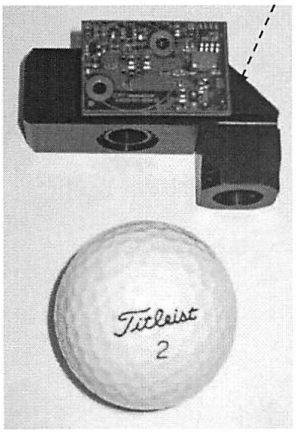
Figure 6. A single-channel real-time $PM_{2.5}$ monitor that will be used in the Green Housing Study.

RTI personal MicroPEM™ (scalable version) showing relative size; inlet location

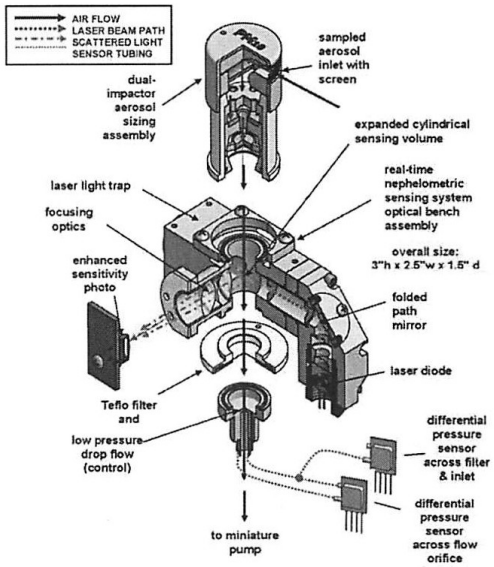


Personal MicroPEM™ with case opened showing nephelometric optical bench location (no filter)

Personal MicroPEM™ showing AA batteries, coin-cell memory battery; and Teflo filter/holder installed in outlet



Personal MicroPEM™ optical bench shown with golf ball to illustrate overall size of prototype



Personal MicroPEM™ optical bench showing: a) inlet/impactor assembly, b) filter/holder assembly, and c) flow and laser beam paths; note extremely large 10 mm cross-section sensing volume

Figure 7. A dual-channel real-time $PM_{1.0}$ and $PM_{2.5}$ monitor that will be used in the Green Housing Study.

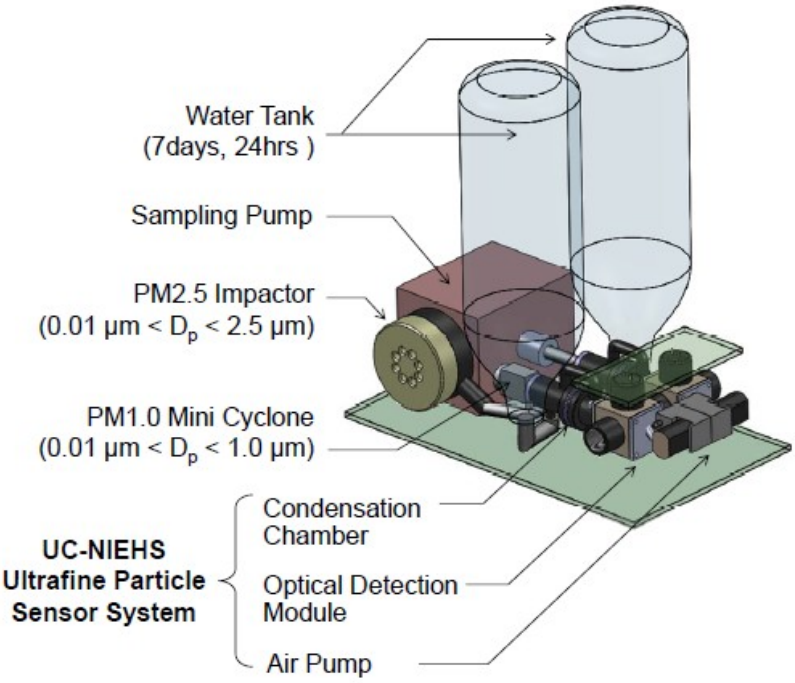
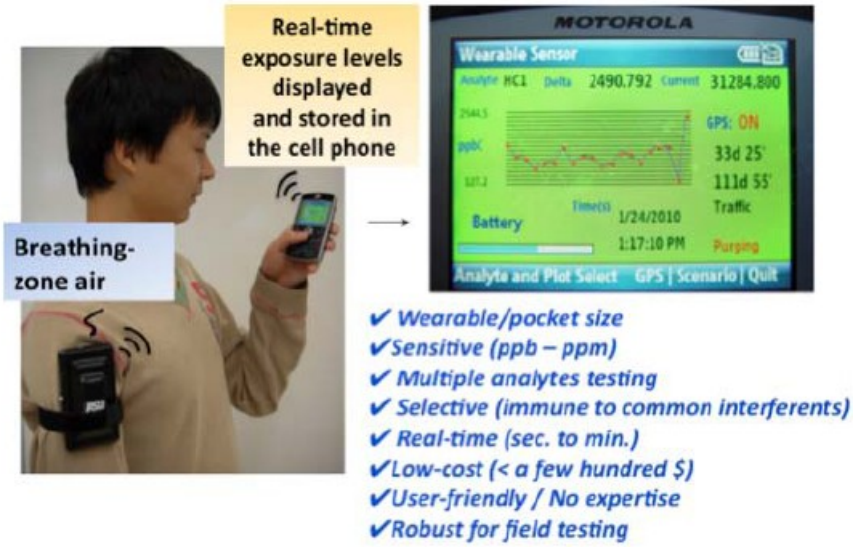


Figure 8. A real-time VOC monitor that will be used in the Green Housing Study.



Urine collection: Urine will be collected for two main purposes: 1) to assess recent ETS exposure via cotinine measurement); and 2) to assess biomarkers of pesticides and VOCs
(Tables 6 and 7).

Table 6. Urinary metabolites of VOCs measured by the CDC's Division of Laboratory Sciences

	Compound	Parent Chemical
DHBMA	N-Acetyl-S- (3,4-Dihidroxybutyl)-L-Cysteine	1,3 Butadiene
MHBMA	N-Acetyl-S- (1-Hydroxymethyl)-2-propenyl-L-Cysteine	1,3 Butadiene
CBMA	N-Acetyl-S- (2-Carboxyethyl)-L-Cysteine	Acrolein
HPMA	N-Acetyl-S- (3-Hydroxypropyl)-L-Cysteine	Acrolein
HEMA	N-Acetyl-S- (2-Hydroxyethyl)-L-cysteine	Acrylonitrile, Bromoethanol, chloroacetaldehyde, ethylene, chloroethylene, 1,2-dichloroethane, ethylene oxide, 1,2-dibromoethane, vinyl chloride
PMA	N-Acetyl-S-(phenyl)-L-cysteine	Benzene
BMA	N-Acetyl-S- (benzyl)-L-Cysteine	Toluene

Table 7. Urinary metabolites of pesticides measured by the CDC's Division of Laboratory Sciences

Blood

Compound	Parent Chemical
cis-2,2-(Dichloro)-2-dimethylvinyl cyclopropane carboxylic acid) (*cis*-DCCA)	Permethrin, cypermethrin, cyfluthrin
4-Fluoro-3-phenoxybenzoic acid (4F3PBA)	Cyfluthrin
Carbofuranphenol (2,3-dihydro-2,2-dimethy-7-hydroxybenzofuran) (CFP)	Carbofuran, benfuracarb, carbosulfan
2-Isopropoxyphenol (IPP)	Propoxur
2-Isopropyl-4-methyl-6-hydroxypyrimidinol (IMPY)	Diazinon
para-Nitrophenol (PNP)	Parathion, methyl parathion, nitrobenzene
3,5,6-Trichloro-2-pyridinol (TCPy)	Chlorpyrifos

collection: Blood will be collected once at baseline following enrollment to assess allergic sensitization (described below). A 10-ml sample (i.e, 2 teaspoons) of venous blood will be collected into 2 tubes (tubes with coagulant for serum collection) by a trained phlebotomist. The tubes will be centrifuged within 2 hours of collection, serum will be aliquoted into sterile microcentrifuge tubes, and then frozen at -80^{o}C until they can be assayed for total and allergen-specifc IgE titer.

Allergy testing: We will use immunoCAP method to assess total and allergen-specific (dust mite, cockroach, cat, mouse, tree mix, grass mix, and weed mix) IgE antibodies in serum. Unfortunately, mold extracts used for measuring IgE are very poor (due to batch-to-batch variability), thus we will not be able to assess sensitization to mold.

Pulmonary function testing: Pulmonary function provides an objective outcome for determining improvements in respiratory health status following the intervention to decrease environmental triggers in the home and improve asthma management. Spirometry (pulmonary function testing or PFTs) will be performed in children with a diagnosis of asthma who are 7-12 years of age. Study participants will be weighed and their heights will be measured using a calibrated scale prior to the start of each testing session. Standard spirometric measures, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), the ratio of FEV_1/FVC, forced expiratory flow between 25-75% of vital capacity ($FEF_{25-75\%}$), and peak expiratory flow (PEF), will be recorded for each patient. All children in this age range may not be able to successfully complete the forced expiratory maneuver required for this test, but attempts to test all children in this age range will be made. All PFT studies will be performed at each home visit to assess possible seasonal variation.

We will not conduct lung function tests on asthmatic children who are in distress; we will reschedule the visit. It is our experience that a phone call to the home approximately 1 hour before the scheduled visit serves not only as a reminder that our research assistants will be visiting the home, but also as an opportunity to inquire if the child will be at home and is ready for the tests (such as lung function, blood draw, etc). If during this phone call, the mother/ primary caregiver indicates that the child is in respiratory distress, then we will advise her to hang up and attend to her child and if necessary seek medical attention.

The technician who administers the lung function test in the home is not qualified to determine if the child's lung function is impaired; accurate interpretation of test results requires review by a trained pediatric pulmonologist. We expect that it would take at least 2-3 months for the pulmonologist (site-specific) to review the lung function curves (typically done in batches)—by that time the lung function could have changed for that child. Lung function tests done in isolation (and at any given timepoint) without consideration of other clinical parameters are difficult to interpret. Therefore, we will mail the results of each of the lung function tests (as they become available) to the mother/ primary caregiver after review by the pulmonologist. The mother/ primary caregiver can then share this information (i.e., repeated lung function tests) with the child's healthcare provider who can better interpret the lung function test results within the context of other relevant parameters (such as recent medication use) that would affect the child's overall asthma management. These results will be provided to participating asthmatic children of both the green and non-green homes to avoid potential bias.

Documentation of the participating asthmatic child's primary care provider will occur at the baseline <u>home</u> visit and participants who do not identify a primary care provider will be referred to one in their local area. A participant who contacts study staff with acute health concerns will be referred to his/her primary care provider or the Emergency Department.

Exhaled Nitric Oxide (eNO): eNO is a known marker of pulmonary inflammation and will provide a non-invasive means of assessing pulmonary inflammation in a large cohort that includes children (Buchvald et al., 2005; Cardinale et al., 2005; Pijnenburg, Hofhuis, Hop, & De Jongste, 2005). Measurement of exhaled nitric oxide will be obtained prior to lung function, and will be obtained according to the American Thoracic Society Guidelines (ATS, 2005). Nitric oxide concentrations will be measured using a chemiluminescent analyzer (NIOX TM System, Aerocrine, Sweden). This equipment is FDA-approved for clinical use in asthma management. Participants will be required to produce at least two reproducible exhalations.

Nasal and throat swabs: Children with asthma are commonly exposed to multiple indoor allergens and environmental tobacco smoke, multi-factorial exposures that may contribute to the increased asthma-related

complications in this population. However, previous studies of environmental interventions for patients with asthma have not used objective measurements (i.e., PCR of nasal swabs) accounted for the role of acute respiratory illness (ARI) as triggers for asthma exacerbation (Morgan et al, 2004). Viral respiratory tract infections have been reported as important triggers for exacerbations of asthma in adults and children (Clark, 1979, Miller et al, 2008). Recent studies based on PCR assays support an important role of viral respiratory tract infections in acute asthma exacerbations (Khetsuriani et al, 2007). By accounting for the role of respiratory virus infections as triggers for asthma exacerbation, we may be able to find stronger associations when aiming to estimate the impact of environmental interventions on improvement of symptoms of asthma and decrease use of health care services. This is because respiratory virus infections may be associated (or interact) with study's outcome and exposure measures, underestimating the effect of the intervention.

Mothers/ primary caregivers of the participating children with asthma will be trained by the home visit technicians to collect nasal and throat swabs from their children during their regular home visits. They will watch the mother/ primary caregiver collecting the swabs. Hopefully, this will allay the mothers/ primary caregivers' anxiety about collecting their children's swabs so that they feel comfortable collecting them when the technician is not there during cold/flu episodes. The mothers/ primary caregivers will then collect one nasal swab and one throat swab after 24-36 hours from onset of at least 2 of the following: feverish, stuffy/runny nose, cough, sore throat, body aches or tiredness, for more than 24 hours or whenever the child is thought to have a cold or the flu. It is estimated that children in this age group may have on average 4-5 episodes of ARI per year (Monto 2002). The specimens and an illness checklist will be collected on each occasion of a suspected ARI by using methods previously described by researchers (Esposito et al. 2010). The specimens can be stored in the participant's refrigerator for up to one week before being picked up by the study coordinator. The study coordinator will be asked to collect the specimens within 1-2 days of being notified of the parent-collected specimens. At the time of swab pick-up, the trained research assistants will also collect a throat swab and another nasal swab from the child in order to validate the sample collected by the parent. The swabs will be combined and transported in either veal infusion broth (VIB) or Hank's transport media on ice to the laboratory processing (within 24 hours). The specimens will then be stored at -70 C at local laboratory facilities before being sent to CDC. Specimens would be tested by RT-PCR for RSV, rhinovirus, influenza viruses, parainfluenza viruses, adenoviruses and human metapneumovirus at CDC's Viral Respiratory Laboratory. Detailed instructions for the collection of the swabs are in Appendix 1.

Assessment for mothers/ primary caregivers of children: The only measurement obtained will be questionnaire data regarding their housing characteristics, socio-demographics, and respiratory health.

Statistical Analysis and Related Issues

Sample size overviews: The most complete data to obtain sample size estimates for our proposed study are derived primarily from studies of allergens and asthma. Based upon our calculations, we estimate that we will need at least 13 green buildings and 13 control buildings with at least 25 apartments in each building for a total n = 650 to detect differences in environmental exposures (notably allergens). In addition, we need at least 548 asthmatic children (n=274 in green and n= 274 in control buildings) to detect differences in asthma symptom days. With an anticipated loss to follow-up over a 1-year period = 20%, we will need at least 688 children with asthma (7-12 years) and 814 homes to assess exposure differences. We will enroll the children from 832 homes in order to ensure adequate power to detect both the asthma and exposure outcomes for the 13 study sites (i.e., 64 homes in each study site). The details of our sample size calculations are listed below and the equations that were used were from a book on longitudinal data analysis by Diggle, Liang, and Zeger (1994).

Sample size calculations for the overall difference between environmental exposures in green vs. control homes can be given as a simple test of two proportions and means; however a specific difficulty arises when trying to adjust for temporal and spatial correlations between measurements. A study that had enough measurements to assess spatial and temporal correlation was an integrated pest management (IPM) study conducted in New York

City (Chew et al. 2006; Kass et al. 2009). We have used the design effect from this study to estimate the number of clusters (or buildings) needed to detect differences in cockroach allergen because IPM is also one of the main green characteristics in the Green Housing Study. Assumptions from the aforementioned study comparing IPM to non-IPM homes are listed below:

1 13 buildings
2 About half were treatment and the other half control
3 3 repeated measures at: baseline (before IPM), 3months later (post-IPM), and 6months later (post-IPM)
4 On average, 25 apartments within each building were measured
5 For the control homes, the correlations between baseline and 3-month follow-up cockroach allergen measurements and 3-month and 6 months follow-up measurements were approximately equal to 0.5.

Design effect due to clustering = 3.62

Equation 1. Sample size for repeated measures – cockroach allegen.

$$m = D * [2(z_{\alpha} + z_{Q})^{2}\{1 + (n-1)\rho\}]/(n\Delta^{2})$$

m = number in each group (e.g., intervention and non-intervention)
n = number of repeated measurements (equals 3 in this scenario)
z_{α} = Z score for alpha = 0.05
z_{Q} = Power, set at 0.80
ρ = correlation among repeated observations
Δ = d/ σ where d is the smallest meaningful difference and σ is the standard deviation
D = Design effect due to clustering (This was not in the formula used by Diggle et al., but was added to adjust for clustering expected in our study)

Note: we also assumed a design effect (e.g., increase (multiplicative) sample needed because of the effects of clustering) equal to 3.62. This is the ratio in clustering sampling variance divided by the simple random variance (of the same size) (i.e., the denominator without clustering taken into account).
When calculating the sample sizes, we used two standardized effect sizes based on the IPM study: 0.37 and 0.30. The effect size of 0.37 is based on the ability to detect a difference of 0.8148 ln units of the *Blatella germanica* cockroach allergen (i.e., Bla g 2) and a standard deviation of ~ 2.2. The effect size of 0.30 is the based on the ability to detect a difference of 0.649 ln units of Bla g 2 and a standard deviation of 2.2. We also assumed an alpha of 0.05 and a power of 80%). The sample size based on changing the expected correlation between repeated measures would result is presented in Table 8.

Assuming a correlation of 0.5 we get the following:

1 With assumption 1, we would need 16 buildings (8 green and 8 control) with at least 25 apartments per building
2 With assumption 2, we would need 26 buildings (13 green and 13 control) with at least 25 apartments per building.

Table 8. Sample size requirements for number of buildings.

Correlation between repeated measures	Sample size requirements (number of buildings)	
	Assuming Delta=0.377	Assuming Delta=0.30
0.2	6	9
0.3	7	11

0.4	8	12
0.5	8	13
0.6	9	15
0.7	10	16
0.8	11	17

*samples size is for each group (e.g., 8 buildings means 8 control and 8 green buildings)

We also estimated the sample size for detecting differences in pesticides and VOCs. To date, there is only one study of an intervention to decrease pesticide exposures that used objective measurements of pesticide levels in residential homes in a non-agricultural environment (Williams et al). This study was conducted in homes of Latina and African-American women living in low-income housing in New York. In the study, 25 homes underwent IPM as an intervention. The pesticide synergist, piperonyl butoxide, is unique to pyrethoid pesticides and this was an analyte that was measured in the study's air samples. We used their pre- and post piperonyl butoxide concentrations (pre = mean 1.66 ± s.e. 0.71 ng/m^3 vs. post = mean 0.8 ± s.e. 0.22 ng/m^3) for our calculations of sample size which are shown in Table 9.

To date, there is only one study comparing the VOC levels in newly-built green homes and conventionally-built homes; therefore, this was not a renovation like our proposed study. We calculated the sample size based on their measurements of formaldehyde in the two types of homes in their study. This study was conducted in Finland. In the study, 6 apartments in each type of building had air measurements for formaldehyde (green-built: mean = 13 µg/m^3, s.d. = 4 vs. conventionally-built: mean 23 µg/m^3, s.d. = 5). We calculated the sample size necessary to detect a decrease in 50%, 25%, and 15%, of the difference in formaldehyde levels observed in their two study groups (see Table 9).

Devos et al (1990) have suggested that the minimum level of an indoor irritant be set with a safety factor of 40 (Devos, Patte et al. 1990). Given that the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value is 368 µg/m^3, a minimum level of formaldehyde below which no irritant effects are expected is 9.8 µg/m^3 (which is the CDC/ATSDR Minimum Risk Level, http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=220&tid=39). Based upon Table 9, we believe that detecting differences of 9.8 µg/m^3 should not be a problem with at least 37 homes in each study group.

Table 9. Calculations of samples sizes for VOCs and pesticides

Analyte	Design Effect	Effect Size (Δ)	Required Sample size (in each group)
Formaldehyde - 15% : 1.5 µg/m^3 - 25% : 3.5 µg/m^3 - 50% : 5 µg/m^3 (based on Tuomainen et al, 2003)	 3.6 3.6 3.6	 0.33 0.77 1.10	 408 75 37
Piperonyl butoxide 0.8 ng/m^3 decrease (based on Williams et al, 2006)	3.6	0.33	418

* $\alpha = 0.05$, $1-\beta = 0.80$

Summary of samples size for environmental exposures: Of the intervention studies relevant to green housing, the sample size calculations based upon the cockroach allergen intervention study provided the most information to inform our estimates of sample size required for the Green Housing Study. Because Dr. Chew was a co-author on the manuscript and had analyzed the cockroach allergen samples in her laboratory, she had

access to the repeated measurements database and this helped to guide our design effect due to clustering of apartments within buildings. The other papers did not have repeated measurements (thus the variance estimates were rather wide) and they also had more restrictive groups (e.g., nonsmoking pregnant women, Finnish families living in newly-constructed apartments) than is planned in the Green Housing Study. Thus, we believe that our conservative estimate to recruit residents in 64 apartments in each of 13 cities (total n= 832 homes) to account for potential loss-to-follow-up, should ensure adequate sample size for assessing differences in exposure levels.

Sample size for assessing asthma outcomes: The calculation for assessing differences in health markers were based upon a multi-site asthma intervention study (Morgan et al. 2004). In this study, 407 asthmatic children with the multi-factorial intervention (asthma trigger education, mattress covers, IPM, HEPA filter units) had fewer days (2.62 days ± 0.12) than those (n=414) without the intervention (3.21 days ± 0.13). Table 10 shows sample sizes with different assumptions of effect sizes using equation 2.

Equation 2. Sample size for asthma morbidity outcomes.

$$m = D * [2(z_{\alpha} + z_{Q})^{2}\{1 + (n-1)\rho\}]/(n\Delta^{2})$$

m = number in each group (e.g., intervention and non-intervention)
n = 1 (note: for differences of differences, we assumed a value of 1)
z_{α} = Z score for alpha = 0.05
z_{Q} = Power, set at 0.80
ρ = correlation among repeated observations
Δ = d/ σ where d is the smallest meaningful difference and σ is the standard deviation
D = Design effect due to clustering (This was not in the formula used by Diggle et al.1994, but was added to adjust for clustering expected in our study). Based upon the Kwon et al (2003) paper that showed a design effect of 1.5 was helpful for designing cluster studies to assess asthma outcomes in national surveys (e.g., BRFSS and NHANES), we assumed a slightly smaller design effect equal 1.2 due to the expected low average number of children per cluster).

Table 10. Sample size requirements for number of children with asthma.

Effect size (i.e., delta)	Sample size requirements (number of asthmatic children)	
	in Green buildings	in Control buildings
0.20	274	274
0.232*	274	274
0.30	206	206
0.35	151	151
0.40	116	116

* Based on observed effect size from Morgan et al (2004) study.

We used Equation 3 to calculate the sample size based on binary outcomes. The assumptions for the equation were based upon an intervention study in Seattle Public housing (Krieger et al., 2005). The Seattle researchers had n= 110 in a high-intensity intervention group and n = 104 in a low-intensity intervention group follow. They assessed the percentage of children in each group with urgent health service use in the past 2 months. Taking the difference between baseline and exit measurements of the two proportions for high-intensity (23.4% - 8.4% = 15% difference) and low-intensity (20.2% - 16.4% = 3.8% difference), we calculated n= 102 in each study group.

Equation 3. Sample size for binary asthma morbidity outcomes.

$$m = [[(z_{\propto}\{2\bar{p}\bar{q}\ (1 + (n-1)\rho)\}^{\frac{1}{2}} + z_Q\{(1 + (n-1)\rho)(p_A q_A + p_B q_B)\}^{1/2}]^2]/nd^2$$

m = number in each group (e.g., intervention and non-intervention)
n = 1 (note: for differences of differences, we assumed a value of 1)
z_α = Z score for alpha = 0.05
z_Q = Power, set at 0.80
ρ = correlation among repeated observations
p_A = proportion of Group A
p_B = proportion of Group B
q_A = 1- proportion of Group A
q_B = 1- proportion of Group B
$\bar{p} =$ ($p_A + p_B$)/ 2
$\bar{q} = 1 - \bar{p}$

d = is the smallest meaningful difference between proportions
D = Design effect due to clustering (This was not in the formula used by Diggle et al. 1994, but was added to adjust for clustering expected in our study). Based upon the Kwon et al paper (2003) that showed a design effect of 1.5 was helpful for designing cluster studies to assess asthma outcomes in national surveys (e.g., BRFSS and NHANES), we assumed a slightly smaller design effect equal 1.2 due to the expected low number of expected of average children per cluster).

Summary of sample size for asthma outcomes: Based upon both the Morgan et al. (2004) and Krieger et al (2005) studies, a sample size of at least n=274 in each group (Green intervention vs. non-intervention) should provide 80% power to detect differences in asthma outcomes such as symptom-days and urgent care visits. As mentioned in the summary above, we will enroll the children from 832 homes in order to ensure adequate power to detect both the asthma and exposure outcomes.

Main Variable Definitions

Type of rehabilitation: The main variable of interest is the type of home (green vs. control); however, within each type, there are different permutations. For example, HUD has two levels of green which are based upon the acceptance of HUD-approved recommendations: Level 1) landlord agrees to implement at least 75% of the dollar amount of green repairs and improvements; and Level 2) landlord agrees to implement at least 50% of the dollar amount. While discretizing the green rehabilitation into Level 1 and Level 2 categories could simplify our analysis, we acknowledge that the two different levels do not necessarily capture green materials or practices that are potentially related to health. For example, a green home could have low VOC paint, or low VOC carpet, or replace the kitchen cabinets with low VOC materials, or have some combination of these activities. A control home may also include some green materials (such as low flow toilets or EnergyStar appliances)—the distinction here is that a control home is not required to use green materials or practices. Therefore, we will attempt to isolate the main effects of specific background variables such as low VOC paint, low VOC carpet, and kitchen cabinet replacement.

Allergens in the homes: Variables related to dust mite (Der p 1 and Der f 1), cockroach (Bla g 2), cat (Fel d 1), and mouse (Mus m 1) allergen in the homes may take the form of continuous measures of specific allergens or

of indicator variables for the presence or absence of certain allergens or combinations of allergens. Allergen concentrations will be reported as μg of allergen per g of collected dust and μg of allergen per unit area vacuumed.

VOCs and pesticides in the homes: Variables related to VOCs (whether total or speciated) and pesticides (pythrethroids, propoxur, and piperonyl butoxide) in the homes may take the form of continuous measures or indicator variables for the presence or absence of certain chemicals or combinations of chemicals. Concentrations will be reported as ppm (and also $\mu g/m^3$) in the case of the VOCs and μg/g in the case of the pesticides.

Conditions of the home environments: Factors that may influence the presence and levels of allergens, VOCs, and pesticides include: the presence of carpets; pests; housing type and age, average winter temperature and relative humidity, air exchange rates.

Wheeze /asthma severity: This information may be used in the form of categorical and continuous variables (number of emergency room visits for asthma, use of asthma medications, lost school days). Nights awakened by asthma, and spirometry measurement such as FEV1 and $FEF_{25-75\%}$).

Additional environmental and host factors for disposition to wheeze/asthma: Other risk factors for the main outcomes of interest include: environmental tobacco smoke; acute respiratory illnesses; gender; socioeconomic status of primary caregiver; degree of acculturation (operationalized); and deficiencies in access to and quality of health care. Many of these factors allow for a variety of formulations. Environmental tobacco smoke, for example, may be analyzed as an indicator variable for the presence or absence of smoking in the home, as count data for the number of smokers in the home, or as a continuous variable for the number of cigarettes smoked per day in the home. The choice of formulation of risk factors will be driven by the aim of clarifying the main relationships of interest, for example the role of allergens in the development of early allergic sensitization and asthmatic airways disorders.

Descriptive statistics: Study participants will be characterized with regard to demographic variables such as age, gender, and race; clinical variables such as symptom frequency, use of emergency hospital care, allergy sensitivity and pulmonary function, and environmental variables such as indoor allergens (cockroach, mouse, cat, and dust mite). Categorical variables will be summarized by frequencies, while continuous variables will be summarized by mean, standard deviation, median, and range. Levels of mold, indoor allergens, pesticides, and VOCs will be log-transformed to compute geometric means and geometric standard deviations. Where appropriate, other transformations or non-parametric analysis methods will be used.

Regression models: In general, for the regression analyses, primary interest lies in the coefficients for the binary "exposure" variable (green vs. control). The regressions will also include background variables such as pesticide, VOC, and allergen levels; these variables are included to adjust for differences between households, and we are particularly interested in the coefficients. We will also include interactions between exposure and the background variables. Significant coefficients for these interactions are important because they imply that the exposure has a larger effect under some conditions in comparison to others. In addition, it will be important to consider nonlinear models to allow, for example, for a threshold of allergen exposure.

In the case of dichotomous outcomes, multiple logistic regression will be used to calculate odds ratios (in the case of rare events such as overnight hospitalizations due to asthma attacks). When rare events exceed 10%, then risk ratios will be calculated from the logistic regression (J. Zhang & Yu, 1998). Hierarchical linear modeling will be used for evaluating effects of individual apartment, neighborhood and regional factors on levels of environmental agents. The main outcomes are allergen, VOC, and pesticide levels in the home; however, several factors should be adjusted in the analysis, including but not limited to smoking in the home, proximity to major roadways, and region of the country. For example, researchers in Baltimore found a low prevalence of both cockroach exposure and sensitization among children in high SES African American families (Sarpong, Hamilton, Eggleston, & Adkinson, 1996). This observation highlights a possible mechanism through which factors operating at the social/environmental level (e.g., deteriorated built environment) might contribute to asthma among disadvantaged urban children, i.e., via increased exposure indoor allergens (V.A. Rauh et al., 2002). Conceivably, the greenest of homes could still have poor indoor air quality due to some of the aforementioned factors.

The analytical plan for specific hypotheses are:

Hypothesis 1: Green housing will lead to 1) lower levels of environmental contaminants compared with those of control housing, and 2) lower levels of related biomarkers in the residents of green vs. control housing.

The longitudinal study here outlined will permit estimation of:

Geometric mean (GM) and standard deviation (GSD) for each of the environmental analytes (e.g., pesticides, VOCs, mold, and indoor allergens) by rehabilitation type (green vs. control).

Geometric mean (GM) and standard deviation (GSD) for each of the biomarkers for pesticides and VOCs by rehabilitation type (green vs. control).

Correlations between environmental measurements and biomarkers (stratified by several characteristics including but not limited to age and gender).

Proportion of green vs. control homes that have pesticides that are currently banned for residential use by EPA.

Hypothesis 2: If irritants and allergens are lower in green vs. control housing, residents of green housing should experience fewer and less severe asthma exacerbations.

The longitudinal study here outlined will permit estimation of:

Odds ratios (OR) or Rate Ratios (RR) for exposures to environmental agents and cumulative incidence of wheeze and/or other asthma-related morbidity measurements (among children ages 7-12 with asthma).

Odds ratios (OR) or Rate Ratios (RR) for exposures to environmental agents and cumulative incidence of wheeze and/or other asthma-related morbidity measurements (among mothers/ primary caregivers). This analysis is also secondary; we expect that asthma among adults will be influenced by other factors unrelated to green housing (e.g., their own smoking habits, occupational exposures).

Missing data (e.g. loss to follow-up)

We anticipate the inevitable occurrence of missing data, including dropouts. First, if the missingness of the data is sufficiently small and the associations of interest are sufficiently large, the simple device of imputing upper and lower bound data, if possible, will suffice. That is, a small amount of missing data and a large effect size will allow a unique inference to stand no matter whether the missing data are imputed at their minimum or maximum possible values and used as such. This is consistent with the most conservative approaches adopted in clinical trials wherein subjects lost to follow-up are assumed to have died or to have otherwise suffered the worst possible endpoint. In general however, we must anticipate that we may be facing larger missingness and/or smaller effect sizes and/or impractical upper and lower bounds, such that primary inference changes

between the extremes. In this case we will use the multiple imputation procedure of Rubin (Rubin, 1985) to address the problem. In this technique, a fair amount of effort is devoted to the construction of an imputation model or set of models to provide best estimates of missing endpoints. These best estimates may include the best case or worst case scenarios; the point is that they should most fairly represent data that are missing given the observable information at hand. The imputation models may need to assume data missing at random or they may need further specification to allow for non-ignorable missingness. Each analysis must develop its own best imputation model for missing data, using available observed covariates and non-missing endpoints.

Database management system

All interview, environmental, and other data recorded on paper forms will be reviewed for coding problems and corrected prior to data entry. All records will be entered with range and logic checks and all discrepancies resolved with reference to the paper records. When possible, laboratory data will be downloaded from their respective software to computers in ASCII format in order to decrease data entry errors. Otherwise, biologic and environmental sample information will also be recorded on forms which mirror the computer screen in order to facilitate data entry. Chain of custody for biologic and environmental samples will be maintained at each study site and (de-identified data will be maintained at CDC). All data will undergo a series of quality control checks designed to detect missing data points and invalid datapoints, such as incorrect dates. All data will be converted to SAS format for analysis with participant number, visit type, and visit date used to link across computer and paper data files. At regular intervals, the data will be queried for routine descriptive statistics on all interview items, environmental measures, and clinical data. These will be scrutinized for patterns suggesting outliers, scoring errors, data entry errors, etc. Problems suggesting protocol deviations need for retraining, or similar issues will be resolved through meetings of the research team and field staff.

PCs running ACCESS software will be used for data management with original and working analytic data files backed up regularly to a password protected server on a local area network, which is itself backed up nightly. All paper records and removable computer disks containing confidential data generated during the study will be kept in locked file cabinets; all other electronic data will be maintained in password protected folders. Access to either will be limited to authorized staff. Survey instruments have been designed in Microsoft ACCESS ®, which will facilitate data entry into this relational database. Biologic and environmental sample information will also be recorded on forms which mirror the computer screen in order to facilitate data entry. Chain of custody for biologic and environmental samples will be maintained at each study site. All data will undergo a series of quality control checks designed to detect missing data points and invalid datapoints, such as incorrect dates.

Confidentiality of the Data

Data from paper questionnaires will be entered by the contracted data collectors into a database (e.g. Microsoft Access) which will also be password-protected. Dates of birth and home addresses are primary direct identifiers and the contractor's removal of other direct identifiers (such as name, phone numbers, e-mail addresses) will minimize identification but not completely eliminate it. A unique Study ID will be assigned by the contractor as a key identifier for all study forms. The environmental and biological samples and measurements will only be identified by study ID. Contracted data collectors will maintain their paper files in locked cabinets and their electronic files will be stored on secured servers with password protection. Encrypted data files will be sent electronically to Green Housing Study investigators at CDC. Data will be stored on highly-secured CDC servers in Atlanta, GA. The servers are housed in a secure computer room complete with climate control, emergency power, and an uninterruptible power supply (UPS). Daily back-ups and integrated security are implemented through the CDC computer services infrastructure. All data access is password-protected, and all network communications use encryption. All servers and PCs that are part of the CDC infrastructure are protected by both host-based firewalls and software in order to prevent the undetected

installation of "spyware". Only Green Housing Study investigators at CDC will be given access to read the encrypted data files.

CDC Green Housing Study investigators will receive electronic files with date of birth, medical information, biological specimens, employment status, and home address identified by study ID number. If there were a breach of confidentiality for any of the above IIF, some effect on the respondent's privacy could occur; however, the screening form will be the only form that contains name, home address, phone number, e-mail address, and study ID together; only the contracted data collectors will have this form. The contracted data collectors will only use name, phone number, e-mail address, and home address for locating the study participant and ensuring that follow-up questionnaires and clinical and environmental measurements are repeated accordingly. Contracted data collectors will be required to have human subjects training in accordance with their institution's Institutional Review Board (IRB) and/or the CDC's IRB.

Quality Control and Quality Assurance

Training of study staff will occur centrally at CDC prior to beginning recruitment. The training will include lecture, demonstration, and practice components to insure that all staff are fully trained. Staff will complete certification to demonstrate acceptable levels of knowledge regarding each study component that they will be involved in performing.

The site PIs and study coordinators will be responsible for insuring that all procedures are performed according to the protocol. Periodic reviews of the procedures will be conducted by the study coordinator.

A Green Housing Study Manual of Procedures will be provided to all investigators and staff members. This manual will include detailed descriptions, including SOPs (standard operating procedures) and case report forms, for each study activity or procedure.

Representatives from the CDC will conduct site visits periodically to assess adherence to the protocol and progress of enrollment. Other areas of review will include data collection procedures, data entry, timeliness of form completion and data entry, and security measures for study data.

Ethics/Protection of Human Subjects

Institutional Review Board/Ethics Committee

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate ethics review committee or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are placed into use. Only institutions holding a current US Federal-Wide Assurance issued by the Office for Human Research Protections (OHRP) may participate.

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of will be provided to the participants. Consent forms describing in detail the study procedures and risks will be given to the participant. Written documentation of informed consent is required prior to starting the study. Consent forms will be IRB-approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. Spanish- and Chinese-speaking participants will be provided with consent documents in Spanish or Chinese and the consent discussion will be facilitated or conducted by a a bilingual (Spanish/English or Chinese/English) interviewer. The participants and their parents/guardians may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the

participants will be protected by emphasizing to them that the quality of their medical care or housing situation will not be adversely affected if they decline to participate in this study.

Assent Process

Study participants will be 7-12 years of age and all will be engaged in a discussion of the study procedures and intervention and risks and potential benefits. Assent forms written in appropriate language for children will be reviewed with children and their mothers/primary caregivers and ample time will be provided to discuss the study procedures, intervention, risks and potential benefits. Written documentation of assent is required prior to starting the study.

Participant Confidentiality

Following HIPAA guidelines, a participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number and these numbers rather than names will be used to collect, store, and report participant information. Data reported in medical journals or scientific meetings will be presented in aggregate for participants as a whole. No individual participant will be identified in any way.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the principal investigator at CDC.

Reporting results to study participants

Overview

Results will be given to the study participants for their individual housing unit and clinical tests (when applicable). There are no government standards for residential levels for any of the environmental agents that we are measuring in the study homes. However, during the participants' final home visit, we will: 1) give them the first environmental results that we collected from their home; 2) give them the first clinical results (blood and urine tests) that we collected from the enrolled child; 3) discuss the results with the study participants; and 4) give them information (e.g. local health department phone numbers and a DVD and/or pamphlets) on how to lower environmental agents in their homes. The rest of their results will be mailed to them within one year after they finish the study. The property managers will receive a general report on their complex (not individual unit results). Also, we will consult with building management about appropriate methods of reducing exposures.

Site Monitoring

Site monitoring will occur under the supervision of the CDC PI, Dr. Ginger Chew. Schedule
CDC staff will conduct site visits according to the following schedule:

- Prior to enrollment of the first study participant to ensure that all equipment is in place, and that space and staffing are appropriate.

- After the first 2 study participants have completed the 6-month home visits.
- Subsequently, annually.

- If issues or concerns arise, an ad hoc site visit will be scheduled at the discretion of the CDC.

Procedure
CDC staff will review a random sample of participant charts (de-identified) at each site visit to ensure appropriate completion of all case report forms, and adherence to regulatory policies. A written report of the findings from the site visit will be provided to the site and CDC PI.

Safety Monitoring
The CDC IRB will review any event as requested by the Investigators or CDC.
They will review the study annually, including accrual and adverse events (AE). The CDC IRB will review accrual and adverse events annually.

Safety parameters
Safety parameters will include clinical observation and administration of an unstructured questionnaire of the study participant and mother (if applicable) regarding any events during the course of enrollment in the study. Clinical observation will occur at each of the clinic visits and unstructured questioning will occur at each of the clinic visits.

Definition of Adverse Events and Serious Adverse Events
An adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease in a study participant, whether or not it is considered to be study-related. Any worsening of a pre-existing condition or illness is considered an adverse event. An adverse event is considered unexpected when its nature or severity is not consistent with the descriptions in the protocol or consent form.

A serious adverse event (SAE) is defined as any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. This includes, by may not be limited to, any of the following events:

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of the therapy, whether or not considered intervention-related, must be reported.

2. Life-threatening: Any adverse therapy experience that places the subject or subjects, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).

3. Inpatient hospitalizations or prolongation of existing hospitalization.

4. Persistent or significant disability or incapacity

5. An event that required intervention to prevent permanent impairment or damage.

Assessment of AEs
At every point of contact with the study participant (home visits, clinic visits, and telephone calls, study participants will be asked in an unstructured manner whether they have had any problems since their last study visit. All reportable AEs will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the participant to be stable. All serious adverse events will be followed through resolution by a study physician and reviewed by a study physician.

Adverse events may be discovered through any of these methods:
- Observing the participant
- Questioning the participant which should be done in an objective manner
- Receiving an unsolicited complaint from the participant.

Exacerbations of asthma are ordinary, anticipated complications of asthma observed in patients receiving standard of care. Asthma exacerbations requiring hospitalization for 5 or more days or intensive care admission will be considered serious adverse events. For reporting purposes, the date of onset of the exacerbations will be the date of hospital admission and the date of resolution will be the discharge date.

Grading and Relationship Assignment
Adverse events will be recorded and graded 1 to 5 according to the general grade definition below:

Grade 1 Mild - Transient or mild discomforts, no or minimal medical Intervention therapy required, hospitalization not necessary (nonprescription or single use prescription therapy may be employed to relieve symptoms, e.g. acetaminophen or ibuprofen).

Grade 2 Moderate - Mild to moderate limitation in activity; some assistance may be needed, no or minimal intervention/therapy required, hospitalization possible

Grade 3 Severe - Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.

Grade 4 Life-threatening - Extreme limitation in activity, significant assistance required; significant medical therapy intervention required, hospitalization or hospice care probable.

Grade 5 Death

The relationship to study procedures will also be recorded. Adverse events will be assessed as definitely related, probably related, or possibly related, or not related.

An adverse event is considered related to the study procedures if there is a reasonable possibility that the adverse event may have been caused by the procedure.

1. Definitely related: An adverse event that follows a temporal sequence from administration of the procedure; follows a known response pattern to the procedure; is confirmed by improvement after stopping the procedure, and cannot be reasonably explained by a known characteristic of the participant's clinical state or by other therapies or interventions.

2. Probably related: An adverse event that follows a reasonable temporal sequence from administration of the procedure, is confirmed by improvement after stopping the procedure, and cannot be reasonable explained by the known characteristics of the participant's clinical state or other therapies.

3. Possibly related: An adverse event that follows a reasonable temporal sequence from administration of the procedure and follows a known response pattern to the procedure, but could have been produced by the participant's clinical state or by other therapies.

4. Unlikely: An adverse event whose temporal relationship to the study procedures makes a causal relationship improbable and in which other interventions or underlying disease provides plausible explanations.

5. Not related: An adverse event that does not follow a reasonable temporal sequence after administration of the procedure and most likely is explained by the participant's clinical disease state or other therapies.

AE Event Reporting and Management

An Adverse Event Form will be used for reporting all adverse events. An additional form will be required for serious adverse events to collect additional information. Information that will be documented includes a brief description of the event, onset and duration of the event, severity grade of the event, resolution status of the event, and relatedness to the study procedures. Any medical intervention will also be documented.

SAE forms will be faxed to the CDC to the attention of the PI. SAEs will be reported to the CDC by the Study Coordinator and Site Investigator either within 24 hours or within 5-7 days as indicated below:

1. SAEs that do not include a death or life-threatening event will be reported within 5 to 7 days to the CDC.

2. Any death or life-threatening SAE (Grade 4 or 5 SAE) must be reported to the CDC within 24 hours. The PI of the CDC will be notified by email. The site's IRB must also be notified within 24 hours of the site's awareness of the event.

3. The following attributes must be assigned:
a. Description
b. Date of onset and resolution (if known when initially reported)
c. Severity
d. Assessment of relatedness to the study procedures
e. Action taken

The study site PI (or project coordinator) will notify the CDC IRB of SAEs within 7-10 days. Adverse event reports will be generated by CDC on an ongoing basis and included in annual reports to the CDC IRB.

Study Discontinuation

The study site investigator along with the CDC PI will apply judgment to determine whether an adverse event is of sufficient severity to require that the subject be removed from the study. If necessary, an investigator must suspend any study procedures and institute the necessary medical therapy to protect a subject from any immediate danger.

Subsequent review by the study site PI, IRB, and CDC may suspend further study activities at the site. The CDC and CDC IRB retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Source documents and Access to Source Data/Documents

The following types of data will be collected: environmental laboratory data (allergens, mold, VOCs, pesticides, PM), clinical laboratory data (urinary pesticide and VOC biomarkers, IgE levels, PCR analysis of acute respiratory illnesses), clinical data (lung function, exhaled nitric oxide, symptom report, health care utilization, medication usage).

Each participating site will maintain appropriate medical and research records for this trial, in compliance with good clinical practices (GCP), regulatory and institutional requirements for the protection of confidentiality of participants. Study staff and investigators and site IRBs may access the records. As part of participating in a CDC-affiliated study, each site will permit authorized representatives of the sponsor, CDC, and regulatory agencies to examine (and when required by applicable law, to copy) de-identified clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Timing/Reports

No formal interim analyses are planned. Adverse events and enrollment will be reviewed on an ongoing basis by the PI and the IRBS at CDC and each participating institution. Adverse events and enrollment reports will be generated annually for IRB review.

Study Records Retention

Study documents must be maintained at the research center or a local storage facility for at least five years following the completion of the study. Study documents that must be retained include all participant-related forms, laboratory reports, IRB approval documentation and related correspondence and signed informed consent/assent forms.

V. LIMITATIONS

Generalizability

Geographic location

The proposed study will be conducted in HUD-sponsored housing primarily in urban environments. The majority of HUD properties that participate in the HUD's housing subsidy programs are located in the eastern part of the U.S., thus the geographical distribution of properties available for study is not uniform. In addition, participation in the study is voluntary and before residents can be approached about participation, owners and property managers of the prospective properties must first give consent. As such, our study sample will not be random, which is likely to have implications for the generalizability of our findings.

Socioeconomic status (SES)

The proposed study will be conducted solely in Section 8 housing—thus our study will assess the impact of green housing on the health outcomes of low-income residents. As a result, it may not be appropriate to generalize our findings to children in families with higher socioeconomic status. Also, race (which can be intertwined with SES) could also influence health outcomes either due to genetic susceptibility (K. C. Barnes, 2006) or other unmeasured factors (Drake, Galanter, & Burchard, 2008).

V. SUMMARY OF STRENGTHS

This study is uniquely poised to evaluate relationships between green housing and human health. The nationwide multi-site design will provide contextual information to understand which green building rehabilitation practices are associated with health not only regionally, but nationally. This elucidation then could inform policy about which green components should be implemented without regard to locality, and which components should be modified under certain circumstances (e.g, region or housing type).

The other main strengths of this study are the repeated exposure measurements and the choice of health outcomes (asthma). A cross-sectional design could easily miss the biologically relevant exposures associated with health. By collecting repeated measures of pesticides, VOCs, fungi, and indoor allergens, asthmatic children in both the green and control housing units can be compared prospectively and selection bias will also be minimized. Focusing on sensitive populations such as children with asthma, will give the study the best chance to see relationships between green housing and health, given that those relationships exist.

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Appendix 1

Instructions for collection of nasal and throat swabs for assessment of acute respiratory illness

Green Housing Study

INSTRUCTIONS FOR COLLECTING NASAL AND THROAT SWABS (for Mothers/ Primary Caregivers)

- **Please collect a nasal and throat swab** from your child if he/she has at least 2 of these symptoms for more than 24 hours: fever or feels feverish, stuffy or running nose, cough, sore throat, body aches or tiredness.
- Please collect the nasal swab **as soon as you notice your child has had symptoms for at least 24 hours**, but you may do it up to 7 days from when their symptoms started.
- **Equipment you will need**
  - A clean nasal swabs
  - A clean throat swab
  - A clean tongue depressor
  - A container tube with study label
  - A specimen bag
  - Study labels
- **Before collecting the swab**
  - Gather all equipment
  - Place a study label on the container tube and place a study label on the symptom checklist. Also place the date that you collect the swabs on the checklist paper.
  - Wash your hands with soap and warm water before taking the swab

- **Collecting the swab**
  - With your child seated, tilt their head back gently and keep their head stead by placing a hand on their chin.
  - With the other hand, place the end of a clean swab in the front part of one of their nostrils and gently rub the inner wall. Make sure there is mucous on the swab. If there is no mucous, try getting the sample from that side of the nose again.
  - Remove the swab from the first nostril and place that same swab in the front part of the other nostril and gently rub the inner wall. Again, make sure there is mucous on the swab.
  - Remove the cap from the container tube.
  - Place the swab in the tube and seal the tube lid until it is tight. If the swab does not fit in the container tube, break off the end of the swab with your hand and then seal the lid.
  - Gently tilt the child's head back again. Ask he/she to open their mouth wide. Use the tongue depressor to get a good view of the back of the throat. Rub the swab several times around back of the throat. Place the throat swab in the same tube as the nasal swab. Break off the end of the swab and tightly close the lid.
  - Place the container tube with the swabs in the specimen bag.
- **After getting the swab**
  - Wash your hand using soap and warm water.

- Place the specimen bag with the tube into your refrigerator
- Fill out the symptom check list and please make sure that a study label and the date that you collected the specimen are placed on the checklist paper.
- As soon as you collect the nasal swab, please call the study nurse (XXX-XXX-XXXX) to arrange for pick-up.
- When they pick up the swab, they will also be collecting additional swabs (nasal and throat) on your child, so please make sure your child and an adult will be available during the pick-up time.

IF YOU HAVE ANY QUESTIONS OR PROBLEMS, PLEASE CALL YOUR STUDY COORDINATOR AT
XXX-XXX-XXXX

Green Housing Study

INSTRUCTIONS FOR COLLECTING NASAL AND THROAT SWABS (for Study Technicians)

- **When you will be contacted**
  - Mothers/ primary caregivers have been instructed to collect nasal and throat swabs when their child has at least 2 of the following symptoms for more than 24 hours: fever or feels feverish, stuffy or running nose, cough, sore throat, body aches or tiredness.
  - Please arrange to pick up the specimen as soon as possible after the specimen has been collected. Please make sure the child and an adult will be available during the pick-up time, since you will be collecting additional specimens.
- **Equipment you will need**
  - Nasal and throat swabs
  - Collection tube
  - Tube holder
  - Tongue depressor
  - Specimen bag
  - Cooler with cold ice packs
  - Gloves
  - Study labels
- **Before collecting the swabs**
  - Gather all equipment
  - Label the collection tube with the study label and collection date.
  - Wash your hands with soap and warm water. Place gloves over clean, dry hands.

- **Collecting the swabs**
  - With the child seated, tilt their head back gently and place one hand on their chin to steady their head.
  - With the other hand, place the end of a clean nasal swab in the front part of one of their nostrils and gently rub the inner wall. Make sure there is mucous on the swab. If there is no mucous, try getting the sample from that side of the nose again.
  - Remove the swab from the first nostril and place that same swab in the front part of the other nostril and gently rub the inner wall. Again, make sure there is mucous on the swab.
  - Place the nasal swab in the transport medium tube being careful to avoid touching the sides or rim of the tube and close the lid after breaking the end of the swab off. Place the tube in the tube holder.
  - Gently tilt the child's head back again. Ask he/she to open their mouth wide. Use the tongue depressor to get a good view of the posterior pharynx and tonsils (back of the throat). Rub the swab several times around the posterior pharynx and tonsils (back of the throat). Place the oral swab in the same transport medium as the nasal swab being careful to avoid touching the sides or rim of the tube. Break off the end of the swab and tightly close the lid.
- **After collecting the swab**
  - Place the viral transport tube in a specimen bag and place it in the cooler.
  - Remove your gloves and wash your hands with soap and warm water.
  - Obtain the parent collected nasal swab specimen from the family's refrigerator and place it in the cooler. Make sure the tube is labeled and also collect the symptom checklist from the parent.
- **Storage of specimens**
  - When you arrive at the storage laboratory, please check to make sure all the tubes are properly labeled and logged into the study log book. Please store them in -70 C until shipped to CDC.

IF YOU HAVE ANY QUESTIONS OR PROBLEMS, PLEASE CALL THE STUDY COORDINATOR AT XXX-XXX-XXXX.