Original Study Protocol For: A Randomized Controlled Trial to Reduce Childhood Lead Exposure and Lead-Associated Neurobehavioral Deficits

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Note: This protocol is one of the funded grant proposals responsible for initiating the HOME Study.

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Original Research Design and Methods
The proposed cohort study will employ a longitudinal cohort of 400 women and their children followed from early pregnancy (< 16 weeks gestation). A nested, randomized, single-blinded, prospective design will investigate the efficacy of lead hazard reduction, in the primary prevention of lead exposure, among 400 children followed prenatally to 36 months of age (Figure 1). We have an established NICHD-funded Maternal-Fetal and Neonatal Network Center that will collaborate with the 3 hospitals and affiliated prenatal clinics to identify eligible women, conduct entry interviews, obtain maternal urine and blood samples, and collaborate with the research staff regarding storage, labeling, and transport of data/specimens from prenatal clinics and hospitals. At delivery, research nurses will collect, label, store, and transport cord blood and meconium samples. The existing research nurse team has participated in many similar perinatal studies and is experienced in communicating with pregnant women, collecting demographic and clinical data, and collecting biologic samples in the perinatal period. Women will be retained if their infants are born prematurely.

**Figure 1: Cohort for Study of Prevalent Toxicants**

1. **Eligibility Criteria**
Women who are < 16 weeks pregnant; who have resided in the same house for at least 3 months and deny having plans to move in the next 12 months, will be eligible for the proposed study. To target children who are at increased risk for exposure to lead, we will stratify enrollment so that ~ 200 (50%) children will be from the city of Cincinnati, 100 (25%) will reside in the suburbs, and 100 (25%) will reside in rural parts of Hamilton, Brown and Adams counties. This enrollment scheme will allow us to compare the prevalence and adverse effects of various neurotoxicants across socioeconomic strata and geographic settings. We will be able to examine environmental
neurotoxicants that may contribute to racial and social disparities in developmental outcomes. By increasing the variability of exposures and developmental outcomes, we also anticipate that the analyses will be more robust.

2. Recruitment and Enrollment
Beginning in February, 2002, pregnant women < 16 weeks gestation will be recruited to participate in the study (Table 4). We will identify women by using medical billing data from each hospital and its affiliated clinics. Pregnant women will be contacted by regular mailings and then by telephone utilizing labor and delivery pre-registration information obtained from the admissions office of the University of Cincinnati Medical Center, Christ Hospital and Mercy Anderson Hospital (letters of support in Appendix). Women who receive obstetrical care at these hospitals and affiliated clinics are routinely encouraged to pre-register in the first trimester for hospital admission in anticipation of the birth of their infant. We estimated that over 70% of women attending these hospitals received 2 or more prenatal clinic visits prior to 20 weeks gestation. A similar method of enrollment was successfully used in our ongoing NIEHS-funded study and a MCHB-funded trial of pacifier use and breast-feeding duration at the University of Rochester.

A research assistant will obtain pre-registration records on a weekly basis and mail a contact letter to prospective participants. The contact letter will inform expectant women of a study being conducted by the Children’s Hospital to investigate ways to prevent lead poisoning and other toxicant exposures in children. The letter also will inform prospective participants that a research assistant will be contacting them by telephone to discuss the study. The letter will inform women who do not wish to be contacted to call the study office or return the pre-addressed and stamped postcard enclosed with the mailing. Approximately 1 week after the contact letter is mailed, a trained interviewer will telephone women who have failed to contact the study office to evaluate their eligibility and invite those who are eligible to participate in the study.

2.1. Participation
Participation in child health studies is high in Cincinnati. Participation in a recent community breastfeeding study was 85%\(^{125}\). In the NICHD Neonatal Research Network high-risk follow-up, a multicenter study, the participation rate in Cincinnati was higher (> 90%) than other NICHD-funded centers. More specific to an environmental exposure study, the participation rate for our recently completed randomized, controlled trial of dust control was 275 (64%) of 428 eligible subjects\(^{126}\). Thus, we are confident that the numbers of eligible subjects and rate of participation are more than adequate to successfully conduct the proposed study.

3. Retention
We do not anticipate any problem retaining 90% or more of the sample population. The rate of retention at 18-months for the NICHD-funded high-risk infant follow-up was 98%\(^{127}\). In our randomized trial of dust control, involving 276 families, 90% of children completed the 18 months trial\(^{126}\). This latter study included periodic venipuncture and the incentives were less than in our proposed trial. We therefore estimate that our attrition rate will be 10% or less. We must therefore enroll 400 participants to allow for
10% attrition and maintain a sample size with adequate power (n= 360). (See “Sample Size,”)

Families often relocate to other housing. If a family moves outside of the metropolitan area, we will retain them in the study if they reside within a 3-hour radius. To maximize retention, we will maintain routine telephone contact with each family. To further improve our chances of maintaining contact with families, we will provide a $10 gift certificate when a family notifies us that they are relocating or changing their telephone number. We also will identify telephone numbers and addresses of 3 friends or family members at the beginning of the trial and at 12-month intervals to obtain updated address and telephone number for the enrolled families, if necessary.

4. Nested Randomized, Controlled Trial of Lead Hazard Control
Children will be enrolled prior to their birth and before they are exposed to lead in their home environment. We estimate that 300 (75%) of the 400 children will have > 1 source of lead identified in their home environment. Lead hazard reduction, as determined by random assignment, will therefore be conducted in the housing units of about 150 (50%) children who live in housing that contains residential hazards; the remaining children (~ 50%) will be assigned to the Control Group (Figure 1). All children will be followed until they attain 36 months of age regardless of whether they relocate during the study period. If a child relocates during the first 24 months of life, we will conduct lead hazard reduction in the child’s new residence, if lead hazards are present (see definition of lead hazard, page 11). We will determine the re-accumulation rate of lead-contaminated dust following lead hazard reduction. After conducting baseline sampling, we will conduct home visits at 12-month intervals, take environmental samples and assess the duration of benefits associated with lead hazard reduction, as measured by dust lead loading.

4.1 Definition of Lead Hazards
For the purpose of the nested, randomized, controlled trial, we will define lead hazards as one or more of the following environmental samples exceeding the following values:

1. Floor lead loading > 5 μg/ft²;
2. Interior window sills lead loading, 100 μg/ft²;
3. Window troughs lead loading 1000 μg/ft²;
4. Soil lead concentration in bare soil > 400 ppm;
5. Water lead concentration > 5 ppb.

4.2 Lead Hazard Control
If one or more residential lead hazards are present, housing units that were randomly assigned to the lead hazard reduction group will undergo lead hazard reduction. During this process, residents will be relocated to a lead-safe environment, if necessary. Lead hazard reduction, as defined in HUD’s Guidelines for the Evaluation and Control of Lead-Based Paint Hazards in Housing. There is a maximum of 5 core elements included in the intervention:
1. Stabilize flaking, peeling or deteriorating interior lead-based paint. All paint in poor condition will be repaired, especially rooms where young children spend time (play area, kitchen, child’s bedroom).

2. Create smooth and easily cleaned floors. This may include polyurethane coating wood floors or installing new vinyl flooring.

3. Install trough liners in windows to create a smooth and easily cleaned surface.

4. Remove lead-contaminated dust. The intervention will conclude with a comprehensive cleaning effort to remove dust from all floors, windowsills, and window troughs. Clearance levels will be: < 5 μg/ft² for floors, < 25 μg/ft² on interior windowsills and < 100 μg/ft² on window troughs. Dust lead levels below these values were associated with significantly lower risk of children developing an elevated blood lead level $^{128,35}$ (Attachment 1.6).

5. Cover bare lead-contaminated soil in play areas with mulch or groundcover.

5. Environmental Sampling and Surveys
5.1. Survey Methods
At the first home visit, the team will verify eligibility, explain the potential risks and benefits of this study, and obtain informed consent, including permission to access the child’s medical and pharmacy records. The team will conduct an extensive baseline interview, inspect the home, and take environmental and biologic samples (Table 4). During the first home visit, we will gather information on exposure and potential confounding variables, including in utero exposures to environmental tobacco smoke, pesticides, lead hazards, and alcohol use. Demographic characteristics will be obtained including maternal level of education, occupation, race, income level, marital status, and age of the mother or respondent. Smoking among members of the household and type of health insurance will also be documented. Environmental samples will also be taken to identify exposures to settled pesticides and residential lead hazards, as described below.

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* Indicates cord blood sample.
† Soil and water lead samples will also be taken for new housing, if children relocate.
** PCB’s will initially be assayed in a sub-sample (n=50) to assess frequency of detectable levels. If adequate proportion are detectable, further assays will be done on the remaining subjects.

6. **Outcome Measures**

6.1 **Child Development**

The Bayley Scales of Infant Development ® Second Edition (BSID-II) \(^{129}\) will be utilized to assess cognitive and motor development at 12 and 24 months of age. This scale is well respected for its construction, reliability, and standardization. Subscales reveal a Mental Development Index, a Psychomotor Development Index, and Behavior Rating Scale scores. The test will be administered to the child by a rigorously trained examiner, requiring 40-60 minutes. The caregiver will be present. Drs. Kimberly Yolton and Kim Dietrich (neurobehavioral core), who have extensive experience in administration, training, and supervision of this assessment, will conduct training on proper administration and scoring of the BSID-II, as well as periodic quality control checks.

6.2 **Child Behavior**

At 36 months of age, each child’s primary caregiver will complete the Behavioral Assessment System for Children (BASC) \(^{130}\). The scale is applicable for children aged 2 ½ to 18 years of age and includes 138 behaviors that are rated by frequency (never, sometimes, often, and almost always). The BASC has the following subscales:
aggression, hyperactivity, conduct problems, anxiety, depression, somatization, attention problems, learning problems, atypicality, withdrawal, adaptability, leadership, social skills, and study skills. Composite scores for externalizing problems, internalizing problems, other problems, and adaptive skills are derived. The BASC is particularly useful in distinguishing between ADHD and non-ADHD children, an area of particular interest related to the effects of lead and ETS exposure. The BASC utilizes T scores in the normative data set. These are standardized scores, with a mean of 50 and a standard deviation of 10. In general, an individual's behavioral T scores of 60 or above are concerning; those of 70 and above are considered clinical in severity. Test-retest validity of the BASC scale is reported as .85 for the preschool version over a two to eight week period.

6.3. Cognitive Ability
The Differential Abilities Scale (DAS) will be used to assess cognitive ability and achievement at 36 months of age. The DAS comprises 17 cognitive and 3 achievement subtests which result in a General Conceptual Ability score that is similar to an intelligence quotient. Additional cluster scores are obtained on Verbal and Nonverbal Ability among preschool children. The test requires direct administration and scoring of items to the child, by a trained examiner, with the caregiver present. The basis of standardized norms is a mean of 100 and standard deviation of 15. The full test requires about 60 minutes to complete, and the caregiver will be present. Training on proper administration and scoring of the DAS, as well as periodic quality control checks, will be conducted by Douglas Ris, Ph.D. (neurobehavioral core), who has extensive experience in administration, training, and supervision of this assessment.

6.4. Executive Function
Executive function will be assessed through standardized techniques developed by Espy in which delayed response and delayed alternation paradigms are utilized. The 4 specific tasks will include delayed response, delayed alternation, spatial reversal, and self-control. These procedures will require approximately 30 minutes to complete. We have used these techniques in our NIEHS-funded study.

6.5. Growth, Health and Hearing
General health assessments will be collected at each clinic and home visit. Specific attention will focus on the development of respiratory disease, asthma, otitis media, growth, and hearing among the children prenatally or postnatally exposed to environmental toxicants.

Height/Length
Height and length measures will be obtained at each clinic visit. For children under 24 months of age, supine measures will be taken using an Elland measuring board. This method requires one person to hold the child against the headboard, applying gentle traction, flexing the foot, and adjusting the footboard to rest firmly against the child's heels. A second person records the length to the nearest tenth centimeter (0.1 cm). For children 24 months and older, upright height will be measured using a Genetech Accustat Stadiometer. Shoes will be removed, and children will be asked to stand
straight with heels together. Using the adjustable headboard, height will be measured to the nearest tenth centimeter (0.1 cm).

Weight
Weight will be measured at each clinic visit. Children will be weighed without clothing but will wear a clean diaper or under pants. For children less than 24 months of age, the child will be placed on a Scale Tronix Pediatric Scale. When the child has settled, weight will be recorded to the nearest hundredth kilogram (0.1 kg). For those 24 months and older, children will be asked to stand on a Scale Tronix 5005 scale. Weight will be recorded to the nearest hundredth kilogram (0.1 kg).

Head Circumference
Head circumference measures will be obtained at all clinic visits using a Barlow cloth measuring tape. The tape will be placed across the frontal bones just above the eyebrows, around the head above the ears, and over the occipital prominence. Measurements will be recorded to the nearest tenth centimeter (0.1 cm).

Hearing
Pure-tone audiometric thresholds will be assessed in children at 36 months utilizing play audiometric techniques. Children will be tested in a booth. We will assess auditory acuity between 0-80 dB at 500, 1000, 2000, and 4000 Hz, utilizing ascending/descending threshold technique. Children will start at 80 dB at 500 Hz for the purposes of training. A pure-tone audiometric hearing assessments will be done by a trained research assistant with extensive experience conducting hearing tests with young children. We have used this method in the Cincinnati Longitudinal Cohort project. All children will also be screened for middle ear pressure using tympanometry prior to hearing testing. Children who fail the hearing examination will be referred to the CHMC Audiology Department for diagnostic testing.

6.6 Neonatal Characteristics
Infant birth weight, gestational age, birth length, head circumference, and Apgar scores at one and five minutes will be recorded by the NICHD-Maternal Fetal Network research nurses. Although this is not an endpoint of our primary hypotheses, several neurotoxicants have been associated with lower birth weight, prematurity, and decreased head circumference. These measure will, in some cases, be used as covariates or confounders for our analyses examining the neurobehavioral effects of prevalent toxicants 26, 103, 3.

7. Environmental Samples
At baseline, the environmental technician will inspect the residence for housing size (to adjust for ETS exposure), house age, and general housing condition. A visual inspection of the interior and exterior painted surfaces, a measure we have shown to be highly correlated with dust lead loading, will be done to rate the condition of the surfaces 29. We will not use a portable x-ray fluorescence analyzer, however, since it provides no
additional information 13, 35, 112 (Attachment 1.2). The type and condition of floors and carpets will also be documented. We will use forms and protocols from our CDC-funded, longitudinal cohort study in the proposed cohort study (Attachment 4).

7.1. Dust Sampling
The environmental technician will take composite dust samples to measure settled pesticides and lead. We will assay composite floor samples for pyrethroids and organophosphate pesticides at 12 and 24-months visit. Dust sampling for lead-contaminated floor dust will be done to characterize the exposure of children to lead, to achieve clearance levels, and assess the efficacy of lead hazard reduction. Dust samples will be frozen at -70°C for future investigations.

7.2. Pesticide Sampling of Settled Dust.
Sampling for floor dust will be accomplished using a vacuum device specifically fabricated for NHEXAS (National Human Exposure Assessment Survey) conducted in Arizona. The sampler consists of a Hoover ‘Port-a-Power’ vacuum unit, a standard flexible vacuum hose, a cupped stainless steel mesh support screen in a lock-tight Delrin housing, and a 3.5 in. wide stainless steel steam cleaner detailer attachment (Production Metal Forming) as the inlet. An ultra-thin Teflon-faced/polyester-backed filter 154 is placed against the support screen and sealed by an O-ring between two sections of the housing 143. An integrated dust sample is collected from a 2 m² area in the center of the most-frequently used room of the house.

7.3. Lead Sampling in Settled Dust
Dust lead measures will be taken with the wipe method (µg/ft²) for all carpeted and non-carpeted surfaces. These protocols are identical with those used by the U.S Department of Housing and Urban Development, the Rochester Lead-in-Dust Study, the ongoing CDC-funded study in Rochester, and the ongoing NHANES Survey. Laboratory analysis of dust will be done using flame atomic absorption for the interior windowsills and window troughs (EPA Method 239.1). For floors, we will use graphite furnace atomic absorption analysis if the dust lead levels are below 5 µg/sample. The lower detection limit is 1 µg for the flame atomic absorption and 0.01 µg for the graphite furnace analysis. Extensive quality control for all laboratory procedures, analyses, and field sampling, as described in the Laboratory Core, will be done.

7.4. Soil Measurements
Three core sub-samples will be taken on each side of the house at the perimeter of the foundation where bare soil is present (a maximum of 12 core samples) and will be combined for a composite foundation sample. All core samples will be taken at a depth of 1/2 inch. For each of the composite surface samples, the soil will be homogenized and then sieved to obtain a coarse (total soil fraction) using a 10 mesh sieve. Analyses for lead concentration will be done for the total fraction using acid digestion method 3050 and atomic absorption analysis (EPA method 239.1) after the soil samples are dried to a constant weight. The limit of detection for soil lead concentration is 1 ppm.

7.5. Water Measurements
One water sample will be taken for each child at baseline or if the child moves to new house. The water sample will be a 30-minute stagnation sample taken from the kitchen faucet by the environmental technician. All samples will be analyzed in duplicate by using EPA method 200.9. The limit of detection for water lead concentration is 1 ppm.

Original Statistical Methods
We will first describe the distribution (mean, standard deviation) of neurobehavioral outcomes, biomarkers of exposures to various neurotoxicants, and environmental levels of exposures. Categorical variables will be summarized as proportions or in a contingency table format. Following the descriptive statistics, unadjusted analyses will be conducted to examine bivariate relationships between each outcome variable and various risk factors or covariates. For example, the hypothesis about the effects of lead hazard reduction on blood lead concentration and neurobehavioral outcomes will be addressed with a comparison of the intervention and control groups. Outcome measures, including mean cognitive scores, mean blood lead concentration, and mean dust lead loading will be compared by group assignment using t tests. Categorical outcomes, including proportion of children having clinical scores for behavioral problems, hearing loss, and blood lead level $> 10 \mu g/dL$, $> 15 \mu g/dL$ and $> 20 \mu g/dL$, will be compared between groups by using chi-square tests.

Because some outcome and exposure variables will be measured at two or more points in time (e.g., Bayley II, growth and height) the statistical analysis must take into account the correlation of measurements taken on the same individual. The most appropriate analysis for accomplishing this objective for continuous outcomes is the repeated measures mixed effects linear model. This model has a fixed effects component (e.g. group differences) and a random effects component (e.g., subjects within groups). These can estimate trends over time both within individuals and between groups of individuals while adjusting for the effects of confounders such as age, race, gender and HOME scores.

The residuals of these models require a normal distribution for validity of statistical tests. When residuals are not found to follow a normal distribution, appropriate transformations of the outcome variables will be made. For example, for distributions that are skewed to the right, a log transformation may be appropriate.

To examine categorical (usually dichotomous) outcomes over time, we will use generalized estimating equations (GEE’s). These models are similar to the mixed effects linear models in that they permit the appropriate treatment of observed outcomes within children that are not independent.

To address hypotheses concerning the effectiveness of the exposure intervention measures, the lead exposure measurement data will be thoroughly examined. Statistical approaches to exposure assessment methodology, developed by Dr. Hornung, will be used to evaluate the accuracy of lead exposure estimation and to impute lead levels in the event of missing data. These techniques involve the use of regression models.
and cross-validation approaches. Similar analyses will also be conducted for the other outcomes.

**Sample Size**

Hypothesis:
Children in the Lead Reduction Group will have blood lead levels that are 3.4 $\mu$g/dL (40%) or lower, significantly higher cognitive scores, less hearing loss, greater growth velocity, and fewer behavioral problems than the Control Group at 36 months of age.

We calculated sample size estimates using the most well defined endpoint, cognition. Using our estimated reduction in IQ for children with blood lead concentrations below 10 $\mu$g/dL (1.16 increase in IQ for each unit decrease in blood lead). [See preliminary research, page XX] and a standard deviation of 11.5 (Baghurst 1996, Deitrich 1993, Wasserman 1996, Canfield in press), we have 80% power to detect a 3.4 unit increase in IQ (corresponding to a 40% decrease in Pb) with 181 kids per group. Thus, a sample size of 400 is adequate to this hypothesis.
Changes to Original Research Protocol

We note that some aspects of our original protocol changed in response to logistical considerations, funding constraints, and new follow-up. Specifically:

- We did not measure residential dust lead loadings in dust samples collected after age 2 years.
- We did not administer a hearing screening, A-B task, or DAS test.
- We administered the BSID-II to children at age 3 years.
- We conducted new follow-up of children at ages 4, 5, and 8 years. We administered additional repeated measures of several instruments (e.g., BASC-2) at these visits. We also administered the Wechsler Primary and Preschool Scales of Intelligence-III (WPPSI-III) and Wechsler Intelligence Scale for Children-IV (WISC-IV) at ages 5 and 8 years, respectively. These two tests were done instead of the DAS.
- We did not use the Epsy tasks to assess executive function. Instead, parents completed the Behavior Rating Inventory of Executive Function at ages 3, 4, 5, and 8 years. At ages 5 and 8, we administered the Conner's Continuous Performance Task to assess impulsivity and attention.

Changes to Original Statistical Analysis Plan

- We did not examine blood lead concentrations ≥ 15 or 20 μg/dL because of the very small number of children with blood lead concentrations this high. In addition, the CDC reduced the blood lead concentrations of concern from 10 to 5 μg/dL during the course of this study. Thus, blood lead concentrations ≥2.5 and ≥5 μg/dL were used as our endpoints.
- We used a linear mixed model with a 5-knot restricted cubic polynomial spline for child age to account for the parabolic relation between blood lead concentrations and child age in our exploratory analyses.
- We used linear regression with generalized estimating equations (GEEs) for all analyses testing the effect of the lead-hazard intervention on repeated dust lead loadings, childhood blood lead concentrations, or neurobehavioral outcomes.
Changes to Original Statistical Analysis Plan
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