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The Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) Study

Study Design

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Exposure Measurements & Analysis Branch

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Abstract

The research study, "Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants," (CTEPP) is a pilot-scale project involving about 260 children, which investigates the possible exposures that young children may have to common contaminants in their everyday surroundings. These contaminants include several pesticides, phenols, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, some of which are suspected of being endocrine disrupters. The targeted compounds are persistent in the indoor and sometimes the outdoor environments, so that very low levels may exist in the children's surrounding microenvironments and provide a source of chronic, non-acute exposure. The primary purposes of the research are to increase our understanding of children's exposures to persistent pollutants, to gain information on the various activities, environmental media, and pollutant characteristics that may influence children's exposures, and to generate further questions and hypotheses for future research.

Young children, especially those of the preschool ages 1-5, are hypothesized to have greater exposures than do older children or adults to persistent organic pesticides and other persistent organic pollutants, including some compounds that may have endocrine-disrupting effects or developmental toxicity. These greater exposures may result from what children eat and drink, where they spend their time, and what they do there. The impact of the exposures may be greater on young children because of their smaller body masses, immature body systems, and rapid physical development. Very young children learn about their environment by exploring not only the appearance and texture of objects, but also their taste and smell. Thus nondietary ingestion can play an important role in their exposures.

The Food Quality and Protection Act of 1996 (FQPA) sets new, more stringent standards for pesticide residues in foods, and provides increased emphasis on health protection for infants and children. The exposure component of the risk assessment for pesticides is now required to

- consider the susceptibility of children to increased exposure, and
- account for aggregate exposures to the pesticides from all sources, including food, drinking water, and non-occupational applications of the pesticides in homes, schools, daycare centers, and other microenvironments.

Essentially, the FQPA states that exposure assessments must be conducted for infants and children and that these exposure assessments must include and be reliable for all sources of pesticide exposure. However, very little information on children's aggregate exposures is available at the present time, the methods for obtaining this information need improvement, and the pathways and media through which such exposures may take place are known uncertainly.

Thus, the CTEPP study has direct practical utility to FQPA. It will provide data on aggregate chronic, sub-acute pesticide exposures and pathways for approximately 260 children in several microenvironments, improve the methods for determining their exposures and pathways, and allow generation of hypotheses for further research . The objectives of CTEPP are thus twofold: (1) To measure the total exposures at sub-acute levels of a small set of preschool children in several NC and OH counties to a suite of persistent pesticides and other persistent organic pollutants that they may encounter in their everyday environments, and (2) To apportion the exposure pathways and to identify and formulate the important hypotheses to be tested in future research. Therefore, CTEPP investigates the total exposures to persistent organic compounds in the environment of a group of pre-elementary school children through the ingestion, inhalation, and dermal absorption pathways, in several non-occupational settings, through multiple environmental media. Targeted organic chemical pollutants include polycyclic aromatic hydrocarbons; chlorinated, carbamate, triazine, pyrethroid, and organophosphate pesticides; phthalate esters; phenols; and polychlorinated biphenyls. The specific compounds were selected because they may be carcinogenic, mutagenic, acutely or chronically toxic, or possibly disruptive to the human endocrine system; and because they are widespread and often persistent in the indoor or outdoor environment.

Children who stay at home with an adult caregiver and children who attend preschool or day care are included in the study. Emphasis is on the younger children aged 18 months to 4 years. Exposures of the children and their primary adult caregivers living in the same household are estimated through the collection and analysis of samples of food, beverages, and drinking water; indoor and outdoor air; hand wipes; house dust, classroom dust, and play area soil; and smooth floor and food preparation surface wipes. Urine samples are also collected for analysis for biomarkers of exposure. Children who are not able to provide one or more spot urine samples during the day (who are not at least partially toilet-trained) and children who are still being breast-fed are excluded. Information about the children's activities during the sampling period is collected via activity diaries and food diaries. Approximately 10% of the children are videotaped for 3-4 hr periods during the sampling to supplement and validate the activity diaries and observations. The range of exposures through multiple environmental pathways and media is estimated. Potential external doses are determined through a combination of micro-environmental measurements and time-activity diaries; and insofar as is possible, effective doses are estimated through the analysis of urinary biomarkers. Sample collection in the targeted NC and OH counties will extend over a two-to-three year period.

Outline

III. Introduction
IV. Objectives
    A. Long-Range Objectives
    B. Clients
    C. Hypotheses
    D. Specific Objectives of the Study
V. Approach
    A. Sample Size
    B. Sampling Plan
    C. Sampling, Sampled Media, and Target Chemicals
    D. Analysis Methods
    E. Supporting Information
    F. Human Subjects Approval
    G. Information Collection Request
    H. Quality Assurance
    I. Statistical Analysis of Data
    J. Data Analysis and Model Evaluation and Refinement
    K. Initial Calculation of Exposure, Potential Daily Intake and Potential Daily Dose
    L. Peer Review
    M. Milestones
VI. Personnel and Implementation
VII. Funds
VIII. Selected Outputs
IX. References

Tables

Figures

Appendices

I. Introduction

Young children, especially those of the preschool ages 1-5, are hypothesized to have greater exposures to persistent organic pesticides and other persistent organic pollutants than are older children or adults. These greater exposures may result from what children eat and drink, where they spend their time, and what they do there. The impact of the exposures on children's health may be greater than that on adults' health, as a result of children's smaller body masses, immature body systems, and rapid physical development [P1, V1]. Very young children learn about their environment by exploring not only the appearance and texture of objects, but also their taste and smell. Thus non-dietary ingestion can play an important role in their exposures.

The Food Quality and Protection Act of 1996 (FQPA) sets new, more stringent standards for pesticide residues in foods, and provides increased emphasis on health protection for infants and children. The exposure component of the risk assessment for pesticides is now required to

- consider the susceptibility of children to increased exposure, and
- account for aggregate exposures to the pesticides from all sources, including food, drinking water, and non-occupational applications of the pesticides in homes, schools, daycare centers, and other microenvironments.

Essentially, the FQPA states that exposure assessments must be conducted for infants and children and that these exposure assessments must include and be reliable for all sources of pesticide exposure. However, very little information on children's aggregate exposures is available at the present time, the methods for obtaining this information need improvement, and the pathways and media through which such exposures may take place are known uncertainly.

Thus, the CTEPP study has direct practical utility to FQPA. It will provide data on aggregate chronic, sub-acute pesticide exposures and pathways for approximately 260 children in several microenvironments, improve the methods for determining their exposures and pathways, and allow generation of hypotheses for further research. It will allow improvement of the methods used to obtain physical exposure data, and it will facilitate the identification of the important exposure pathways. The objectives of CTEPP are thus twofold: (1) To measure the total exposures at sub-acute levels of a small set of preschool children in several NC and OH counties to a suite of persistent pesticides and other persistent organic pollutants that they may encounter in their everyday environments, and (2) To apportion the exposure pathways and to identify and formulate the important hypotheses to be tested in future research. Therefore, CTEPP investigates the total exposures to persistent organic compounds in the environment of a group of pre-elementary school children through the ingestion, inhalation, and dermal absorption pathways, in several non-occupational settings, through multiple environmental media. Targeted organic chemical pollutants include polycyclic aromatic hydrocarbons; chlorinated, carbamate, triazine, pyrethroid, and organophosphate pesticides; phthalate esters; phenols; and polychlorinated biphenyls. The specific compounds were selected because they may be carcinogenic, mutagenic, acutely or chronically toxic, or possibly disruptive to the human endocrine system; and because they are widespread and often persistent in the indoor or outdoor environment.

Although studies of young children's exposures to various environmental pollutants have been done in the past, these have been confined largely to studies involving one specific pollutant, for example lead, one environmental source, for example, environmental tobacco smoke (ETS), or to studies involving one pathway or route of exposure, for example, inhalation [O1, O2, R1, W9]. A few small studies have evaluated methods for sampling and analysis to be used in exposure studies, for example, the Household Infant Pesticide Exposure Study (HIPES)

[L1]. To allow management and reduction of the possible risk from a given pollutant or pollutant class, however, it is necessary to know the total exposure to individuals from all environmental media with which they come in contact, through all pathways. This total exposure estimate can then be used to derive an estimate of the potential intake or applied dose of the pollutant, which can in turn be used to estimate the potential health impact on the individual. The pioneering research in the application of such Total Exposure Assessment Methodology (TEAM) was done by Wallace and coworkers in the late 1980s [W9]. The first major TEAM study, of volatile organic compound (VOC) exposures, was completed in 1985. A large prospective study of the exposures of farmers and farm families to agricultural pesticides – the Agricultural Health Study (AHS) – is ongoing, but its focus is not primarily on children, nor does it include families of nonfarmers [A1]. The Minnesota Study [U1], which is a component of the National Human Exposure Assessment Survey (NHEXAS) pilot studies, focuses on children's exposures, but is limited to households with recent pesticide applications and to children ages 3-12. Additionally, the Minnesota study measures total exposures in only 50 households, and to only four target pesticides: chlorpyrifos, diazinon, malathion, and atrazine. It therefore does not include the more persistent pesticides or other persistent industrial chemicals that have been used in the past, such as DDT or PCBs.

However, there are many questionnaire and epidemiologically based studies of children's exposures reported in the literature. Several recent studies have implicated pesticide exposures and exposures to other xenobiotics, for example potential endocrine disrupters, as possible causes of children's health problems [B2, D1, D2, D3, D4, H2, K1, K2, K3, L2, L3, M3, M4, O7, P2, P3, R2, R4, R6, S7, T1, W10, Z1, Z2], and several have estimated the exposures of small numbers of children to specific pesticides [B1, B6, E1, H1, L4, L5, N4, S2, W8].

Over the past four years, Wilson and Chuang, in a series of small methodology studies, have used the TEAM approach to examine the total exposures of preschool children in low-income families to polycyclic aromatic hydrocarbons [C7, C10, C12, W5]. On the basis of their findings, these investigators extended the research to a small study of total exposures of preschool children who attend day care centers to an extended list of target persistent chemicals [W1, W2, W6, W7]. The results of these studies are provocative in that they suggest that young children's exposures to some persistent pollutants may be greater than those of adults who inhabit the same microenvironments, especially when the potential dose, which takes into account a child's body mass, is considered. Additionally, for these sensitive young persons, both dietary and nondietary ingestion appear to be significant pathways for exposure to some compounds. These findings are exemplified in Figures 1 and 2. Figure 1 shows the greater potential dose of polycyclic aromatic hydrocarbons for children than for adults in the same household in a nine-home study [W5]. Figure 2 shows the relative importance of exposures through three major pathways for several classes of persistent chemicals measured in several care centers [W1, W2, W6, W7]. Because of the very small size of these studies (nine participants or fewer) , however, a larger study is needed to confirm these findings with greater confidence.

The survey, recruitment, sampling, and analysis methods, and the associated activity logs and questionnaires that were developed or refined in the above small methodology studies of preschool children's exposures; and the findings of those studies are the initial basis for this expanded pilot study [C1, C2, C3, C8, C9, C11, C14, G1, H3, M1, N1, N5, N7, S1, T2, W12].

The CTEPP study is intended to apply the methods already developed as much as is possible to field measurements of exposures. However, because of the high unit cost of measuring the total exposures of a large number of children, it is possible to include only about 260 children. For this pilot study, a two-frame sampling plan has been developed, which will

allow random sampling of preschool children who attend day care centers and who stay at home. This plan, shown schematically in Figure 3, will produce data that are representative of children in six counties in each of two states, North Carolina and Ohio. However, it is important to note that the results of this pilot study will apply only to the study population of 260 children, and no inferences to larger populations can be made.

The field study is an investigation of the total exposures to persistent organic compounds in the environment of pre-elementary school children through the ingestion, inhalation, and dermal absorption pathways. Targeted organic chemical classes include polycyclic aromatic hydrocarbons; chlorinated, carbamate, triazine, pyrethroid, and organophosphate pesticides; phthalate esters; phenols; and polychlorinated biphenyls. The specific compounds were selected because they are carcinogenic, mutagenic, acutely or chronically toxic, or potentially disruptive to the human endocrine system [C15, C16]; and because they are persistent and often ubiquitous in the environment. Although some of the pesticides, for example the organophosphates, are not generally thought to be persistent, in the absence of sunlight and moisture – in the indoor environment – they degrade slowly if at all, and hence may pose an exposure risk for many years.

Children who stay at home with an adult caregiver and children who attend preschool or day care are included in the study. Emphasis is on the younger children aged 18 months to 4 years. Exposures of the children and their primary adult caregivers living in the same household are estimated through the collection and analysis of samples of food, beverages, and drinking water; indoor and outdoor air; hand and forearm wipes; house dust, classroom dust, and play area soil; and smooth floor and food preparation surface wipes. Urine samples are also collected for analysis for biomarkers of exposure. Children who are not able to provide one or more spot urine samples during the day (who are not at least partially toilet-trained) and children who are still being breast-fed are excluded. Information about the children's activities during the sampling period is collected via activity diaries and food diaries. Approximately 10% of the children are videotaped for 3-4 hr periods during the sampling to supplement and validate the activity diaries and observations. The range of exposures through multiple environmental pathways and media is estimated. Potential external doses are determined through a combination of microenvironmental measurements and time-activity diaries; and insofar as is possible, effective doses are estimated through the analysis of urinary biomarkers. Sample collection in the targeted NC and OH counties will extend over a two-to-three year period.

The expected benefits include a greater understanding of children's total exposures to persistent pesticides, possible endocrine disrupters, and similar pollutants; improved knowledge of the environmental pathways that are most important in young children's exposures; and generation of hypotheses for further research on children's exposures.

CTEPP has direct practical utility in meeting the requirements of the Food Quality and Protection Act (FQPA). The FQPA establishes a more stringent health-based standard for pesticide residues on foods and provides increased emphasis on health protection for infants and children. FQPA allows EPA to establish, modify, leave in effect, or revoke a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if it is determined to be "safe." Safe is defined to mean that "there is a reasonable certainty that no harm will result from aggregate exposures to the pesticide." Risk assessments, including both hazard and exposure assessments, are required to establish "safe." For FQPA the exposure component of the risk assessment is required to

- consider the susceptibility of children to increased exposure, and

- account for aggregate exposures of the pesticide from all sources including food, drinking water, and non-occupational applications of the pesticides in homes, schools, daycare centers, and other microenvironments.

As a part of this process, an additional tenfold margin of safety "shall be applied to account . . . for completeness of the data with respect to exposure." Essentially, the act states that exposure assessments must be conducted for infants and children and that these exposure assessments must be reliable for all sources of pesticide exposure.

The critical exposure data needed with regard to FQPA are given in the EPA draft policy paper, *Exposure Data Requirements for Assessing Risks from Pesticide Exposure of Children* (May, 1999). This document defines the components of a complete data set; it also provides criteria with respect to reliability of the data. The document then describes why the elements of a complete and reliable data set are currently not available. Critical elements that are missing are presented in the document. They were also discussed at a meeting of the EPA Science Advisory Panel on June 25, 1999. Based on both of these sources, the greatest uncertainties in the assessments are associated with exposures to pesticides from non-occupational applications in homes, schools, and daycare centers. This is especially true for assessments for very young children. Critical data gaps are associated with

- location and activity patterns for children,
- pesticide use in microenvironments where children spend their time,
- pesticide distributions in these microenvironments
- factors for estimating exposure from microenvironmental concentrations (that is, hand-to-surface and hand-to-mouth contacts, transfer coefficients for various contacts, time spent in microenvironments, and surface area contacted). For some scenarios, exposure factors are based on data for fewer than 10 children in a single age group or from a single set of laboratory experiments.

II. Objectives

A. Long-Range Objectives

The general objective of this research is to support the mission of the National Exposure Research Laboratory (NERL) to characterize, predict, and diagnose human exposure [N2].

Within this framework, the CTEPP study has two major objectives:

(1) To measure the total exposures of a small set of preschool children, approximately 260 children total, in several NC and OH counties, to sub-acute levels of a suite of persistent pesticides and other persistent organic pollutants that they may encounter in their everyday environments, and

(2) To apportion the exposure pathways and identify the important hypotheses to be tested in future research.

The long-range objectives of this research are thus responsive directly to FQPA requirements, to EPA goals as expressed in the NERL research strategy [N6], which defines several long-term goals related to the Strategic Plan for the Office of Research and Development [O3] and those defined in the EPA Children's Risk Strategy [O4].

Furthermore, this research supports directly the Government Performance and Results Act (GPRA) goals for EPA in the following way:

- ORD Science Sub-Objective #2.2: The research will provide improved tools and data for more quantitative human health risk assessments. It will enhance the scientific basis for identification, characterization, and assessment of exposures that pose the greatest health risks. It will provide information on the exposures of a group of individuals chosen from a susceptible population, preschool children, to persistent organic pollutants in the environment.

Annual performance goals to which this research is relevant include Goal 194, Provide Exposure and Effects Methodologies; and Goal 837, Initiate Field Exposure Study of Children to Two EDCs.

B. Clients

Clients for the results of this research include the EPA Office of Children's Health Protection, and the EPA Office of Prevention, Pesticides, and Toxic Substances. Additionally, the results will complement related research funded by the EPA Office of Research and Development under its Science to Achieve Results (STAR) grants program, the National Institute of Environmental Health Sciences, the EPA National Health and Ecological Effects Research Laboratory (NHEERL), and the Consumer Product Safety Commission (CPSC), the scientific community, and the public, particularly parents and caregivers of young children. Some of the specific ongoing projects to which CTEPP is complementary are, for example, at NIEHS, Dr. Matt Longnecker is looking at persistent organochlorine pesticides and phthalate esters in mothers' blood and the relationship with children's health outcomes; Dr. Jane Hoppin is also examining phthalate esters and their potential effects on the health of young children. The Environmental and Occupational Health Institute at Rutgers University is conducting a nine-subject study of exposures of children to chlorpyrifos after crack and crevice application, "Children's Post-Application Pesticide Pilot Study." Current STAR grants include, among others, "Assessing levels of organophosphate insecticides, which could expose children from pets treated with flea control insecticides," Dr. Janice Chambers et al.; "Exposure of children to pesticide in Yuma County, Arizona," Dr. Mary Kay O'Rourke et al.; and "A study of pesticide exposures in Minnesota children," Dr. Edo Pellizari et al. (Organophosphates only) [U1].

Most importantly, the enhanced knowledge of children's total exposures and the improved exposure measurement methodologies afforded by CTEPP will benefit many young children in addition to the study population.

C. Hypotheses

The main objectives of the CTEPP study, as discussed above, are: (1) To measure the total exposures of a small set of preschool children in several NC and OH counties to chronic, sub-acute levels of a suite of persistent pesticides and other persistent organic pollutants that they may encounter in their everyday environments, and (2) To apportion the exposure pathways and identify the important hypotheses to be tested in future research. There are several hypotheses that can be tested within this group of children using the CTEPP data.

Under main objective (1), total exposure measurement, it is possible to ask the questions:

- Are the targeted children's exposures at home and at day care/preschool equally important?
- Are exposures approximately the same or significantly different for the targeted children in low-income households compared with the targeted children in middle/upper-income households?
- Are exposures approximately the same or significantly different for the targeted urban and rural children?

Under main objective (2), apportionment of exposure pathways, it is possible to ask:

- Are the exposure pathways and their relative importance different for the different chemical classes of persistent pesticides and other persistent organic pollutants?
- Is the ingestion pathway a major pathway for exposure of the targeted adults and preschool children living in the same household?
- Is diet the major contributing factor to the ingestion exposure of this group of children and
- In the sample population, are children's exposures to the targeted pollutants approximately the same or significantly greater than those of the adults living in the same household?

As mentioned previously, these hypotheses can be tested for the subpopulation of approximately 260 children, who reside in the selected counties, and who are the focus of the CTEPP study. The results will <u>not</u> be generalizable to larger populations of children, for example, they will not be generalizable to "all children in NC or in OH (or in the US, for that matter)," or to "all children in low-income and middle-income families," or to "all day care centers," and so on. Neither can they be used to test such hypotheses as "are exposures of NC children the same as or different from those of OH children?"

D. Specific Objectives of This Study

The specific objectives of this study are thus as follows:

- Estimate the total exposures of a group of young, pre-school children to selected persistent organic pesticides and other persistent organic pollutants via all three environmental pathways: ingestion, inhalation, and dermal absorption. Include all environmental media that are likely to provide the opportunity for significant exposures. Through the use of collected data on activity patterns, environmental and biological measurements, and appropriate exposure models, estimate the exposure and potential dose of each of the target chemicals. Compare the

potential doses with actual, biological doses estimated from urinary biomarkers of exposure.

- Obtain comparisons, by stratification of the sampling, between children who stay at home and who attend pre-school or day care, of children in low-income and in middle/upper-income families, and of children in urban and in rural environments. Compare actual dose estimates, obtained from urinary biomarkers measurements, for adults and children in the same households, with potential dose estimates obtained from exposure measurements. Include children in six counties in each of two states: North Carolina and Ohio.
- Apportion the pathways of exposure for the various target chemicals included in this study, using actual, CTEPP-measured, multimedia concentration data and observational and questionnaire data. Identify those microenvironmental media and activities that contribute most to the total exposures.

III. Approach

A. Sample Size

A preliminary estimate of the number of children and households to be sampled was derived from the results of the PAH studies described earlier [W5, W7, C7, C10, C12]. For children in 24 homes, the mean potential dose of B2 PAH (PAH that are probable human carcinogens) was 34 ng/kg-day, with a standard deviation of 24 ng/kg-day. To test whether the potential dose is the same for children in low- and middle/upper income families, a two-sample t test was used, at the 5% significance level. The minimum sample sizes necessary to detect differences in various potential doses of B2 PAH at two statistical powers are shown in **Table I**. At 80% power, with a mean difference in the potential dose of 25%, approximately 126 participants are needed in each of the two groups being compared. An improved estimate of the sample size necessary, based on the results of the day care study [W2, W6, W7, W1], which includes most of the target chemicals in this study led to the results shown in **Table II**, described in the following paragraphs.

To support the sample size calculations, data on children's exposures to persistent organic pollutants (POP) from the PAH studies [C7,C10,C12,W5,W7] and the two day care studies [W1, W2, W6, W7, C13] were reviewed. The review assessed the distribution and variability of POP concentrations in house dust, indoor and outdoor air, solid and liquid food, and soil for seven target POP, namely: B2 PAH, organophosphates, phthalate esters, phenols, diazinon, chlorpyrifos, and bisphenol-A. In addition, the distribution of hydroxy-PAH in urine was reviewed. It was found that

(1) POP concentrations tend to be lognormally distributed.

(2) Although there are differences in the variability of POP concentrations among the six media and in urine, the standard deviations of log-transformed (ln) POP concentrations generally range from 0.50 to 2.0.

(3) Differences in geometric mean POP concentrations between low-income and higher-income families as well as between daycare centers and homes generally range from 0 to 500%, between city and rural areas, they range from 0 to 150%, and between smokers' and non-smokers' homes, they range from 0 to 250% (B2-PAH only), depending on the compound and medium.

Based on the analysis of the historical and current data, the calculations were performed with the following assumptions:

(1) A two-sample t-test was conducted at the 5% significance level on ln-transformed POP to compare the POP exposures in the following groups of children:
   -- low-income families versus middle/upper income families,
   -- at daycare centers versus at home,
   -- inner city versus rural areas,
   -- smokers' homes versus nonsmoker's homes.

   The comparison of POP exposures in smokers' versus non-smokers' homes was performed on B2 PAH only, because only these two groups have data from the PAH exposure studies.

(2) Sample sizes were computed that provide 80 or 90 percent power for detecting a significant difference between the two groups when the actual percent difference ranges from 10 to 200 percent. (The power represents the level of confidence desired to detect a specified difference between the two groups. An experiment

designed to have 90 percent power for detecting a specified difference will be more sensitive than one designed to have 80 percent.)

(3) Sample sizes were computed assuming that the standard deviation of ln-transformed POP concentrations is either 0.5, 1, 1.5, or 2.

Table II summarizes the estimated sample sizes required to detect specific differences between any two groups of children, i.e. low- and middle/upper income children, at-center and at-home children, or inner-city and rural children. For example, to detect a difference between two groups of children if the standard deviation of ln-transformed POP is 1.0 and the actual percent difference between the two groups is 100 percent, roughly 34 children are needed in each group to give 80% power. If the standard deviation of ln-transformed POP is 1.5, the number of children increases to approximately 75 per group.

For all seven target POP concentrations and all six media (floor dust, indoor and outdoor air, solid and liquid food, and soil), the median percent difference in POP concentrations between the two groups of children was 60 percent, and the median standard deviation in ln-transformed POP concentrations was 1.0. As shown in Table II, if the standard deviation in ln-transformed POP concentrations is 1.0 and the actual percent difference between the two groups of children is 50 percent, then a sample size of approximately 100 children per group will provide 80 percent power for detecting a statistical difference in POP exposures between any two groups of children. Under the same conditions, a sample size of approximately 130 children per group provides 90 percent confidence that a statistical difference will be detected between the two groups. To allow for missing samples and other data issues, a sample size of 120 to 160 children per group is recommended.

To test the above hypotheses with maximum power, at least 120 children each from low-income and middle/upper income families (targeted at 80 % power), who will be between the ages of 18 mo and 5 yr at the time of sampling, would participate. Those under age 4 will be preferred. Children must be able to provide spot urine samples during the day, and those who are still being breast-fed will be excluded. Children who attend daycare centers and children who stay at home will be included. They will be monitored at their homes and at the centers. Ideally, the 120+ children in each group (low-and middle/upper income) would be evenly distributed in each subgroup, for example, inner city versus rural, to provide the same power. U.S. Census Bureau definitions of urban and rural will be used. Low-income families are defined as those who meet the qualification criteria for the Women, Infants, and Children program (WIC), i.e., household income not exceeding 185% of the federal poverty level.

If equal numbers of children were selected in each stratification, there would be 128 households in each category, as summarized in **Table III.** The total number of households would be 256. Overall, there would be 128 households in each category: rural, urban, low-income, middle/upper income, at home during the day, and at pre-school or day care during the day. Based on the sample size requirements in **Table II** and an estimated standard deviation of 1.0, 128 children per group would allow detection of a difference of 50% between groups at 90% power, or with a standard deviation of 2.0, detection of a difference of 100% at 80% power.

To obtain a probability-based stratified sample, the sample group of low-income subjects would be smaller than the sample group of middle/upper income subjects; and the rural group would be smaller than the urban group. Extreme oversampling of the low-income or rural groups, however, would induce imbalance in sampling rates and weights and inefficient sampling design. Alternatively, balancing the sizes of the two groups leads to better statistical power for group comparisons. To increase the representativeness of the study, allow intergroup

comparisons, and meet the study objectives, yet stay within the confines of reasonable expenditures of resources, a sampling plan has been developed that takes into account the necessary compromises between the aforementioned conflicting statistical goals.

B. Sampling Plan

The sampling plan that is presented here is expected to accomplish the following:

- Acquire the data that are necessary to meet the major objectives of the CTEPP study regarding total exposure measurement, evaluation and refinement of models, and apportionment of exposure pathways for young children.
- Increase the representativeness of CTEPP by recruiting using two sample frames.
- Maximize the response rates for participation, with a target response rate of 75%.
- Maximize the amount of useful information that can be obtained, while balancing the conflicting demands of representativeness and hypothesis testing, and
- Minimize the total cost of the study, recognizing that the per-child unit costs to measure total exposures are high.

A target sample of 128 children (and associated caregivers) in each state will be obtained. This sample will be balanced evenly between the day care and no day care components. The sampling design will oversample the low-income strata, but sample sizes will still be smaller for the low-income than for the middle/upper income group overall. Sample sizes will also be smaller in the rural than in the urban stratum.

Although every attempt will be made to obtain samples that are truly representative of the populations from which the samples are drawn, there are potential confounders that may limit this representativeness. For example, the no day care component will be drawn from those households that have telephones; this will exclude families that have no phone, which means that the most indigent families, families who have recently moved, migrant workers' families, and others may not be represented. By inclusion of day care centers that serve primarily low-income clients, this limitation will be partially ameliorated. A small degree of self-selection into the day care sample is also possible, if families who receive public assistance are more likely to apply for day care. Because of the difficulty of obtaining physical and biological samples from children who are still breast-fed or who are not toilet-trained, these children will also be underrepresented. Through analysis of the pre-monitoring questionnaire data and related Census data, it should be possible to obtain rough estimates of the fraction of the targeted population who are underrepresented; these estimates can then be used to control for the confounders.

Nevertheless, the information that CTEPP will generate will be tremendously useful in meeting the objectives of the study and in testing the study hypotheses, as discussed earlier.

The proposed sample design provides a compromise in sensitivity between analytical inferences and population-based inferences. This sampling plan is described in detail in Appendix A, and is shown schematically in Figure 3.

C. Sampling, Sampled Media and Targeted Chemicals

As in the small pilot studies, the sampled media will be indoor and outdoor air, house and classroom dust, play area soil, solid and liquid food, drinking water, hand skin surface, and urine. Additional sampling in CTEPP includes hard floor surface wipes and wipes of the most-used food preparation surface, in those households and child care centers where pesticides have been applied in the previous seven days.

Dislodgeable residues using a polyurethane foam (PUF) roller, food preparation surface wipes, and hard floor surface wipes will be collected in those households that have had pesticide

applications indoors or outdoors in the 7 days previous to sampling. Indoor and outdoor air samples will be collected by continuous sampling over 48 hr at 4 L/min, using a URG (University Research Glassware, Chapel Hill NC) sampler with a 10 μm inlet and a cartridge containing a quartz fiber filter and XAD-2 resin and PUF [R3] in series. The soil and dust samples will be obtained at the end of each 48-hr sampling period. Dust samples will be collected in the room that the child uses most, using an HVS3 vacuum sampler (Cascade Stack Sampling Systems, Bend OR) [L1, R3] for carpeted areas or a wipe sample for uncarpeted, hard-surfaced areas. Participants will also be asked to donate a vacuum cleaner bag of floor dust, collected during the month previous to sampling, which will be used for further methods development. Soil samples will be collected by scraping up the top 0.5 cm of soil in an 0.095 m^2 (1 ft^2) area in the middle of the child's play area [L1]. Smooth floor surface wipes will be collected in the area that is pointed out by the teacher or parent as that area where the child is most likely to spend time. Food preparation surface wipe samples will be collected from the most-used food preparation surface. Diet samples will be obtained by the duplicate plate method [N3, F1], collecting duplicate servings of all foods that the child is served over the two-day period. In the post-monitoring visit, the caregiver will be asked to describe the food sample contents and confirm the food diary information. Solid food, liquid food, and drinking water will be collected separately in glass containers to avoid phthalate ester contamination likely with some food storage containers. Handwipe samples, with a gauze pad wetted with 50% isopropanol in water, will be collected prior to participants' washing their hands, just before lunch and just before supper on each of two days [G1]. Urine samples will be approximate 48-hr collections, collected as spot urine samples accumulated over the two-day sampling period. If the household has applied pesticides in the preceding 7 days, the spot urine samples will be analyzed separately. Otherwise, the urine samples will be combined for each 48-hr period. Sampling methods are described in detail elsewhere [W1, W2, W6, W7, C10, C13, T2].

Targeted chemicals include representatives of several compound classes: polycyclic aromatic hydrocarbons; phthalate esters; organochlorine, organophosphate, carbamate, triazine, and pyrethroid pesticides; phenols; acid herbicides; and polychlorinated biphenyls. **Table IV** summarizes the target compounds and the reasons for their selection.

D. Analysis Methods

Methods for chemical analysis of the targeted chemicals in the environmental media of interest were developed previously and are available for use in this research [C10, C12, C13, S4, S5, H3, N5, N7]. These methods are summarized in **Table V**.

E. Supporting Information

Information needed for the interpretation of the chemical results will be collected through survey instruments that were developed and utilized for the small pilot studies [W1, W2, W6, W7, C10, C12, C13], and modified as appropriate for this study. Extensive information on housing characteristics will be obtained, including details on home interior, exterior, location, GPS coordinates, and surrounding areas. Each subject's age, weight, gender, and race or ethnicity will be recorded. The questionnaire includes questions regarding pesticide use, smoking habits, heating, cooking, and cleaning activities, income/education level of the household, and other information relevant to understanding the chemical measures, such as carpet and hard-surface floor area, location of residence and school, size of residence etc. Additionally, an activity log for the child and the adult, a diary of the foods eaten during the sampling period, and food logs or menus for the two weeks preceding sampling will be collected. Because active

children breathe more, eat more, and move around more than those who are passive in a possibly polluted environment, the activity logs will include classification of the level of the child's activity. Approximately 10% of the children will be videotaped for 3-4 hr each during the sampling period to supplement the activity logs. Subsequent videotape analysis and interpretation will be done using published methods, refined as necessary for CTEPP [F1, G2, L6, Z3].

Because the above information may include some sensitive information, or information that could conceivably be used to identify individual subjects, it is necessary to protect the privacy of the participants. A Certificate of Confidentiality has been obtained to protect the information from involuntary release. Additionally, researchers will not disclose any study information that can be associated with individual participants without the participants' consent, and study data will be coded into the data base without individual identifying information.

F. Human Subjects Approval

Collection of urine samples from the children and their caregivers requires human subjects approval, both from EPA and through the Institutional Review Boards (IRB) of participating contractors. These approvals have been obtained.

G. Information Collection Approval

Because this study involves collection of information on more than nine subjects, through the use of questionnaires, activity logs, and food diaries, approval of the Office of Management and Budget (OMB) is required. This review process, known as the Information Collection Request (ICR) under the Paperwork Reduction Act of 1995, will be assisted by the fact that many of the procedures and survey instruments have been field-tested successfully in the pilot studies. The process of obtaining ICR approval was begun in February 1999 by publication of a CTEPP outline in the *Federal Register*. OMB approval of the ICR was given in March 2000.

H. Quality Assurance

A Quality Systems and Implementation Plan (QSIP), which combines the work plan and the quality assurance project plan, has been developed for this study. The requirements for the quality assurance program are stated in EPA Order 5360.1, "Policy and Requirements to Implement the Quality Assurance Program." This order requires that quality assurance becomes an integral part of all data collection activities and is totally integrated into the program, to assure the reliability of environmental measurements and data. Guidance is found in EPA documents EPA QA/R-2 and EPA QA/R-5.

Included in the QSIP are Project Quality Objectives (PQOs) and, for individual target analytes, Data Quality Objectives (DQOs). These will be set before field sampling begins. Preliminary PQOs include the following:

Recruiting

- Eligibility: The initial recruitment activities will screen the eligibility of the study participants. Children who stay at home with an adult caregiver and children who attend preschool or day care are included in the study. Emphasis is on the younger children aged 18 months to 4 years. Children who are not able to provide one or more spot urine samples during the day (who are not at least partially toilet-trained) and children who are still being breast-fed are excluded.
- Response: With intensive recruiting efforts and guaranteed confidentiality, we expect to achieve response rates of about 85% in each of these two stages for the day care sample component. For the random digit-dialing (RDD) sample

component, we anticipate that about 75% of eligible households will participate in the study. A variety of non-monetary and monetary incentives will be used [K4]; we are seeking advice on non-monetary incentives from the department of developmental psychology at the North Carolina State University.

Statistical Power

- Sample Size: Sufficient to detect a 50% difference in POP exposures with a standard deviation of 1.0 at 90% power

Sampling and Analysis

- Standard Operating Procedures (SOPs) are included in the QSIP
- Method Precision: Relative standard deviation ≤ ±25% for urine samples; ±15% for other samples. These are set specifically for different analytes and different media.
- Recoveries: ±80 – 120%
- Limits of Detection (LODs): These are both medium-specific and compound-specific. For PAH, for example, the LODs are 0.03 ng/m^3 in air, 1 ng/g in soil, 0.02 ng/g in food, and 0.017 ng/mL in urine.

I. Statistical Analysis of Data

All the questions that are posed above are amenable to hypothesis testing. Therefore, the data will be analyzed and fitted to distributions, which will be tested for normality. If the distributions are normal, then hypothesis testing will use two-sided t tests (alpha = 0.05). If the data are not distributed normally, then the non-parametric two-sample K-S test will be used on the distributions (alpha = 0.05). Because of the small number of samples involved in individual categories of the stratified design (See Table II), testing will be done on lumped categories, such as low vs high income.

J. Data Analysis

Interpretations that will be sought in the data analysis include all significant relationships among the study variables for the population tested, with emphasis on the stratification variables discussed above. Additionally, interpretive relationships will be sought between the questionnaire data, such as reported pesticide use or parental occupation, and the chemical and physical data acquired. Appendix B provides the CTEPP Data Analysis Plan.

K. Initial Calculation of Exposure, Potential Daily Intake, and Potential Daily Dose

The exposure values (ng/day) for inhalation and ingestion (dietary and nondietary) can be converted to units of maximum potential dose by assuming 100% absorption in the body and normalizing for body mass. Various factors can be found in the literature to account for physical, chemical, and/or physiological processes. For maximum estimates, this conversion gives upper limits on the amount of a pollutant available for delivery to target organs. In subsequent refinement of the exposure estimates, literature absorption factors for the various targeted compounds will be used as they become available.

The potential daily dose of a target compound in ng/kg body mass per day can be estimated using the following equations, which together comprise the most commonly used Microenvironmental Exposure Model (MEM):

$$D_{inh} = \frac{C_i * t_i + C_o * t_o}{t_i + t_o} * \frac{V}{W}$$

$$D_n = \frac{t_i * D_i + t_o * P_o}{t_i + t_o} * \frac{M \times 1000}{W}$$

$$D_d = \frac{C_f * M_f * 1000}{W}$$

where

D_{inh} = the estimated daily dose through inhalation, ng/kg
D_n = the estimated daily dose through nondietary exposure, ng/kg
D_d = the estimated daily dose through dietary exposure, ng/kg
W = the body weight of the subject, kg
C_i = indoor air concentration, ng/m^3
C_o = outdoor air concentration, ng/m^3
t_i = subject's time spent indoors, min
t_o = subject's time spent outdoors, min
V = the estimated subject's daily ventilation rate, m^3
D_i = target compound concentration in the floor dust, µg/g
P_o = target compound concentration in the play area soil, µg/g
M = subject's estimated daily dust/soil intake, g
C_f = target compound concentration in the daily food samples, µg/kg
M_f = the daily mass of food intake, kg

For those target compounds that are likely to be absorbed through the skin surface, an additional increment to the total daily exposure may occur. As a first approximation, this can be estimated as:

$$D_{derm} = M_w \times A_{exp} / A_w \times F_{derm} / W$$

where

D_{derm} = the estimated dose through dermal absorption, ng/day
M_w = the mass of a target compound in the wipe sample, ng
A_{exp} = the exposed skin surface of the subject, m^2
A_w = the area of the skin from which the wipe sample was taken, m^2
F_{derm} = the fraction of the applied compound that can be absorbed through the skin.

Although exposure factors for children and adults are available in the literature for inhalation and soil ingestion [E2, B3, S3], and for dermal absorption of some compounds, there are uncertainties in these factors, which are especially large for the dermal and nondietary ingestion routes of exposure. Some studies in the past have assumed ventilation rates of 20 m^3/day for adults and 15 m^3/day for children [O6, B3]; more recent values are estimated according to the subject's age. Estimated ventilation rates will be based on the EPA Exposure Factors Handbook recommendations [E2], currently 6.8, 8.3, 11.3, and 15.2 m^3/day for children ages 1-2 yr, children ages 3-5 yr, adult females, and adult males, respectively. Dust soil ingestion rates will be based on the values published in the peer-reviewed literature [E2, S3, L1] , currently 0.06 g/day for children and 0.1 g/day for adults. These factors will be used in the initial calculations with the MEM. As better estimates become available, they will be incorporated in the model.

L. Peer Review

Peer review of the study, its implementation, and its outputs is an important part of assuring the relevance, significance, quality, and scientific merit of this research. Internal peer review is a part of each step of the study, including the study design, the combined work plan and quality assurance project plan (QSIP), work assignments/task orders, progress and final reports, and publications. External peer review by a panel of outside experts in the human exposure field was obtained for the study design in January 1999, and the peer reviewers' comments are incorporated in this design. External peer review will be obtained for the resulting publications. Additionally, an external advisory panel of experts in the exposure field will provide feedback on the research at appropriate intervals.

M. Milestones

This research is expected to span a period of four to five years, beginning in FY98, and will occur in several phases. A list of some milestones is given below.

<u>Phase I Milestones – initiated in FY98</u>

- Design a pilot study of children's total exposure to persistent organic pesticides and other persistent organic pollutants that considers all three environmental pathways: ingestion, inhalation, and dermal absorption, and all environmental media that are likely to provide the opportunity for significant exposures.

- Obtain peer review of the study design and develop a Quality Systems Implementation Plan (QSIP), which follows the Quality Integrated Work Plan (QIWP) template that has been developed for the North American Research Strategy on Tropospheric Ozone. This template is available on the Internet at the following location: http://cdiac.esd.ornl.gov/programs/NARSTO/narsto/html. Use of this template ensures that the implementation plan meets the American National Standards Institute (ANSI) E-4 standard. The QIWP is equivalent to the NERL Quality Systems Implementation Plan (QSIP).

- Initiate human subjects review (Institutional Review board, IRB) and EPA human subjects approval.

- Initiate the Information Collection Request (ICR) process with the Office of Management and Budget (OMB).

- Select and modify or improve sampling and analytical methods.

- Develop a communication strategy.

Phase II Milestones – Initiated in FY99

- Obtain ICR approval.

- Obtain human subjects approval.

- Initiate and complete field sampling in six counties in each of two states: North Carolina and Ohio. (No recruiting or field sampling will be conducted during the U.S. Census 2000 period, specifically, March 1, 2000 to June 30, 2000.)

Phase III Milestones – Initiated in FY00

- Analyze samples.

- Interpret the results in the light of the CTEPP objectives.

- Publish the results in one or more peer-reviewed scientific journals.

IV. Personnel and Implementation

Insofar as possible, this research is intended to be an in-house activity of the National Exposure Research Laboratory. The NERL team members who are involved in the study include:

Dr. Nancy K. Wilson, Principal Investigator

Dr. Wilson is a research chemist with extensive experience in the human exposure field, including study design, sampling and analysis, and interpretation of results. She has a B.S. in chemistry from the University of Rochester, and an M.S. and Ph.D. in physical chemistry from Carnegie-Mellon University. *After Dr. Wilson retired Dr. Marsha Morgan becomes the PI and TOPO for the CTEPP study.*

Dr. Marsha Morgan, Staff

Dr. Marsha Morgan was a NERL postdoctoral fellow on the study and became the EPA PI and TOPO for the CTEPP study in September 2000. She has experience in analytical laboratory and field work, as well as in toxicology. She has a B.S. in pre-medicine zoology from Ohio University, a MS in environmental health from East Tennessee State University, and a Ph.D. in environmental toxicology and animal science from Michigan State University.

Gary Evans, Co-Principal Investigator

Mr. Evans is a chemical engineer with extensive experience in exposure measurements and modeling. He will be responsible for many aspects of the questionnaires and activity pattern measurements.

Dr. Robert G. Lewis, Staff

Dr. Lewis is a research chemist with extensive experience in the human exposure field, especially in the methods development and application areas. He has a significant and extensive background in the measurement of pesticides exposure in environmental and human media, including that of young children. Dr. Lewis has a B.S. in chemistry from the University of North Carolina, Chapel Hill, and a Ph.D. in organic chemistry from the University of Wisconsin, Madison.

Thomas R. McCurdy, Staff

Mr. McCurdy is a physical scientist with extensive experience in atmospheric measurement and exposure, with activity patterns, with project management, and with the statistical handling of research data. He has over 15 years of exposure modeling and assessment experience.

Dr. Elaine Cohen-Hubal, Staff

Dr. Hubal is a research chemical engineer with a background in mathematical modeling of environmental and biological systems. She has a B.S. in chemical engineering from MIT and an M.S. and Ph.D. in chemical engineering from North Carolina State University.

Carvin Stevens, Staff, Quality Assurance Overseer

Mr. Stevens is a chemist with wide experience in a variety of areas, including field measurements, chemical analysis, and quality assurance.

Dr. Maurice Berry, Consultant

Dr. Berry is the NERL Program Manager for dietary exposure research. He has a background in dietary exposure measurement, modeling and methods development. He also has experience in numerous multimedia measurements programs and will serve as an advisor and consultant to the project.

Dr. James Quackenboss, Consultant

Dr. Quackenboss is a NERL research scientist with an extensive background in environmental chemistry, mechanisms of exposure, and field measurements of exposure. He will serve as an adviser and consultant to the project.

Professor Amy Halberstadt, Consultant

Dr. Halberstadt is a professor in the field of developmental psychology at the North Carolina State University. She has advised us on several aspects of the child videotaping, and will also advise us on the selection and presentation of non-monetary incentives to day care centers, parents, and children to increase response rates.

Because of the extensive field work that this research will entail, it was anticipated that most of the field work and chemical analysis would be done through extramural contracts. A task order to Battelle Memorial Institute under Contract 68-D99-011 for field and analytical support was awarded in August 1999.

V. Funding

VI. Selected Outputs

#	APG/APM	Product Code	ORD Peer Review	Date	Type, Title, and Lead NERL Author
1	194	X8		7/98	Draft study design, "Children's Total Exposure to Persistent Pesticides and Other Persistent Pollutants," Nancy K. Wilson [COMPLETE]
2	194	X7	4	1/99	Peer input to draft study design, "Children's Total Exposure to Persistent Pesticides and Other Persistent Pollutants," Nancy K. Wilson and Carvin Stevens [COMPLETE]
3	194	X6	4	8/99	Study design, "Children's Total Exposure to Persistent Pesticides and Other Persistent Pollutants," Nancy K. Wilson [COMPLETE]
4	194	X6	4	12/99	QSIP/QIWP, "Children's Total Exposure to Persistent Pesticides and Other Persistent Pollutants," Nancy K. Wilson [COMPLETE]
5	194	X9		3/00	Human subjects approval, "Children's Total Exposure to Persistent Pesticides and Other Persistent Pollutants," Nancy K. Wilson [COMPLETE]
6	194	X9		4/00	OMB approval, "Children's Total Exposure to Persistent Pesticides and Other Persistent Pollutants," Gary Evans [COMPLETE]
7	837	X8		9/99	Protocol for field exposure study of children to two endocrine disrupters, Nancy K. Wilson [COMPLETE. Included in #3 above.]
8	194	C8	4	1/01	Progress Report on Recruitment, To be determined.
9	194	C2	3	6/01	Journal article, "Results of Field Sampling and Chemical Analyses," To be determined.
10	194/New	C8	4	5/02	Report, "Statistical Analysis and Interpretation of Results," To be determined.
11	194	C2	3	12/02	Report/Journal article, "Children's Exposures to Persistent Organic Pollutants," To be determined.

#	APG/APM	Product Code	ORD Peer Review	Date	Type, Title, and Lead NERL Author
12	194	C2	3	12/03	Report/journal article "Children's Exposures to Persistent Organic Pollutants," To be determined.

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Cellulose sponges wet with isopropyl alcohol were used to wipe children's hands, with quantitative removal of chlorpyrifos and pyrethrin. Applicability to 29 other pesticides is suggested, including acid herbicides.

G2 D. Gross, "Issues Related to Validity of Videotaped Observational Data." *Western J. Nursing*, **13**, 658-663 (1991).

A review of strategies for obtaining useful videotaped observational data.

H1 M. Heil, B. Schiller, A. C. Huggett, and F. Haschke, "Toxicological Aspects of Food for Infants and Children." *Monatsschrift Kinderheilkunde*, **144** Suppl. 2, S224-S229 (1996).

The author estimates exposure to pesticide residues in food from food analyses and the estimated diet of a 4-mo old child.

H2 P. T. C. Harrison, P. Holmes, and C. D. N. Humfrey, "Reproductive Health in Humans and Wildlife – Are Adverse Trends Associated with Environmental Chemical Exposure." *Sci. Total Environ*., **205**, 97-106 (1997).

Trends in the incidences of testicular and breast cancer, and concern about reduced semen quality, cryptorchidism, hypospadias, and polycystic ovaries may be associated with endocrine disruptors. Suspected compounds include naturally occurring steroids, phyto- and myco-estrogens, synthetic hormones, organotins, organochlorine pesticides, polychlorinated biphenyls, dioxins, alkylphenols, polyethoxylates, phthalates, and bisphenol-A. However, there is no direct causal evidence in humans.

H3 J. P. Hsu, H. G. Wheeler, Jr., H. J. Schattenberg, III, D. E. Camann, R. G. Lewis, and A. E. Bond. "Analytical Methods for Determining Nonoccupational Exposures to Pesticides," *J. Chromatogr. Sci.* ***26***, 181-189 (1988).

K1 W. R. Kelce and E. M. Wilson, "Environmental Antiandrogens – Developmental Effects, Molecular Mechanisms, and Clinical Implications." *J. Molec. Medicine*., **75**, 198-207 (1997).

A review of the mechanism of toxicity and clinical implications of environmental chemicals that inhibit androgen-mediated sex development. These EDCs include the fungicide vinclozilin and the pesticide DDT and its metabolite DDE.

K2 R. J. Kavlock, G. P. Daston, C. DeRosa, P. Fennercrisp, L. E. Gray, S. Kaattari, G. Lucier, M. Luster, M. J. Mac, C. Maczka, R. Miller, J. Moore, R. Rolland, G. Scott, D. M. Sheehan, T. Sinks, and H. A. Tilson, "Research needs for the risk assessment of health and environmental effects of endocrine disruptors–a report of the U. S. EPA-sponsored workshop." *Environ. Health Perspect*., **104** (Suppl.4), 715-740 (1996).

A review of research needs in endocrine disrupter risk assessment.

K3 W. Karmaus and N. Wolf, "Reduced Birthweight and Length in the Offspring of Females Exposed to PCDFs, PCP, and Lindane." *Environ. Health Perspect*., **103**, 1120-1125.

The newborn infants of 221 teachers who had been exposed to pentachlorophenol (PCP) and lindane in wood panels and chlorinated dibenzo-p-dioxin and chlorinated dibenzofurans in indoor air were compared to the infants of 189 teachers who had not been exposed. The median difference was 175 g birth weight and 2 cm birth length.

The reductions in birth weight and birth length were significant at the $p = 0.04$ and $p = 0.02$ level, respectively.

K4 R. A. Kulka, "The Use of Incentives to Survey 'Hard-to-Reach' Respondents: A Brief Review of Empirical Research and Current Practice." Proceedings of the Seminar on New Directions in Statistical Methodology, Council of Professional Associations on Federal Statistics (COPAFS), Bethesda, MD, May 1994.

L1 R. G. Lewis, R. C. Fortmann, and D. E. Camann, "Evaluation of Methods for the Monitoring of the Potential Exposure of Small Children to Pesticides in the Residential Environment." *Arch. Environ. Contam. Toxicol.*, **26**, 37-46 (1994). HIPES study.

L2 J. K. Leiss and D. A. Savitz, "Home Pesticide Use and Childhood Cancer--A Case-Control Study." *Amer. J. Publ. Health*, **85**, 249-252 (1995).

For 252 child cases and 232 controls, yard treatment was associated with soft tissue sarcomas (odds ratio ~4.0). Home pest strip use was associated with leukemia (OR ~1.7-3.0). The findings suggest that the use of home pesticides is associated with some types of childhood cancer.

L3 M. P. Longnecker, W. J. Rogan, and G. Lucier, "The Human Health Effects of DDT (Dichlorodiphenyltrichloroethane) and PCBs (Polychlorinated Biphenyls) and an Overview of Organochlorine in Public Health." *Ann. Revw. Public Health*, **18**, 211-244 (1997).

Many organochlorines are EDCs in experimental assays. High-level exposures to some OC compounds appear to cause abnormalities of liver function, skin, and the nervous system. Neonatal hypotonia or hyporeflexia has been associated with PCB exposure. Epidemiological data is not convincing that OC compounds cause cancer. However, if animal data is included, a recent risk estimate of 10 (exp-4) per year for chlorinated dioxins and some PCBs has been suggested.

L4 C. Loewenherz, R. A. Fenske, N. J. Simcox, G. Bellamy, and D. Kalman, "Biological Monitoring of Organophosphorus Pesticide Exposure Among Children of Agricultural Workers in Washington State." *Environ. Health Perspect.*, **105**, 1344-1353 (1997).

Children up to 6 yr old who lived with pesticide applicators were monitored for OP pesticide exposure, by measuring the urinary metabolite dimethylthiophosphate (DMTP). Of 88 children, 47% of applicators' children and 27% of non-applicators' children had detectable levels of DMTP. Younger children and those who lived less than 200 feet from an orchard had higher levels.

L5 C. S. Lu and R. A. Fenske, "Air and Surface Chlorpyrifos Residues following Residential Broadcast and Aerosol Pesticide Applications." *Environ. Sci. Technol.*, **32**, 1386-1390 (1998).

Ambient air and surface chlorpyrifos residues were measured for seven days following broadcast (Dursban) and total release aerosol (K-RID) chlorpyrifos applications for flea control in dormitory rooms. Broadcast applications resulted in 7.5 times more total deposited chlorpyrifos on carpets than aerosol applications;

dislodgeable residues on carpets were 2 times greater. Residues on nontarget surfaces such as furniture were 140-150 times greater from aerosol applications than from broadcast applications. However, the estimated total absorbed doses (12-33 μg/kg) were near the no observable effect level (NOEL 30 μg/kg) on the first day, and lower on following days.

L6 A. Lohaus, "The Effect of Videotaping on Preschool and Primary School Children." *Zeitschrift Pedagogische Psychologie,* **1**, 131-140 (1987).

Videotaping improved the performance of 105 children ages 5-11 on tasks requiring convergent and divergent thinking. The results were independent of the children's ages.

M1 L. S. Miller, D. B. Davis, C. S. Preven, J. C. Chuang, J. C. Johnson, J. M. Van Emon, and N. K. Wilson. "Analysis of Soil and Dust Samples for Polychlorinated Biphenyls by ELISA." Presented in the Immunochemistry Summit VI symposium at the national meeting of the American Chemical Society, Las Vegas NV, September 1997.

M3 R. Meinert, P. Kaatsch, U. Kaletsch, F. Krummenauer, A. Meisner, and J. Michaelis, "Childhood Leukemia and Exposure to Pesticides--Results of a Case-Control Study in Northern Germany." *Europ. J. Cancer*, **32A**, 1943-1948 (1996).

For 219 cases of childhood leukemia, there was a significant association with pesticide use in home gardens. Parental agriculture-related exposure was not significant.

M4 D. Mukerjee *et al.*, "Assessment of risk from Multimedia Exposures of Children to Environmental Chemicals." 28th Annual Critical Review*, J. Air & Waste Manage. Assoc.,* **48**, 483-501 (1998).

A review of the adverse effects observed in children associated with exposure to environmental chemicals. Exposure factors and equations for estimating total exposures and potential doses through the various environmental pathways are presented. Extensive references.

N1 M. G. Nishioka and K. D. Andrews, "Method Validation and Application for Semivolatile Organic Compounds in Dust and Soil: Pesticides and PCBs." Final Report, Contract 68-D4-0023, WA 1-08, Task 3. EPA 600/R-97/141 (1997).

N2 National Academy of Sciences, Committee on Risk Assessment of Hazardous Air Pollutants, "Science and Judgment in Risk Assessment." National Academy Press, Washington DC, 1994.

N3 National Academy of Sciences, "Pesticides in the Diets of Infants and Children." National Academy Press, Washington DC, 1993.

N4 Nonoccupational Pesticide Exposure Study (NOPES), Final Report, Atmospheric Research and Exposure Assessment Laboratory, U. S. Environmental Protection Agency, Research Triangle Park NC, 1990. EPA/600/3-90/003.

N5 M. G. Nishioka, H. M. Burkholder, M. C. Brinkman, S. M. Gordon, and R. G. Lewis, "Measuring Transport of Lawn-Applied Herbicide Acids from Turf to Home--Correlation of Dislodgeable Turf Residues with Carpet Distribution and Carpet Surface Residues." *Environ. Sci. Technol.*, **30**, 3313-3320 (1996).
A study of the track-in of 2,4-D and dicamba from lawn pesticide applications.

N6 National Exposure Research Laboratory, Research Strategy, 1997 draft.

N7 *Development of Analytical Methods for Lawn-Applied Pesticides in House Dust*, Report No. 600/R-97/110, US Environmental Protection Agency, Research Triangle Park, NC, November 1997.

N8 M. C. Brinkman, J. E. Sawchuk, and S. M. Gordon. "Sample Management and Reporting of Results Using Database Software." Presented at the 7th Annual Meeting of the International Society of Exposure Analysis, Research Triangle Park, North Carolina, November 1997.

O1 W. R. Ott, "Human Exposure Assessment: The Birth of a New Science." *J. Expos. Anal. Environ. Epidem.*, **5**, 449-472 (1995).

O2 W. R. Ott and J. W. Roberts, "Everyday Exposure to Toxic Pollutants." *Scientific American*, February 1998, pp. 86-91.

O3 Office of Research and Development, Strategic Plan, U. S. Environmental Protection Agency, EPA/600/R-96/059, May 1996; updated 1997, EPA/600/R-97/015.

O4 Office of Research and Development, U. S. Environmental Protection Agency, Children's Risk Strategy, draft document, June 1997.

O5 M. O'Malley, "Clinical Evaluation of Pesticide Exposure and Poisoning." *Lancet*, **349**, 1161-1166 (1997).
Pesticide exposure effects range from skin irritation, acute toxicity to complex systemic illness as a result of cholinesterase inhibition, e.g. from OP exposure. Possible links to asthma from exposure to OP pesticide contaminants.

O6 ORETG, Occupational and Residential Exposure Test Guidelines (1994, 1997). U.S. Environmental Protection Agency Office of Prevention, Pesticides, and Toxic Substances, Washington, DC, Series 875.

O7 N. Olea, P. Pazos, and J. Exposito, "Inadvertent Exposure to Xenoestrogens." *Eur. J. Cancer Prevention*, **7**, Suppl 1, S17-S23 (1998).
Defines endocrine disruptor (EDC) as an exogenous substance that causes adverse health effects in an intact organism or its progeny, secondary to changes in endocrine function. The following anthropogenic compounds are identified as EDCs: o,p-DDT, kepone, methoxychlor, phenolic derivatives, and PCBs. Also toxaphene, dieldrin, endosulfan, t-butylhydroxyanisole, benzylbutylphthalate, 4-hydroxy alkyl

phenols, and bisphenol-A. However, evidence for ED by these compounds in humans is meager or nonexistent.

O8 W. R. Ott, *Environmental Statistics and Data Analysis*, CRC Press, Boca Raton, FL, 1995.

P1 F. D. Perera, "Environment and Cancer: Who Are Susceptible?" *Science*, **278**, 1068-1073 (1977).

Physiological factors associated with the decreased detoxification capability, DNA repair, and immune function in the elderly and in the very young make these groups more susceptible to environmental insults. There is a hormonal association with deregulation of growth and differentiation through receptor binding.

P2 J. M. Pogoda and S. Preston-Martin, "Household Pesticides and Risk of Pediatric Brain Tumors." *Environ. Health Perspect.*, **105**, 1214-1220 (1997).

An investigation of the risk of household pesticide use from pregnancy to diagnosis in mothers of 224 children with brain tumors and 218 controls. Risk was significantly elevated for prenatal exposure to flea/tick pesticides (OR 1.7). Sprays and foggers were the only products significantly related to risk (OR 10.8). Elevated risk was not observed for termite or lice treatments, pesticides for nuisance pests, or yard and garden insecticides, fungicides, herbicides, or snail killer.

P3 F. D. Perera, R. M. Wyatt, W. Jedrychowski, V. Rauh, D. Manchester, R. M. Santella, and R. Ottman, "Recent Developments in Molecular Epidemiology – Study of the Effects of Environmental Polycyclic Aromatic Hydrocarbons on Birth Outcomes in Poland." *Amer. J. Epidem.*, **147**, 309-314 (1998).

Biomarkers of PAH exposure (DNA adducts) and physical characteristics of newborns from a heavily industrialized city and a rural town in which coal heating is predominant were compared. Infants with high levels of DNA adducts had significantly decreased birth weight, length, and head circumference. Cotinine (a marker for environmental tobacco smoke exposure) was also significantly associated with decreased birth weight and length.

R1 J. W. Roberts and P. Dickey, "Exposure of Children to Pollutants in House Dust and Indoor Air." *Rev. Environ. Contam. Toxicol.*, **143**, 59-78 (1995).

R2 D. C. Rice, "Neurotoxicity Produced by Developmental Exposure to PCBs." *Mental Retardation Developmental Disabilities Res.*, **3**, 223-229 (1997).

Prospective studies suggest decreased reflexes, retarded psychomotor development in early childhood associated with PCB exposure. Decreased IQ and reading ability were evidenced at age 11. Animal models reveal changes in activity and cognitive function with developmental exposures to PCBs.

R3 J. W. Roberts, W. T. Budd, M. G. Ruby, A. E. Bond, R. G. Lewis, R. W. Wiener, and D. E. Camann, "Development and Field Testing of a High Volume Sampler for

Pesticides and Toxics in Dust." *J. Expos. Anal. Environ. Epidem.* **1**, 143-155 (1991), ASTM Standard Practice D 5438

R4 N. C. Rawlings, S. J. Cook, and D. Waldbillig, "Effects of the Pesticides Carbofuran, Chlorpyrifos, Dimethoate, Lindane, Triallate, Trifluralin, 2,4-D, and Pentachlorophenol on the Metabolic Endocrine and Reproductive Endocrine System in Ewes." *J. Toxicol. Environ. Health,* **54**, 21-36 (1998).

Carbofuran caused a significant increase in serum concentrations of thyroxine, the major secretory product of the thyroid and a principal regulator of metabolism; all other pesticides except trifluralin caused a decrease in thyroxine. Serum concentrations of cortisol were increased by trifluralin and chlorpyrifos. Insulin concentrations were increased by dimethoate, lindane, trifluralin, triallate, and pentachlorophenol. Estradiol concentrations were increased by lindane and trifluralin. Luteinizing hormone (LH) was decreased by trifluralin, lindane, and dimethoate, but increased by triallate. Pentachlorophenol and triallate caused increased severity of oviductal intraepithelial cysts.

R5 R. A. Rudel, S. J. Melly, P. W. Geno, G. Sun, and J. G. Brody, "Identification of Alkylphenols and Other Estrogenic Phenolic compounds in Wastewater, Septage, and Groundwater on Cape Cod, Massachusetts." *Environ. Sci. Technol.,* **32**, 861-869 (1998).

The potential EDCs nonylphenol, octylphenol, and their ethoxylates, bisphenol-A, nonylphenol, and phenylphenol were analyzed in wastewater, septic effluent, and wells. Nonylphenol was detected in all septage samples. Phenylphenol and bisphenol-A were detected in septage and wastewater. Bisphenol-A and some ethoxylates were detected in several drinking water wells.

R6 J. R. Reigart *et al.*, "Report of the Children's Health Protection Advisory Committee to the U. S. Environmental Protection Agency Regarding the Selection of Five Regulations for Re-Evaluation," Children's Health Advisory Committee, May 28, 1998.

The committee recommends re-evaluation of five regulations in the light of recent data and the fact that protection of children was not adequately considered in the original regulations. The five regulations are Mercury, Farm Worker Protection Standard, Triazine Pesticides, Organophosphates and Carbamates, and Air Quality and Asthma. Of the triazines, atrazine is identified specifically because of its carcinogenicity and potential for causing hormonal developmental effects, and because it has been detected in drinking water throughout the Midwest and other parts of the nation. Of the organophosphates and carbamates, methyl parathion, dimethoate, and chlorpyrifos are identified specifically because they represent the bulk of the dietary risk of neurotoxicity.

S1 D. B. Shealy, M. A. Bonin, J. V. Wooten, D. L. Ashley, L.L. Needham, and A. E. Bond, "Application of an Improved Method for the Analysis of Pesticides and their Metabolites in the Urine of Farmer Applicators and their Families." *Environ. Int.*, **22**, 661-665 (1996).

S2 N. J. Simcox, R. A. Fenske, S. A. Wolz, I. C. Lee, and D. A. Kalman, "Pesticides in Household Dust and Soil--Exposure Pathways for Children of Agricultural Families." *Environ. Health Perspect.*, **103**, 1126-1134 (1995).

OP pesticides were higher in dust in farm homes than in non-farm homes for 59 residences in WA. Tested pesticides included azinphosmethyl, chlorpyrifos, parathion, and phosmet. Dust concentrations were greater than soil concentrations.

S3 E. J. Stanek, III and E. J. Calabrese, *Human and Ecological Risk Assessment*, **1**, 133 (1995).

S4 L. S. Sheldon, J. Keever, J. Beech, J. M. Roberds, and P. Gross, "Manual of Analytical Methods for Determination of Selected Environmental Contaminants in Composite Food Samples." Final Report, Contract 68-C2-0103, U.S. Environmental Protection Agency, Cincinnati, OH.

S5 L. S. Sheldon, J. T. Keever, J. M. Roberds, J. B. Beach, and J. N. Morgan, "Methods for Measuring Base/Neutral and Carbamate Pesticides in Composite Dietary Samples." *J. Expos. Anal. Environ. Epidem.*, **7,** 37-60 (1997).

S6 M. D. Shelby, R. R. Newbold, D. B. Tully, K. Chae, and V. L. Davis, "Assessing Environmental Chemicals for Estrogenicity Using a Combination of *in vitro* and *in vivo* Assays." *Environ. Health Perspect.*, **104**, 1296-1300 (1996).

Suspected or known EDCs studied include 17-beta-estradiol, diethylstilbestrol, tamoxifen, 4-hydroxytamoxifen, methoxychlor, the methoxychlor metabolite 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE), endosulfan, nonylphenol, o,p'-DDT, and kepone.

S7 J. D. Sherman, "Chlorpyrifos (Dursban)-Associated Birth Defects: A Proposed Syndrome, Report of Four Cases, and Discussion of the Toxicology." *Int. J. Occup. Med. Toxicol.,* **4**, 417-431 (1995).

It is suggested that four cases of unusual birth defects are associated with maternal exposure to Dursban.

T1 R. D. Thomas, "Age-Specific Carcinogenesis–Environmental Exposure and Susceptibility." *Environ. Health Perspect.*, **103**, 45-48 (1995).

Emphasizes the importance of dietary exposure of children relative to cancer risk.

T2 K. W. Thomas, L. S. Sheldon, E. D. Pellizzari, R. W. Handy, J. M.. Roberds, and M. R. Berry, "Testing Duplicate Diet Sample Collection Methods for Measuring Personal Dietary Exposures to Chemical Contaminants." *J. Expos. Anal. Environ. Epidem.*, **7**, 17-36 (1997).

U1 U. S. Environmental Protection Agency, *Proceedings of the Science to Achieve Results (STAR) Program Workshop on Children's Exposure to Pesticides*, Washington, DC, April 1998.

U2 U. S. EPA Standard Operation Procedures (SOPs) for Residential Exposure Assessments, Draft, Contract 68-D4-W6-0030, Work Assignment 3385.102, Versar, Inc., prepared for the Residential Exposure Assessment Work Group, Office of Pesticide Programs, Health Effects Division, Washington, DC, July 1997.

V1 T. Vial, B. Nicolas, and F. Descotes, "Clinical Immunotoxicity of Pesticides." *J. Toxicol. Environ. Health*, **48**, 215-229 (1996).
Author suggests potential risk, especially during chronic exposure or to immunocompromised persons such as those who are old, malnourished or young, but evidence is scarce.

W1 N. K. Wilson, J. C. Chuang, and C. Lyu, "Multimedia Concentrations of PAH in Several Day Care Centers." *Polycyclic Aromatic Compounds,* in press (1999).

W2 N. K. Wilson, J. C. Chuang, and C. Lyu, "Exposures of Nine Children Who Attend Day Care to Persistent Pesticides and Other Organic Pollutants." *J. Expos. Anal. Environ. Epidem.* (1999), to be submitted for publication.

W3 N. K. Wilson, J. C. Chuang, and M. R. Kuhlman, "Sampling Polycyclic Aromatic Hydrocarbons and Other Semivolatile Organic Compounds in Indoor Air." *Indoor Air,* **4**, 513-521 (1991).

W4 N. K. Wilson and J. C. Chuang, "Indoor Levels of PAH and Related Compounds in an Eight-Home Pilot Study." In M. J. Cooke, K. Loening, and J. Merritt, Eds., *Polynuclear Aromatic Hydrocarbons: Measurements, Means, and Metabolism*, Battelle Press, Columbus OH, 1991, pp. 1037-1052.

W5 N. K. Wilson, J. C. Chuang, and C. Lyu, "Evaluation of Field Methods for Estimating Exposure of Children in Low-Income Families to Polycyclic Aromatic Hydrocarbons." *Measurement of Toxic and Related Air Pollutants: Proceedings of the 1996 EPA/AWMA International Symposium*, Pub. VIP-64, AWMA, Pittsburgh PA, 1996, pp. 797-802.

W6 N. K. Wilson, J. C. Chuang, and C. Lyu, "Measurements of Persistent Organic Chemicals in Several Day Care Centers." Presented at the 1997 annual meeting of the International Society of Exposure Analysis, Research Triangle Park NC, November 1997.

W7 N. K. Wilson, J. C. Chuang, and C. Lyu, "Multimedia Microenvironmental Concentrations of PAH in Day Care Centers." Presented at the 16th International Symposium on Polycyclic Aromatic Compounds, Charlotte NC, November 1997.

W8 R. W. Whitmore, F. W. Immerman, D. E. Camaan, A. E. Bond, and R. G. Lewis, "Nonoccupational Exposure to Pesticides for Residents of Two U. S. Cities." *Arch. Environ. Contam. Toxicol.*, **26**, 47-59 (1994).

W9 L. A. Wallace, "Human Exposure to Environmental Pollutants: A Decade of Experience." *Clin. Exper. Allergy*, **25**, 4-9 (1995).

W10 B. Weiss, "Pesticides as a Source of Developmental Disabilities." *Mental Retardation Developmental Disabilities Res.*, **3**, 246-257 (1997).

Organochlorine pesticides have been linked with developmental neurotoxicity; the evidence for organophosphate pesticides is ambiguous.

W11 N. K. Wilson, J. C. Chuang, and C. Lyu, "Persistent Pesticides and Other Organic Pollutants in Multiple Environmental Media in Nine Day Care Centers." Journal article to be submitted for publication.

W12 R. S. Whiton, C. Witherspoon, and T. J. Buckley, "A Modified HPLC Method for Determination of Polycyclic Aromatic Hydrocarbon Metabolites in Human Urine." *J. Chromatog.*, **B 665**, 390-394 (1995).

Z1 S. H. Zahm and S. S. Devesa, "Childhood Cancer--Overview of Incidence, Trends, and Environmental Carcinogens." *Environ. Health Perspect.*, **103**, 177-184 (1995).

8000 child cancer occur annually in the US. There is a well-established link with one EDC (diethylstilbestrol). Some pesticides are possibly EDCs and some data suggest higher susceptibility in children.

Z2 S. H. Zahm and M. H. Ward, "Pesticides and Childhood Cancer," *Environ. Health Perspect.*, in press (1998). Presented at the U. S. Environmental Protection Agency Conference on Avoidable Causes of Childhood Cancer, Arlington VA, September 1997.

Z3 V. G. Zartarian, J. Streicker, A. Rivera, C. S. Cornejo, S. Molina, O. F. Valadez, and J. O. Leckie, "A Pilot Study to Collect Micro-Activity Data of Two- to Four-Year-Old Farm Labor Children in Salinas Valley, California." *J. Expos. Anal. Environ. Epidem.*, **5**, 21-34 (1995).

Methods were developed to videotape activity patterns of children. Four children in farm labor families were studied. Questionnaires the day after taping and comparison with the videos tested the hypothesis that recall is inadequate for specifying children's activity patterns. However, the presence of the observers did alter the children's behaviors to some extent.

Appendix A

Data Analysis and Modeling

In the CTEPP study, multiple persistent organic pollutants (POP) in multiple chemical classes, including pesticides, will be measured in multiple environmental media. Separate chemical analyses will be carried out for each target compound in each environmental medium. In some cases comparisons across target compounds and compound classes will be carried out, for example to determine whether or not the relative exposure distribution across pathways is consistent across compounds.

I. Design

The CTEPP design is a probability-based, stratified sample. Stratification will be performed at the various sampling stages for the two sample components, the day care sample and the telephone sample. These two sample components will be selected independently in the primary strata defined by state (NC and OH). Additional first-stage stratification will be urban and rural area classification performed at the county level. At subsequent sampling stages, the sample will be also stratified by income levels: low income versus middle/upper income.

However, the main analysis groups (or domains) need to be distinguished from design strata. Key study estimates will be computed for groups defined by:

- Children in urban versus children in rural households
- Children in low-income versus children in middle/upper income households
- Children who attend day care versus children who do not

Whenever possible, comparisons will also be made across these groups. For example, we will compare the exposure of urban and rural children, and similarly, of low- and middle/upper-income children. However, we will *not* compare finer cross-classes such as:

- urban low-income versus urban middle/upper-income, or
- low-income day care versus low-income home care children, or
- income subgroups of the day care component.

It should also be qualified that the small study sample sizes will not support definitive comparisons about different subgroup exposures.

Nevertheless, the multivariate regression modeling approach will adjust for potential effects of these covariates while estimating the effects of each independent variable. The independent variables for these models will include each of these dimensions (as dummy two-level variables).

A target sample of 128 children and associated caregivers in each state will be obtained. This sample will be balanced evenly between the day care and no day care components. The sampling design will over-sample the low-income strata, but sample sizes will still be smaller for the low-income than for the middle/upper-income group overall. Sample sizes will also be smaller in the rural than in the urban stratum.

The sample design provides a compromise in sensitivity between analytical inferences and population-based inferences. On one hand, a more representative sample provides more nearly proportional representation of these groups rather than equal representation. Proportional representation would be more appropriate if the analytic goals were restricted to population-

based inferences. On the other hand, equal group sample sizes maximize the power of group comparisons, an important element of analytical inferences.

Similar trade-offs arise in the weighting procedures, briefly discussed in Section 4.2, and in the use of weights in the analyses. For the model-based analyses, weights will not be necessary, especially when aggregating sample components where survey weights may exhibit high variability.

2. Analysis Objectives

2.1 Total exposure estimates

The first major objective of the CTEPP study is to measure the total exposures of the study subjects to a suite of persistent pesticides and other persistent organic pollutants (POP). We will characterize children's total exposures to POP and their urinary biomarker concentrations within the individual strata and compare exposures and biomarker concentrations across strata. One factor at a time comparisons, averaged across all other factors, will be carried out. No comparison between the two states will be performed.

These comparisons will include, for example:

- Urban versus rural
- Day care versus no day care
- Low income versus middle/upper income
- Children versus adults in the same household

2.2 Exposure pathway component analyses

Another major objective of the CTEPP study is to apportion exposure pathways and identify the important media where exposure can occur. The major component exposure pathways are inhalation, dietary ingestion, non-dietary ingestion, and dermal absorption. We will compare the components of exposure across the major pathways, averaging across all the stratification factors. Examples of such comparisons include:

- Ingestion - Dietary versus all others. We will determine the proportion of total exposure attributable to diet (food, beverage, and drinking water).
- Dietary ingestion versus non-dietary ingestion
- Comparisons of percentage distribution of exposure by pathway across the target compounds to be monitored

We will also study how the various exposure pathway components differ across the key subpopulations. Examples of such analyses include:

- Percentage of exposure by pathway between low income and middle/upper income children
- Percentages of exposure by pathway between
  - Urban and rural – Day care and home care
  - Children and adults residing in the same household.

The survey is designed to facilitate the realization of these analysis objectives.

3. Calculation of Daily Potential Exposure

The exposure concentrations in the various media, along with activity patterns, dietary patterns, and various physiological and body size parameters will be combined using the EPA microenvironmental exposure model (MEM) [E2, EPA Exposure Factors Handbook, 1996] to

derive estimates of daily exposures through the various pathways: inhalation, dietary and nondietary ingestion, and dermal absorption. The EPA microenvironmental exposure model is displayed below.

The microenvironmental exposure model converts exposure values (ng/day) for inhalation and ingestion (dietary and nondietary) to units of maximum potential (internal) dose by assuming 100% absorption in the lung and digestive tract and normalizing for body mass. Various factors can be found in the literature to account for physical, chemical, and/or physiological processes. For maximum estimates, this conversion gives upper limits on the amount of a pollutant available for delivery to target organs. In subsequent refinement of the exposure estimates, literature absorption factors for the targeted compounds will be used as they become available.

The MEM estimates potential daily dose of a target compound in ng/kg body mass per day using the following equations:

$$D_{inh} = \frac{C_i * t_i + C_o * t_o}{t_i + t_o} * \frac{V}{W}$$

$$D_n = \frac{t_i * D_i + t_o * P_o}{t_i + t_o} * \frac{M \times 1000}{W}$$

$$D_d = \frac{C_f * M_f * 1000}{W}$$

where

D_{inh} = the estimated daily dose through inhalation, ng/kg
D_n = the estimated daily dose through nondietary exposure, ng/kg
D_d = the estimated daily dose through dietary exposure, ng/kg
W = the body weight of the subject, kg
C_i = indoor air concentration, ng/m^3
C_o = outdoor air concentration, ng/m^3
t_i = subject's time spent indoors, min
t_o = subject's time spent outdoors, min
V = the estimated subject's daily ventilation rate, 20 or 15 m^3
D_i = target compound concentration in the floor dust, µg/g
P_o = target compound concentration in the play area soil, µg/g
M = subject's estimated daily dust/soil intake, 0.06 or 0.1 g
C_f = target compound concentration in the daily food samples, µg/kg
M_f = the daily mass of food intake, kg

For those target compounds that are likely to be absorbed through the skin surface, an additional increment to the total daily exposure may occur. As a first approximation, this can be estimated as:

$$D_{derm} = M_w \times (A_{exp} / A_w) \times (F_{derm} / W)$$

where

D_{derm} = the estimated dose through dermal absorption, ng/day
M_w = the mass of a target compound in the wipe sample, ng
A_{exp} = the exposed skin surface of the subject, m^2
A_w = the area of the skin from which the wipe sample was taken, m^2
F_{derm} = the fraction of the compound that can be absorbed through the skin.

Although exposure factors for children and adults are available in the literature for inhalation and soil ingestion, and for dermal absorption of some compounds, there are uncertainties in these factors, which are especially large for the dermal and nondietary ingestion routes of exposure. It is commonly assumed that the ventilation rate is 20 m^3/day for adults and 15 m^3/day for children, and that the dust/soil ingestion rate is 0.06 g/day for adults and 0.1 g/day for children (EPA, *ibid.*). These factors will be used in the initial model. As refined estimates become available, they will be incorporated in the model.

The results of applying the potential daily dose model discussed above, and also in the study design, will be a vector of estimated daily component intake doses (ng/kg) for each subject via inhalation, dietary ingestion, nondietary ingestion, and dermal absorption. The overall daily total dose is the sum of these component doses.

All of the target pollutant concentrations in multiple sample media (air, dust, soil, food, and wipe), activity patterns, food and beverage intake profiles, and physiological parameters specified in the microenvironmental exposure model will be determined for each child in the study. Thus the comparisons of the children's total potential doses or component potential doses across pathways or across strata will be carried out based on the totality of pathways considered in the microenvironmental exposure model, namely inhalation of indoor and outdoor air, non-dietary ingestion from dust and soil through hand-to-mouth activity, dietary exposure, and dermal exposure through contact with the floor or other surfaces.

The comparisons of potential dose between children and their caregivers will also be addressed. In the households where the adult caregivers stay at home with the children (half the adults sampled, about 128), virtually the same suite of measurements and characteristics will be determined for the adults as for the children. This includes the target pollutant concentrations determined in the various media, food and beverage profile diaries, and urine biomarkers. The determinations for the caregivers are made with the same frequency and at the same times of day as for the children. The only difference in data collection is that activity profiles for the children are recorded in activity diaries, whereas those for adults are assessed in post-monitoring interviews. In the households where the child attends day care and the caregiver works outside the home during the day, the caregivers' activities, exposure, diet, and urine biomarkers are measured when the caregivers are at home, but not during the portion of the day when they are at work. The daily exposure information must thus be interpreted as the portion of exposure that can be attributed to the residential environment.

Therefore comparisons between exposures to children and their caregivers will be made separately within the day care and stay-at-home strata. The comparisons can be made based on the full set of media-specific responses, but for those adults who work outside the home, their exposures are interpreted as the residential component.

4. Data Analysis

The principal data analyses to satisfy the primary and secondary objectives will be based on the microenvironmental model-derived total daily intake dose and its component pathway doses. These analyses will be discussed below. It should be noted that this discussion does not imply that these will be the only uses of the data. It is very likely that the data will be used for many additional analysis purposes and to develop, refine, and evaluate additional mechanistic exposure and dose models. If it is found that the nature of the statistical comparisons differs from one state to the other, separate comparisons will be done by state. Note that no state-to-state comparisons will be performed.

4.1 Preliminary Analysis. Distributional Assumptions and Outlier Testing

The four microenvironmental model-based, component-specific intake (potential) doses and the corresponding total intake dose for each child will be organized into a multi-factorial structure, each factor corresponding to a stratification factor at two levels. The models may include other important variables that will be measured for children and households in the study. These variables can be selected based on a step-wise regression procedure. Distributional assumptions will be made and outlier detection procedures will be carried out separately for each of the estimated component doses and for the total dose.

-- Distributional Assumptions. Test for Normality. Most environmental pollutant concentrations, including POP concentrations, have been reported in the literature to conform to lognormal distribution models [Ott, *Environmental Statistics and Data Analysis*, CRC Press, 1995]. Consequently goodness-of-fit of the derived pathway-specific component doses and the external total dose to the lognormal distribution will be assessed. For each target compound and for each response we will calculate the (natural) logarithm of the dose and fit a fully saturated, homogeneous variance analysis of variance model to this data matrix, modeling all main effects and all interactions. This corresponds to making a simple mean value correction within each cell. If no compound is detected for a component concentration, we will set the concentration equal to half the detection limit and proceed as if it is a measured value. For purposes of this

preliminary analysis, all responses will be treated as if they were independent. Studentized residuals (i.e., residual divided by the standard error of the residual) will be calculated based on the analysis of variance fit. The studentized residuals will be plotted on a normal probability scale to assess conformance to a normal distribution model. Goodness-of-fit tests for normality will be carried out using the Wilk-Shapiro (W) test. When applied to large amounts of data, goodness-of-fit tests can be very sensitive to minor departures from distributional assumptions. If the test for normality is not significant ($p>0.05$), we will accept the normality assumption and conduct further analyses based on a lognormal distributional model. If the normality test is significant ($p\leq 0.05$) we will assess the shape of the normal probability plot to see if the departures from straight-line behavior are minor or substantial. Sometimes one or more apparent outliers can result in significant departures from normality based on the goodness-of-fit test. Thus we will identify all studentized residuals in excess of three in absolute value. If one or more are isolated values, that is, they are removed from their nearest neighbors, we will treat them as tentative outliers. By contrast, if the entire probability plot departs from straight-line behavior, it will be treated as a departure from normal distributional assumptions. In the latter case we will assess the assumption of constant variance by use of Levene's test on the absolute residuals. If appropriate we will relax the assumption of homogeneous variance and will refit the analysis of variance model.

If the departure from normality can be explained by one or a small number of outliers or by heterogeneous variances then we will adopt a normal distribution model in the logarithmic transforms of the responses. Otherwise subsequent tests of hypotheses will be carried out based on a rank transformation of the responses.

-- Outlier Detection. All studentized residuals in excess of three in absolute value will be considered to be tentative outliers. The concentration values or activity or physiological parameter values contributing to these extreme values will be reviewed in the basic data records for correctness. If errors are found, they will either be corrected or the outlier will be deleted. If no errors are found, the extreme responses will be considered to be natural variation and will be retained in the data set.

4.2 Survey Weights and Weight Adjustments

Most of the statistical analyses will use weighted survey data. As pointed out in Section 1 of this appendix, however, unweighted data will be used for the model development and validation parts of the analyses directed at analytical, model-based inferences rather than population-based inferences.

Survey weights will account for unequal sampling probabilities and reduce potential biases due to nonresponse. Sampling weights are needed for unbiased estimation under the sampling design. Nonresponse adjustments will force estimates based on participating children, for key characteristics, to match those of the entire sample or the entire universe of eligible children.

The first step in weighting the data is the computation of sampling weights that account for the varying probabilities of selection for different subgroups of children. Sampling weights will be computed separately for the two sample components (or frames). In each component, the probabilities of selection will be unequal due to stratification and disproportionate sampling (i.e., oversampling of certain strata). In addition, the day care sample weights may also need to reflect selection with probabilities proportional to size (PPS), a method that may be used for the first-stage sample of centers. Sampling weights will be computed as the reciprocal of the probabilities

of selection at each sampling stage, and assigned to sample day care centers and children. The weights assigned to participating children will also be assigned to their parents and households. These weights will be used in analyses of measurement data collected on a parent- or household-level.

The next step in weighting consists of non-response adjustments. We plan to use weighting class (and/or post-stratification) adjustments that make use of class totals known either on a frame basis, that is, population cell totals; or on a sample basis, that is, for non-participating as well as for participating households. For example, weighting classes may be based on design strata, such as counties/states, income groupings and rural versus urban. Non-response adjustments, designed to reduce the potential bias of non-response, will force the weights for responding households to sum to known population totals within each cell (post-stratum, or weighting class).

4.3 Adjustments for Cluster Sampling

The day care center portion of the sample selection will be based on a two-stage cluster sample. The sample size estimates are based on the assumption of 14 participating day care centers, from six counties, in each state. From these 14 day care centers, 64 day care children within each state will be sampled (an average of 4.6 children per participating center). Each day care center may be considered a cluster, so the children sampled from the same day care center would be anticipated to have correlated responses. A substantial portion of the children's 24-hour daily exposures is obtained from the same day care center. The indoor and outdoor air concentrations, food concentrations, floor sample concentrations, and play soil concentrations obtained at the day care center would be the same for all these children. Furthermore, children attending the same day care center may live near each other and share similar living conditions. This would lead to correlated target compound concentrations at home.

The correlation in response among children in the same day care center will be estimated by incorporating day care center as a random effect in the analysis of variance model. This will lead to two components of variation, σ^2_{adc} and σ^2_e. The variance component σ^2_{adc} corresponds to variation among day care centers. The variance component σ^2_e corresponds to the variance within day care centers. The correlation between two responses in the same day care center is $\rho = \sigma^2_{adc} / (\sigma^2_{adc} + \sigma^2_e)$. The correlation reflects the cluster design effects and will be incorporated into the analyses. Separate values of ρ will be calculated for each response and each target compound.

The analysis of variance model will also include the systematic factors (state, urban vs. rural, low vs. middle/upper income, day care vs. no day care) and possibly other important covariates that may be selected based on statistical criteria such as a step-wise regression procedure. Note that while a factor for state will be included in the model, no comparison between the two states will be performed. If results of the comparisons between urban and rural, low-income and middle/upper income, and/or day care and non-day-care are found to rely on the state, these comparisons will be made for each state separately.

4.4 Descriptive Statistics

Mean values and corresponding standard errors will be presented for each stratification factor level (for example, urban, middle/upper income) and for pairs of factors (for example, urban, and middle/upper income), averaged over the remaining factors. The sample means will be weighted averages, using the survey weights as discussed in the section on weight adjustments. Thus the sample averages will estimate the population averages within each

stratum or combination of strata. The standard error estimate will account for the survey weights assigned to each observation, as well as the correlation among responses for children who attend the same day care center. Children who do not attend day care centers provide independent responses. Weighted averages will be based on the logarithms of the responses. Confidence intervals will be calculated about the logarithmic mean under the assumption that the weighted averages are approximately normally distributed. The weighted averages and associated confidence bounds will then be exponentiated to provide inferences in the domain of physical relevance.

4.5 Comparisons to Satisfy Total Exposure Objective

The first analysis objective is to compare estimated total exposure across one stratum at a time (except for state), averaging across the remaining strata, for example, total exposure for low income compared to total exposure for middle/upper income, averaging across urbanicity, day care attendance status, and state). Comparisons to satisfy the objective will be based on the doses calculated using the microenvironmental exposure model. A test of hypothesis of equality of average total doses between the two levels within the stratum will be carried out by comparing weighted averages and corresponding standard errors, using a two-sample, two-tailed t-test. If the goodness-of-fit test for normality and the normal probability plot based on the logarithmic transforms of the responses do not show serious departures from normal distribution assumptions, the comparison between levels will be based on weighted averages of the logarithmic responses within each stratum level and associated standard errors. The standard error calculation will account for weighting and for the correlated responses among children who attend the same day care center. If serious departures from normal distribution assumptions occur, the t-test comparisons between average values in the stratum levels will be based on a weighted mean of ranked responses within each stratum level and associated standard errors. The weights will be the same as those used with the logarithmic transformation, namely the survey weights. The estimated correlation among the children who attend the same day care center will need to be re-estimated, based on the rank transformation data.

Significance levels of the t-tests will be reported. If the t-test is based on the logarithmically transformed responses, the exponentiated mean difference (i.e. ratio of geometric means) and associated 95 percent two-sided t-statistic confidence interval bounds will be reported. If the t-test is based on rank transformed responses, just the exponentiated weighted logarithmic mean difference (i.e. ratio of geometric means) will be reported.

4.6 Comparisons to Satisfy Pathway Apportionment Objectives

These objectives pertain to comparing the components of total dose by pathway. This entails comparing the components of dose to one another, averaging across all the strata or assessing the interaction between components of dose and stratum level. For example, comparing the ratio of dose attributable to dietary ingestion with that attributable to non-dietary ingestion, either averaged across all the strata or else comparing the ratio between rural and urban children.

Such comparisons will be carried out in a similar fashion to the total exposure comparisons. Let D_i, D_j denote the i-th and j-th pathway specific component of dose respectively, or alternatively let D_j denote the total dose, summed across pathways. Let $R_{ij} = D_i/D_j$, the ratio of D_i to D_j. If D_i and D_j are each approximately normally distributed and R_{ij} ranges from 0 to ∞ then X_{ij} may be approximately normally distributed. Suppose R_{ij} is bounded from above by u (e.g. if $D_j = D_{TOT}$ then u=1). In that event transform R to $X = \log [R/(u-R)]$.

Then $-\infty < X < \infty$ and X may be more nearly normally distributed than is R. We will calculate a weighted average of the X's (if the X's are approximately normally distributed) or of the signed ranks of the X's (if the X's depart from normality) across the factor combinations. The weights will be the survey weights, as discussed in the section on weight adjustments. The standard error calculation will reflect the survey weights, as well as the correlation among the X's (or the signed ranks of the X's) for the children who are attending the same day care center. We will also calculate a two-sided t-statistic based confidence interval based on the weighted average and its associated standard error. The transformation on the weighted average and on the upper and lower confidence bounds will be inverted to obtain an estimate of the weighted mean of the R's and associated confidence bounds in a physically meaningful scale.

For inferences about the two-factor interactions between relative doses in different exposure pathways and strata we will compare the ratios of external pathway specific doses among strata. Let $R_{ij} \equiv D_i/D_j$ be as defined above. We wish to compare the average value of the R_{ij}'s between two strata. For example we may wish to compare the ratio of dietary dose to total dose between low income and middle/upper income children. We proceed as above, for the primary analysis objective, either parametrically or non-parametrically, depending on the approximate normality of $X_{ij} = \log\left(\frac{R_{ij}}{1 - R_{ij}}\right)$. We calculate the weighted averages within each stratum, using survey weights as discussed above, and the corresponding standard errors of the mean. To compare the ratio of dietary external dose to total external dose between low income and middle/upper income children we test the hypothesis H_0: $\mu_{lo} = \mu_{mu}$ versus H_1: $\mu_{lo} \neq \mu_{mu}$ where μ_{lo} and μ_{mu} are the population means of the X_{ij} within each stratum, by two-sample, two-sided t-tests.

NOT DOING THIS SECTION AND BEYOND

IV Uses of CTEPP Data to Evaluate and Refine Currently Available Exposure Models

The CTEPP data set will include data from 256 children and their caregivers pertaining to concentrations of target compounds in indoor and outdoor air, dust, soil, handwipes, food, beverage, and drinking water; in addition to activity diaries, food diaries, and physiological information. These data used in combination can provide information to evaluate the performance of existing exposure models and to extend current exposure models to facilitate their more common use, and with a markedly reduced input data burden. Two examples of such applications of the CTEPP data are presented below. The first involves the critical evaluation of a dietary exposure model. The second shows how the data obtained from the CTEPP study can be used to extend the EPA microenvironmental exposure model to markedly reduce the burden of collecting required input data.

5.1 Evaluate the EPA/OPP DEEM Dietary Exposure Evaluation Model

Each child's food concentration of each target compound may be estimated using the food consumption diaries and the EPA/OPP DEEM model. The predicted dietary residue concentrations can be directly compared to the measured concentration levels in the food based on the duplicate plate analysis. It will be determined whether the results are significantly different. The questionnaire data can be used to determine whether are there environmental or home factors, such as cooking, washing and other practices that influence the residue levels found in the food samples. The questionnaire data can also be used to determine if the differences between observed and predicted vary by socio-economic status (SES), housing or measured indoor/outdoor environmental conditions. These and other similar questions will be addressed using the CTEPP measurements or the questionnaire and survey data**.** Deviations between the DEEM model and the measured dietary concentration data can be used to modify the model.

5.2 Extend the EPA Microenvironmental Exposure Model

The EPA microenvironmental exposure model that is discussed in this section requires extensive monitoring inputs, both indoors and outdoors, personal activities, and detailed food consumption data. The CTEPP data set can be used to determine relations between indoor air and dust concentrations and outdoor concentrations which are much simpler and less costly to obtain, as well as activity patterns in the house. Potential models include:

$$C_I = \beta_o + \beta_1 PUA_7 + \beta_2 PUA_{14} + \beta_3 PUA_{30} + \beta_4 C_o + \beta_5 FREQ + \beta_6 PETS + \beta_7 FANS + \beta_8 AC + \beta_9 CLEAN + \beta_{10} COOKING + \beta_{11} INDSOURCES + ERROR$$

$$C_I = \beta_o + \beta_1 PUA_7 + \beta_2 PUA_{14} + \beta_3 PUA_{30} + \beta_4 C_o FREQ + \frac{1}{FREQ} \times \sum \beta_i X_i + ERROR$$

$$C_h = \beta_o + \beta_1 f_s C_s + \beta_2 f_d C_d + ERROR$$

where, (fs, fd = period of outdoor soil or indoor floor/surface dust contact time)

$$C_h = \beta_o + \beta_1 IDE_s C_s + \beta_2 IDE_d C_d + ERROR$$

$$C_d = \beta_o + \beta_1 C_s + ERROR$$

$$C_d = \beta_o + \frac{\beta_1 C_s}{FREQ} \times CLEAN + ERROR$$

These models relate indoor concentration values to outdoor concentrations and activity based variables. Incorporation of these relations into the micro environmental model will simplify the burden of data collection considerably. An index of dermal exposure (IDE) will be calculated using the reported level of the child's activity (high, medium or low) in connection with potential contact with contaminated surfaces based on diary and/or video tape data. IDE score will range at the minimum from 0 to 3 more likely from 0 to 6 depending on the range and type of activities noted or observed. Likewise, we will define an incidental ingestion exposure (IIE) score based on reported hand to mouth and object to mouth activities. A number of these variables will be used as class (indicator) or interaction variables in the predicted regression models. Pesticide use (PU) information will be coded by type and application history. Most recent application within a week will be denoted by the variable PU_7. Earlier applications more than a week but less than 2 weeks ago, and more than a month ago, will be denoted by the variables PU_{14} and PU_{30}, respectively. These variables will be used in the models. We define:

C_I	Indoor air concentration
C_o	Outdoor air concentration
C_d	Indoor dust concentration
C_s	Outdoor soil concentration
C_h	Handwipe concentration
FREQ	Frequency of window and door openings
PETS	Presence of pets in home (0, 1)
FANS	Use of ceiling fans (0, 1)
COOKING	Cooking source and type (0, 1, 2,...)
AC	Use of central air-conditioning and type (0, 1, 2,..)
INDSOURCE	Potential other non-cooking indoor sources
CLEAN	High, low, average amounts of cleaning activities or measures (e.g., doormats, shoes removed indoors, etc.)
PUA	PU x Area of pesticide applied

5.3 Evaluate Physical Dermal Exposure and Dose Models

Physical and mechanistic models of dermal exposure models will be developed using the concentrations obtained in the CTEPP study and transfer coefficients (TC) either derived from the results of the CTEPP study or presently available either in the literature or in OPP's SOPs. Therefore, with CTEPP data we have the opportunity of either: 1) developing these physical models, or 2) evaluating these models against the exposure data generated directly or indirectly during the study. Some examples of these model applications and evaluations are listed below. Note that the superscript "p" refers to predicted and "m" refers to measured exposure (E) or dose (D). ED donates exposure duration and "C" refers to dislodgeable surface or carpet concentrations. Again, time lags are denoted by subscripts. Since a multiplicative model is used in the prediction of dermal exposures, log transforms will be used to convert these equations to an additive regression model form.

E^p_{derm} = C x TC x ED (Predicted dermal exposure or potential dose)

$C_h = \beta o + \beta_1 \ln C_d + \beta_2 \ln TC + \beta_3 ED + ERROR$

$D^m = D_{air} + D_{food/water} + D_{non\text{-}diet} + D_{dermal}$

$E^m_{dermal} = \alpha_{PBPK} (D^m - D_{air} - D_{food/water} - D_{non\text{-}diet})$

where α_{PBPK} is the coefficient or function based on PK or PPBK modeling relating exposures to dose and vice-versa.

$D_{non\text{-}diet} = C_d \times IIE_d \times K_d + C_s \times IIE_s \times K_s$

where K_s and K_d are the incidental soil or dust ingestion estimates used in the equations described earlier or obtained from literature.

$\ln E^m_{dermal} = \beta_o + \beta_1 \ln C + \beta_2 \ln TC + \beta_3 ED + ERROR$

Consequently, we can estimate TC also from:

$TC = \exp(\ln E^m_{dermal} - \ln C - \ln ED)$

or

$TC = \exp(\ln C_h - \ln C - \ln ED)$

Other pesticide application time lag models may be considered if these models prove to have acceptable predictive power.

5.4 Compare Exposures and Urinary Biomarker Data

Predicted total exposures and potential dose will be compared statistically to measured urinary biomarker data in order to evaluate the predictive power of the exposure models developed. Biological dose will be estimated using a PK-based average absorption and metabolic conversion rate, as well as in a few cases direct application of a PK model to the estimated exposure/dose profile [for example, modeling trichloropyridinol (TCP) concentrations in urine associated with multimedia exposures to chlorpyrifos]. Predicted route and pathway-specific exposures will be contrasted as well as summed over to estimate total potential exposures by different study sub-groups. Biomarker measurements will also be correlated with other behavioral and home and day care potential exposure factors. Use of pesticides in homes and day care centers, proximity to busy roadways, cooking, hobbies and cleaning activities which could result in higher indoor and consequently personal exposures will be examined statistically. Stepwise regression models or CART techniques will be used as exploratory models to examine the likelihood of various factors that could lead to elevated exposures and absorbed dose. Children's behavioral characteristics or activities, such as walking barefoot, digging in yard or playground soil with measurable or elevated pesticide levels, sleeping on the floor, low or high hand washing frequencies, habitual thumb sucking, etc. will be analyzed as part of this investigation.

IV Predict Intake Doses With Urinary Biomarker Concentrations

The environmental concentration measurements, activity diaries, and food consumption diaries are difficult, time-consuming, and expensive to obtain. These data however are needed to

obtain estimates of the component pathway external doses and thereby total external dose. In contrast, urinary biomarker concentrations are relatively quick, easy, and inexpensive to measure. They can be obtained for very much larger numbers of children and adults than can full suites of indoor and out environmental measurements. The extent of the ability of the urinary biomarker information to serve as a surrogate indicator of the external component and total doses can be assessed based on the CTEPP data.

The correlation between urinary biomarker data and each of the component pathway doses or total aggregate dose can be assessed by a series of simple regression analyses. Let U_i, $D_{TOT,\,i}$ denote the urinary biomarker concentration and the total external dose respectively within the i-th combination of factors. We would like to determine how well U predicts D_{TOT}. We consider a succession of simple linear regression models.

$$D_{TOT,\,i} = \beta_0 + \beta_1 U_i + e$$
$$D_{TOT,\,i} = \beta_{0i} + \beta_1 U_i + e$$
$$D_{TOT,\,i} = \beta_{0i} + \beta_{1i} U_i + e$$

to determine how well U can act as a surrogate for D_{TOT}, either within particular combinations of strata or across strata. These relations might also be expressed in terms of the logarithmic transformations of D_{TOT} and U. The coefficient of variation and the residual variation about the model indicate how precisely U can predict D_{TOT}. 95 percent 2-sided prediction intervals can be constructed to determine upper and lower prediction bounds on D_{TOT}, conditional on observing U.

Other factors contained in the activity and food diaries can be added to the predictive equations to determine whether they enhance the predictiveness of the relations. Several such factors discussed in the paragraph above, such as pesticide use or cleaning agent use, could enhance the total dose. Component doses can be substituted for D_{TOT} in the above relations to determine how well U can act as a surrogate for a component dose.

IV Additional Analyses

The above discussion on data summarization and the construction of tests of hypotheses and point and confidence interval estimates dealt with statistical displays and procedures designed specifically to address the primary and secondary statistical analysis objectives specified at the beginning of the section. The data set will be very rich and many additional uses will be made of the data.

We will utilize the data (questionnaires, diaries, and POP concentrations in multimedia) generated from the CTEPP study to evaluate and refine U.S. EPA Standard Operation Procedure (SOPs) for Residential Exposure Assessments (Draft Contract No. 68-W6-0030, Work Assignment No. 3385.102, prepared by The Residential Exposure Assessment Work Group: Office of Pesticide Programs, Health Effect Division Versar, Inc. July 18, 1997). For example, the child activity diary data obtained from the CTEPP study can be used to refine the parameters used in the SOP 2.3.2 “Postapplication Potential Dose Among Toddlers from Incidental Nondietary Ingestion of Pesticide Residue on Residential Lawns from Hand-to-mouth Transfer.” We will convert all the collected data from the CTEPP study into EPA TherDBase format. The data will be accessible easily to EPA OPP to evaluate and refine the SOPs for Residential Exposure Assessments.

The previously discussed analyses dealt with estimates of total exposure and component exposure and their comparisons among strata. Additional information obtained from the activity

diaries and the food diaries can be used to explain variations in exposure components among children, either within strata or across strata. Thus, for example, if inhalation exposure or dietary exposure were found to be major components of total exposure, the identification of factors associated with high values of these component exposures can lead to specific recommendations concerning their reduction. For example type, frequency, and amount of pesticide use may be correlated with indoor or outdoor air concentration, which in turn is correlated with inhalation exposure. It might also be related to increased concentrations in food preparation surfaces, which in turn would lead to increases in the ingestion exposure. The food diaries will provide information about types and amounts of foods eaten. This may be a predictor of target compound concentrations in daily food intake.