

Approaches to Environmental Exposure Assessment in Children

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An improved understanding of the contribution made by environmental exposures to disease burden in children is essential, given current increasing rates of childhood illnesses such as asthma and cancer. Children must be routinely included in environmental research. Exposure assessment, both external (e.g., air, water) and internal dose (e.g., biomarkers), is an integral component of such research. Biomarker measurement has some advantages that are unique in children. These include assessment of potentially increased absorption because of behaviors that differ from adults (i.e., hand-to-mouth activity); metabolite measurement, which can help identify age-related susceptibility differences; and improved assessment of dermal exposure, an important exposure route in children. Environmental exposure assessment in children will require adaption of techniques that are currently applied in adult studies as well as development of tools and validation of strategies that are unique for children. Designs that focus on parent-child study units provide adult comparison data and allow the parent to assist with more complex study designs. Use of equipment that is sized appropriately for children, such as small air pumps and badge monitors, is also important. When biomarkers are used, biologic specimens that can be obtained noninvasively are preferable. Although the current need is primarily for small focused studies to address specific questions and optimize research tools, the future will require establishment of large prospective cohorts. Urban children are an important study cohort because of relatively high morbidity observed in the urban environment. Finally, examples of completed or possible future studies utilizing these techniques are discussed for specific exposures such as benzene, environmental tobacco smoke, aflatoxin, volatile organic compounds, and polycyclic aromatic hydrocarbons. — *Environ Health Perspect* 106(Suppl 3):827-832 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-3/827-832weaver/abstract.html>

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Introduction

The number and diversity of chemical toxicants to which humans are exposed have increased significantly in recent decades. Traditional exposure concerns focused primarily on occupational exposures, which generally occur at higher levels than in the community. However, environmental research has shown that serious adverse health effects may result from these

lower exposures as well. This is due to many factors including longer exposure time (not just the work week or a working lifetime) and the fact that highly susceptible populations are more likely to be exposed.

A major priority of future environmental research is the evaluation of these susceptible high-risk populations. Children are one of the most important groups in this regard.

There are many differences between children and adults that are likely to result in greater toxicity in children from similar external environmental exposures (1). For example, children are routinely involved in activities that result in increased opportunity for toxicant contact and absorption, such as playing on the floor and hand-to-mouth activity. They may also have decreased detoxification capacity for many chemicals because of metabolic enzyme differences present during development. However, with the exception of lead and, to some extent, environmental tobacco smoke (ETS), few data are available on the magnitude of children's exposure to most environmental toxicants. Even less information exists to delineate the nature of their unique susceptibility to these toxicants. To remedy these critical data gaps, exposure assessment tools and strategies suitable for children must be developed, validated, and refined, and environmental health studies must routinely include children.

Environmental Exposure Assessment

Exposure represents a critical link in the cascade of events that originates with environmental contamination and may result in adverse health outcomes. To evaluate risk or causative associations, the link between exposure and effect must be rigorously established. This is difficult in environmental studies where exposure levels are low and information to assess past exposures is limited. Exposure assessment in children adds an additional complexity but is necessary because of the many differences between children and adults, which make extrapolation from adult data potentially flawed. There are several tools that can be utilized in exposure assessment; their strengths and weaknesses when used in children will be discussed.

External Exposure Monitoring

Exposure assessment can be conducted through direct and/or indirect approaches. The indirect approach relies on validated models that evolve from well-characterized relationships between causative variables and exposure from studies using direct measurements. Because there is in general a paucity of exposure data on children and the models for adults are not likely valid for children, the indirect approach is not yet reliable or appropriate for children. Therefore, direct measurements are needed.

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Abbreviations used: CO₂, carbon dioxide; ETS, environmental tobacco smoke; MA, *trans,trans*-muconic acid; PAHs, polycyclic aromatic hydrocarbons; U.S. EPA, U.S. Environmental Protection Agency; VOCs, volatile organic compounds.

Direct measurements can be obtained in external (to an individual's body) environmental media or through the determination of contaminants or their metabolites in a biologic medium. Traditionally, exposure assessment has relied on external or ambient exposure monitoring of airborne toxicants. This involves measuring a chemical in air either by area sampling with the monitor in a fixed location, or by personal monitoring in which small pumps are worn by the monitored participants. There are a number of advantages to airborne exposure assessment. Standard assay methods with reference levels, both in the workplace and, in some cases, environmentally, are available for many different chemicals. In addition such monitoring allows a determination of the effectiveness of any exposure controls in use.

Despite its advantages, sole reliance on airborne exposure assessment has limitations as well. Monitoring may not be representative if wide variation in exposure occurs. Airborne exposure assessment measures only one route of exposure, so exposure from chemicals that can be absorbed through the skin or ingested is not included. These latter routes may be particularly important in children because of their hand-to-mouth activity and crawling, which allow skin contact. Infants also have a larger surface-to-volume ratio than adults, resulting in more proportionate skin surface across which absorption can occur (1). Another important limitation is that exposure indicates only the current level of chemical present in the environment. That level does not always reliably predict internal dose, which is the amount of chemical that exposed individuals ultimately absorb into their bodies. Differences in absorption at similar exposure levels occur for many reasons. For example, respiratory rate and size of the respiratory tract are important considerations for inhaled toxicants. These factors also differ between children and adults, allowing children to inhale disproportionately more of an airborne toxicant.

Finally, although the risk of adverse health outcomes increases with air level for most toxicants, there remains significant variation in the severity of those outcomes among individuals exposed at the same level. Knowledge regarding the pathophysiologic processes between exposure and disease outcome is critical in understanding this variation and thus improving the ability to protect exposed populations.

Biologic Monitoring

Biologic monitoring can be divided into two types: internal dose, which is measurement of a chemical or its metabolite(s) in biologic specimens such as breath, blood, or urine; and biologically effective dose, which is the amount of chemical or its metabolite(s) that has interacted with critical cellular macromolecules of the target or surrogate tissue. The term biomarker is often used to refer to the specific chemicals measured in internal or biologically effective dose assays. Incorporation of biomarker measurement into environmental work substantially strengthens such research by providing information on individual variation in absorption and metabolism. This variation is likely to be an essential factor in human susceptibility for toxic outcomes.

Several criteria have been established to assist in the development and validation of biomarker assays (2). These criteria are similar to those used for clinical or other medical screening tests and are essential for any measurement that may ultimately be used for clinical or surveillance purposes. The biomarker should be biologically relevant to the toxic pathway involved in chemical metabolism. It must be feasible to obtain. Specifically, the biologic specimen must be accessible (e.g., urine, not organ biopsy) and the assay must not be so time consuming that it can only be done in a limited number of individuals. Inter- and intraindividual variation, which can be wide in comparison to established clinical tests, must be understood and manageable at least to the extent that group differences and trends over time can be assessed. The assay must be valid and reproducible. Finally, sensitivity, specificity, and positive predictive value must be acceptable.

Biologic monitoring is best used in conjunction with a questionnaire or air monitoring to identify a population with a wide enough exposure range to allow meaningful interpretation of biomarker results. Because all exposures potentially contributing to body burden, and consequently to adverse health effects, are of interest regardless of exposure source or route, an integrated exposure assessment approach is the ultimate goal. This approach has been described and justified by Ott (3) and Liroy (4) and exemplified in community studies involving adult exposures to single classes of pollutants including the Total Exposure Assessment Methodology for Volatile Organic Compounds (TEAM-VOC) Study (5), the

Nonoccupational Pesticide Exposure Study (6), and the Total Human Environmental Exposure Study (7) for polycyclic aromatic hydrocarbons (PAHs). More recent studies are beginning to consider cumulative exposures across both multiple media and pollutants (8,9).

An example of a successful internal dose biomarker is blood lead, which has had an enormous impact on the prevention and treatment of lead exposure in children. Experience with blood lead and other internal dose biomarkers has revealed a number of advantages. Biomarkers integrate exposure from all routes and sources. This is especially valuable for chemicals with two or more substantial routes of exposure from multiple media such as air, food, and water. Their measurement assesses the amount of a chemical that is ultimately absorbed into the body after the influence of exposure factors such as behavior, contact rates, protective measures, and differences in respiratory rate. In addition, if metabolites are measured, information on the processing of the chemical is provided. This can ultimately lead to a better understanding of chemically induced disease processes and improved protection of those at highest risk. Unfortunately, internal dose monitoring has several disadvantages as well. Few chemicals have well-validated assays. Individual metabolite biomarkers may be nonspecific because of formation from more than one parent compound. Target organ damage, which is a more direct measure of toxicity, is not determined.

Biologically effective dose measurement assesses damage at the target organ affected, which is a major advantage. Carboxyhemoglobin for carbon monoxide poisoning is a commonly used example. Biomarkers that determine biologically effective dose by effects on surrogate tissues include measurement of red blood cell cholinesterase in pesticide-exposed populations and DNA or protein adducts in white blood cells. The main disadvantage is that even fewer assays have been developed and many are quite time consuming. Also, most biomarkers are short-term exposure measures and do not provide information on past levels of exposure.

The use of biomarkers is especially justified when *a*) exposures occur through multiple routes and pathways; *b*) there is significant potential for dermal absorption or ingestion (i.e., from hand-to-mouth activity); or *c*) there is a high ratio of sampling burden to subject ability (cognitive

and physical). These criteria, outlined in Table 1, suggest that biomarker use for study of environmental exposures in children could be extremely useful.

Adaption of Exposure Assessment Techniques for Children

Biomarkers and other exposure assessment techniques can be adapted for use in children in several ways. First, unique recruitment strategies are needed. Pediatric clinics and child-specific facilities such as schools or day care are good recruitment sites. Parental involvement in the study is another helpful technique. This ensures better cooperation on the part of the child and parental involvement allows for a more complex study design. In addition, because so few biologic monitoring data are available in children, meaningful comparison data are provided. Parent-child study pairs are similar genetically and may have similar exposures, at least on the study day. However, the age difference remains, which allows analysis of this important aspect of children's susceptibility. It is important to note that although the parent is often the initial contact, especially for young children, informed consent must still be obtained from the child as well. Consent should be appropriate for age and, for young children, is often a simple oral explanation in the presence of the parent.

Exposure monitoring can be modified by utilizing study equipment that is appropriately sized for children. Smaller air monitoring pumps are now available that are more comfortable for children. Placing pumps in backpacks or fanny packs is also often acceptable to children, as many are used to wearing these packs already. It also uses the out-of-sight-out-of-mind principle, which helps prevent the child from playing with equipment and potentially affecting results. Passive badge monitoring is a lightweight, relatively tamper-resistant monitoring option that is of benefit in

children. The use of activity pattern diaries is another technique that provides exposure information for children; this information can be provided by the parent over the course of the study period, particularly when the children are very young.

Incorporation of exposure biomarkers into study designs provides important additional exposure information. Biomarker measurement is particularly important in children, as their absorbed dose for a given external exposure level may be very different from that of an adult, thus resulting in a different toxic response. When possible, the use of painless noninvasive techniques is preferable. For example, instead of measuring a biomarker in blood, which generally involves venipuncture, that same or a similar biomarker can be often be measured in urine, saliva, or breath. Hair analysis may also have potential as this methodology develops. The ETS biomarker, cotinine, is a useful biomarker in this regard, as it can be measured in saliva, blood, and urine. Urine specimens can be obtained in older children who are toilet trained. In very young children and infants, saliva provides a more accessible biologic specimen. If blood is needed, fetal cord blood, obtained at birth, is an option when the study focuses on exposure in infancy. Obtaining the specimen at a regularly scheduled blood draw (such as for blood lead screening) is another option.

Breath sampling holds particular promise for the assessment of children's exposure because of its noninvasiveness and potential for ease of collection compared to blood and urine specimens. The method can be applied to children as simply as blowing up a balloon. Quantitative assessment of exposure based on breath sampling requires a consistent collection of the alveolar fraction or a means for adjustment to a consistent fraction. The latter approach may be more suitable for children because a rigid collection protocol required for the former may not be

conducive to the limited attention span and cognitive ability of children. Within and between sample variability in alveolar collection can be adjusted based on the sample's carbon dioxide (CO₂) concentration. Because alveolar air contains 4 to 5% CO₂ whereas ambient air contains 0.035%, in the range of 0 to 5%, the concentration of CO₂ will be inversely proportional to the dead air space contained in the sample. Pleil and Lindstrom (10) used this approach to adjust collected samples using a simplified approach of single breath collection.

Application of Biomarker Study Designs for Children

An increasing number of environmental studies now include children. A few examples of completed or proposed work that relate to our research areas of interest are presented below to illustrate the use of the exposure assessment techniques previously discussed. Our collaborative research utilizes biomarkers for benzene and ETS in urban mothers and children. There is current concern that inner-city populations experience increased exposure to environmental toxicants compared to suburban areas (11). The contribution to disease burden made by such exposures is unknown but of obvious importance, as these exposures are potentially preventable. Furthermore, disease burden in inner-city areas is disproportionately higher. In urban Baltimore, Maryland, the focus of our work, residents have an overall cancer mortality rate of 255 per 100,000, which is significantly above the national rate of 172.8 per 100,000 (12).

Urban children may be exposed to multiple toxicants simultaneously and/or sequentially as they mature. Given the child's longer life span compared to adults, the potential adverse health effects can be significant. Our work has focused on chemicals selected by extent of exposure and known toxicity. Benzene is a human leukemogen. It is ubiquitous in the environment and found in higher levels in cities as compared to rural areas. Extensive U.S. Environmental Protection Agency (U.S. EPA) monitoring data has shown that the largest contributors to environmental exposure are tobacco smoke and benzene in gasoline. (Benzene in gasoline was recently reduced through U.S. EPA regulation.) (13). On the basis of this U.S. EPA work, Wallace (13) estimated that the majority of benzene-induced leukemias are due to nonoccupational exposure (13). ETS has been a focus because exposure in

Table 1. Selected criteria for biomarker measurement in exposure assessment.

Criteria	Rationale
Multiple pathways and routes of exposure	Sampling of multiple environmental media is burdensome and complex, increasing the likelihood for measurement error and alteration of subject behavior
Significant potential for dermal exposure or ingestion	Methods for assessing external dermal exposure are not well developed and are associated with considerable uncertainty
Limited physical and cognitive capacity of the subject to participate in environmental monitoring	Some population subgroups such as the very old or very young are physically and/or mentally limited in their ability to participate in environmental monitoring

children increases their risk for respiratory infections such as bronchitis and pneumonia, upper respiratory tract irritation, reduced lung function, and asthma (14). ETS also causes lung cancer in adults and increasing evidence supports a causative role for it in coronary artery disease. Lead is a well-established neurotoxicant in children.

An initial study obtained questionnaire information on sources of benzene and ETS in 79 children who were patients in a lead poisoning prevention clinic (15). Urinary cotinine and *trans,trans*-muconic acid (MA), metabolites of nicotine and benzene, respectively, were measured. Blood lead was obtained for clinical purposes. As expected, the mean blood lead level was elevated at 23.6 µg/dl. Although smoking prevalence is higher in lower socioeconomic populations, we were surprised to find cotinine present in all but one of the samples assayed. This was not a highly sensitive assay, as evidenced by a limit of detection of 1 ng/ml. Even more striking was the fact that 79.5% of children had cotinine values ≥ 30 ng/mg creatinine, a level consistent with household ETS exposure (16). These elevated exposure results are consistent with those of Ogborn et al. (17), who examined ETS exposure in a similar population—asthmatic children receiving care from the pediatrics department at Johns Hopkins (Baltimore, MD). This suggests that inner-city children who are overexposed to lead also have excessive exposure to another environmental hazard, ETS. In addition, the cotinine results emphasize the strength of incorporating biomarkers into the study design. A single urine measurement of this well-validated ETS biomarker revealed more extensive ETS exposure than was apparent on a questionnaire alone.

Most children had more than one source of potential benzene exposure based on questionnaire data. MA was present in 72% of samples assayed. The mean was 176.6 ng/mg creatinine, with a wide range of values (< limit of detection to 2579.2 ng/mg creatinine). The MA results may indicate excessive benzene exposure. However, because this biomarker is not specific for benzene exposure, further validation in the environmental setting is required for full interpretation of these findings. Questionnaire benzene data combined with lead and ETS biomarkers suggest that these children had ongoing exposure to multiple environmental toxicants.

Current work, focused on validation of benzene metabolite biomarkers for use in

environmental exposure, utilizes many of the techniques useful for study of children mentioned above. We are focusing our efforts on mother-child pairs and on using noninvasive biologic specimens such as urine and breath.

Another environmental exposure for which biomarkers have been utilized in exposure assessment in children is aflatoxin, a dietary hepatocarcinogen that is a common contaminant of foodstuffs in developing countries. Studies utilizing the urinary aflatoxin-DNA adduct have demonstrated that aflatoxin-exposed individuals who are also infected with the hepatitis B virus are at particularly high risk for cancer (18). The aflatoxin-albumin adduct has been measured in fetal cord blood at levels that were different than in maternal blood (19). This suggests that the fetal liver is able to metabolize aflatoxin, which results in carcinogenic exposure to fetal liver cells. In addition, another toxic metabolite, aflatoxin M₁, has been measured in breast milk from nursing mothers in The Gambia, West Africa, indicating that infants are exposed by this route even before the child begins to consume contaminated foodstuffs (20). This early childhood aflatoxin exposure may be a contributing factor to the relatively young age at which hepatocellular carcinoma occurs in adults in developing countries.

There are many other environmental exposures in children that could be addressed in studies utilizing the assessment techniques discussed above. Contamination of water supplies by VOCs is one example. Such contamination is ubiquitous, arising primarily from the chlorine disinfection process of water containing organic material (21,22). Hazardous waste sites and leaking underground storage tanks are other sources of these contaminants that may enter the water supply (23). There is increased recognition of the importance of VOC water contamination in human exposure (24). The potential hazards associated with these contaminants include cancer (benzene is a human carcinogen; trichlorethylene and chloroform are animal carcinogens) and hepatic toxicity (e.g., carbon tetrachloride) (25,26).

Exposure through the water medium greatly complicates exposure assessment because of the added routes of ingestion and dermal absorption. Reliable methods are available for assessing exposure by inhalation and ingestion; however, there is considerable uncertainty as to the dermal contribution. Previous studies in adults

have shown that during a shower, the dermal chloroform contribution is comparable to inhalation (27,28). It is hypothesized that children would be more highly exposed than adults because of their high surface-to-volume ratio (29), longer duration bathing activities, and bathing by immersion (30). The dermal exposure contribution that occurs with bathing is also of particular interest in the context of risk assessment or epidemiologic research because there is evidence to suggest that this route of exposure may have greater toxicologic significance relative to ingestion. Inhalation and dermal uptake result in higher dose levels to nonliver organs because chloroform is not subject to first-pass metabolism in the liver as occurs with ingestion. Toxicologic studies showing greater cancer potency for inhaled versus ingested chloroform provides additional evidence as to the possible importance of exposures from bathing (31).

Data characterizing children's exposure to chloroform and other trihalomethanes from bathing are extremely limited, primarily because of lack of methods for evaluating the dermal contribution. Biomarker measurement is one option for improving assessment. VOCs can be analyzed in blood, but the collection by venipuncture is a limitation in children. Several urinary metabolite assays are available but these methods generally lack sensitivity and/or specificity when applied to environmental exposures. However, breath sampling of VOCs is a valid method for evaluating environmental exposure (32,33). This methodology is especially well suited for children because of its noninvasiveness and ease with which samples can be collected.

Children's exposure to PAHs provides another example. PAHs are carcinogens that contaminate multiple environmental media including air, food, water, soil, and house dust, making exposure assessment through sampling of environmental media burdensome, logistically difficult, and expensive. In adults, research suggests that diet is the primary route of exposure (7,34). Similar studies characterizing children's dietary exposure are warranted, as a child's diet differs substantially from that of an adult and child diet studies have not been conducted (35).

A second exposure pathway of likely concern is that of soil and house dust ingestion. The significance of house dust as an exposure medium is well established from lead research (36). However, only recently have data become available that

reveal relatively high levels of PAH contamination (37,38). Of the PAH exposure pathways in children, house dust is the least characterized with the greatest exposure potential. Based on limited data, Roberts et al. (39) estimate that 65% of an infant's total exposure to benzo[a]pyrene comes from house dust. Direct measurements of soil ingestion rates using tracers suggest that children's nondietary ingestion is highly variable (40,41). Because of this variability and the difficulty in quantifying dermal absorption and hand-to-mouth activity, a PAH biomarker is particularly useful in assessing the house dust exposure

contribution. Urinary 1-hydroxypyrene is a biomarker that could be utilized in such studies. A large number of environmental and occupational exposure studies have been conducted that have demonstrated its validity as an exposure biomarker (42-44).

Conclusions

Inclusion of children is essential in future environmental health research. Exposure assessment is an integral component of such research. Comprehensive exposure assessment requires measurement of contaminants in external media and biomarkers. The latter has some advantages that are

unique in children, such as providing information on absorption that may differ from adults because of different behaviors, physiology, and metabolism. Environmental exposure assessment in children will require adaption of techniques that are currently applied in studies of adults as well as development and validation of tools and strategies that are unique for children. Although the current need is primarily for small focused studies to address specific questions and optimize research tools, the future will require establishment of large study cohorts to be followed over time.

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