Characterizing Exposures to Nonpersistent Pesticides during Pregnancy and Early Childhood in the National Children's Study: A Review of Monitoring and Measurement Methodologies

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The National Children's Study is a proposed longitudinal cohort study to evaluate the relationships between children's health and the environment. Enrollment is estimated to begin in September 2005, and 100,000 children will be followed from preconception or early pregnancy until adulthood. Among multiple health outcomes, the study is proposing to investigate whether pre- and/or postnatal exposures to nonpersistent pesticides increase the risk of poor performance on neurobehavioral and cognitive exams during infancy and early childhood. Characterization of exposures will be challenging. Nonpersistent pesticides include many chemicals with biologic half-lives on the order of hours or days. Exposures can occur through multiple pathways (e.g., food and residential or agriculture pesticide use) and by multiple routes (inhalation, ingestion, dermal). Effects may depend on the developmental stage when exposure occurs. Sequential sampling is likely to be required and may involve a combination of environmental and biologic monitoring as well as collection of questionnaire data. In this article we review measurements that can be used to characterize exposures. These include biologic markers, personal and indoor air sampling techniques, collection of dust, surface and dermal wipe samples, and dietary assessment tools. Criteria for sample selection will necessitate evaluation of the time frame of exposure captured by the measurement in relationship to critical windows of susceptibility, the cost and validity of the measurements, participant burden, and variability in exposure routes across populations and at different age periods. *Key words:* **biomonitoring, early childhood, environment, exposure assessment, *in utero*, National Children's Study, pesticides.** *Environ Health Perspect* **113:1092–1099 (2005). doi:10.1289/ehp.7769 available via *http://dx.doi.org/* [Online 12 May 2005]**

Pesticide use is widespread in the United States. A billion pounds or more of conventional pesticides are used annually, and 85% of households store at least one pesticide in their homes (Adgate et al. 2000; Kiely et al. 2004). Approximately 78% of conventional pesticide use is for agriculture, 10% is used in the home and garden, and the remainder is for government, commercial building, and industrial use. Recent biologic monitoring studies indicate that pesticide exposures are ubiquitous, including among women of childbearing age, pregnant women, children, and fetuses (Adgate et al. 2001; Barr et al. 2004; Berkowitz et al. 2003; Bradman et al. 2003; Lu et al. 2000; Whyatt and Barr 2001; Whyatt et al. 2003). To test the hypothesis that exposures to nonpersistent pesticides *in utero* and postnatally increase the risk of poor performance on neurobehavioral and cognitive examinations, the National Children's Study (NCS) will need to characterize exposures to a broad array of pesticides. The Exposure to Chemical Agents and Development and Behavior 2002 Interworking Group to the NCS, for example, has recommended that this hypothesis focus on current-use neurotoxic insecticides, including organophosphates (OPs), carbamates, pyrethroids, and nicotinoids, and additionally consider other current-use pesticides.

Exposure assessment will be challenging. Nonpersistent pesticides do not accumulate in the body and are generally excreted within hours and days, often via water-soluble metabolites in urine. Biologic exposure markers tend to reflect low-level, transient exposures that are highly variable. Further, the pesticides often degrade rapidly in the ambient environment. Although persistence in the indoor environment appears longer (Gurunathan et al. 1998; Lewis et al. 1994; Whyatt et al. 2004a), indoor levels can be highly variable depending on use patterns. Pesticide exposures can also vary by season (Berkowitz et al. 2003; Whyatt et al. 2003), and exposures can occur through multiple pathways and routes. Diet may be a significant source for some children (Clayton et al. 2003). Dermal exposure and nonintentional ingestion as well as inhalation may all be important routes for pesticides used in the home (Clayton et al. 2003; Fenske et al. 1990; Gurunathan et al. 1998; Lewis et al. 1994; Pang et al. 2002; Whitmore et al. 1994; Whyatt et al. 2003). In addition, effects of the pesticides may depend on the developmental stage when exposure occurs (Slotkin 1999). Experimental data for OPs indicate that the developing brain could be vulnerable to exposures from early embryonic life into childhood (Eskenazi et al. 1999; Garcia et al. 2003; Slotkin 1999). Thus, sampling to characterize exposure will need to be intensive and multimedia and will require repeat assessments during pregnancy and early childhood. A combination of environmental and biologic monitoring, as well as collection of questionnaire data, will likely be involved.

Tables 1 and 2 present the sampling framework proposed by the Exposure to Chemical Agents Working Group of the NCS for assessing exposures to nonpersistent pesticides. Details on the NCS and the role of the Exposure to Chemical Agents Work Group are provided in the accompanying article by Needham et al. (2005). A review of monitoring and measurement methods for assessing pesticide exposure is detailed below. Barr et al. (2005a) provide an additional overview of biologic monitoring.

Biologic Monitoring

Biomonitoring has the advantage over environmental monitoring of providing integrating dosimeters summing exposures from all routes and may more accurately reflect the dose to the target tissue. However, biologic half-lives of nonpersistent pesticides are short, and, thus, biomarkers generally provide only

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transient dosimeters. Therefore, repeat sampling designs will be necessary to characterize exposure.

Urinary monitoring. The measurement of pesticide metabolites in urine offers advantages over other potential exposure biomarkers. Urine is easy and noninvasive to collect, and laboratory methods are available to measure many different pesticide- and class-specific metabolites. Collection from adults is straightforward, and pediatric urine bags can be used with very young children. In one study approximately 90% of 6-month-old infants provided samples during assessments (Fenske et al. 2005). However, urine is an unregulated body fluid and varies from void to void in volume and in the concentration of endogenous and exogenous chemicals (Barr et al. 2005b; Wessels et al. 2003). This may not be true for very young children (e.g., < 12 months) because they feed and urinate frequently, but variability in urinary dilution has not been evaluated for this age group. Creatinine adjustment of urinary metabolites has been the standard method for accounting for urine dilution. However, urinary creatinine levels vary by age, sex, race/ethnicity, and body mass index (Barr et al. 2005b). Adjustments of urinary pesticide levels by creatinine may not be appropriate, therefore, in pregnant women and children. A recent study suggests that for multiple regression analyses in health outcome studies, the analyte concentration unadjusted for creatinine should be included in the model, with urinary creatinine added as a separate independent variable (Barr et al. 2005b).

Spot urine samples are easiest to collect, but no studies have assessed whether single or serial spot urine samples can be used to classify daily or chronic pesticide exposures. Several recent studies indicate that pesticide metabolites in children's spot urine samples exhibit high intraindividual variability (Adgate et al. 2001; Koch et al. 2002). In addition, analyses have not been conducted to evaluate whether 24-hr urine samples can be used to classify chronic exposures. It is important to note that a number of urinary validation studies are under way and should be published within the next 2 years. One recent study suggests that first morning void samples may more accurately represent total daily exposure (Kissel et al. 2005). Existing literature evaluating spot versus 24-hr urine samples for nutrients, renal function measures, and some toxicants is mixed (Boeniger et al. 1993; Chitalia et al. 2001; Evans et al. 2000; Hinwood et al. 2002; Kawasaki et al. 1982; Kieler et al. 2003; Lee et al. 1996; Luft et al. 1983; Neithardt et al. 2002; Tsai et al. 1991; Woods et al. 1998).

An additional concern that has recently been raised about urinary biomarkers is that the metabolites in urine may reflect exposure to the metabolites themselves in the environment rather than to the parent compound (Duggan et al. 2003; Wilson et al. 2003). For example, 3,5,6-trichloro-2-pyridinol (TCPy), the specific metabolite for chlorpyrifos, and several dialkyl phosphates, the class-specific metabolites for many OPs, have been found in food samples (Lu et al. 2005; Wilson et al. 2003).

Blood monitoring. Blood monitoring has advantages over urinary measurements in that the parent compound, instead of a metabolite, can be directly monitored (Barr et al. 2002). Pesticide concentrations in blood may more accurately reflect the absorbed dose and the dose available to the target tissue because the measured dose has not yet been eliminated from the body. Whyatt et al. (2004b) recently showed a significant inverse association between chlorpyrifos levels in umbilical cord blood and both birth weight and length, whereas no association was seen between chlorpyrifos in maternal personal air samples measured during pregnancy and either parameter of fetal growth. These results suggest that the biomarker may better reflect exposure from all routes and the amount of insecticides absorbed by the mother as well as the amount of the absorbed dose that has been transferred to the developing fetus (Fenske et al. 2005). Further, unlike urinary levels, no corrections for dilution are necessary when quantifying contaminate levels in blood (Barr et al. 2002). Additionally, it has recently been hypothesized that blood levels may provide a better dosimeter than urinary levels for steady-state exposures (Needham 2005). However, this hypothesis has yet to be validated. The Centers for Disease Control and Prevention (CDC) has developed a sensitive and accurate analytical method for quantifying 29 contemporary-use pesticides in human serum or plasma (Barr et al. 2002). However, laboratory methods are not available for many OPs and other pesticides in blood, including many without specific- or class-specific metabolites in urine. Finally, blood is invasive to collect, although collection can be timed to coincide with medically scheduled blood collections, such as during the pregnancy glucose tolerance test (at 26 weeks gestational age), delivery, and during 12- and 24-month lead screens (Eskenazi et al. 2003; Fenske et al. 2005).

Other biologic monitoring. Laboratory methods are also under development for pesticides in saliva, meconium, and amniotic fluid, although validated methods are available for only a few compounds. Pesticides in saliva should reflect blood plasma levels (depending on the protein-binding capacity) and therefore recent exposure (Lu et al. 1997, 1998). Current saliva collection methods, which use a cotton sponge, could pose a choking hazard to very young children. Meconium, the first bowel void of the newborn, is a concentrated mixture of swallowed amniotic fluid, cells, bile, and other materials and likely accumulates in the third trimester. Measurement of pesticides in meconium could provide an integrated dosimeter for assessment of fetal exposure in the third trimester (Whyatt and Barr 2001). However, this hypothesis has not been validated. Measurement of pesticide metabolites in amniotic fluid is feasible (Bradman et al. 2003), but amniocentesis poses risks to the fetus and therefore can be conducted only when medically indicated. Thus, population-wide sampling is not possible.

Few data are available on levels of nonpersistent pesticides in breast milk. Many nonpersistent pesticides are soluble in water and therefore may partition to the water fraction of breast milk. Furthermore, the log of the octanol–water coefficient (log K_{ow})—a measure of fat solubility—suggests that some

Table 1. Recommended preconception, pregnancy, and perinatal sample collection for nonpersistent pesticide analysis.

Samples	Preconception	Trimester			Perinatal period
		First	Second	Third	
Maternal urine[a,b]	✓	✓	✓	✓	✓
Maternal blood[a,b]			✓[c,d]		✓[d]
Cord blood[a,b]					✓[d]
Meconium					✓
Colustrum/breast milk[a,e]					✓
Maternal saliva[e]	✓	✓	✓	✓	✓
Dietary assessment[e,f]			✓		
Home/personal air sample[a,b,g]		✓		✓	
Home composite dust/wipe[a,b,g]		✓		✓	
Other home samples[b,g,h]	←		Special studies		→
Outdoor samples[b,i]	←		Special studies		→
Questionnaire[a]	✓	✓	✓	✓	✓
Ecologic analysis (e.g., GIS)[a]	✓	✓	✓	✓	✓

✓, sample collection recommended.

[a]Metrics that have been used in prior epidemiologic studies. [b]Media with existing laboratory methods for likely target pesticides (e.g., urine, dust, air, food). [c]Blood collection should coincide with glucose tolerance test. [d]Blood collection that is normal part of medical care. Blood samples crucial for paraoxonase status and acetylcholinesterase activity. [e]Metrics that are more experimental or costly. [f]Duplicate diet sampling, food frequency questionnaire, or other method (see text). [g]We recommend that air and/or composite dust or wipe samples be collected for each home lived in during pregnancy. Other environmental samples should be considered for special studies of selected participants. [h]For example, clothing dosimeters or hand wipes. [i]For example, ambient air samples in agricultural area (see text).

nonpersistent OPs such as malathion (log K_{ow} = 4.5) could partition into the lipid fraction of breast milk. Parathion, malathion, fenchlorphos, and chlorpyrifos have been detected in breast milk in studies from central Asia and India (Lederman 1996; Sanghi et al. 2003). Fonofos and diazinon have been detected in cows' milk or butter fat after acute exposure (Cook and Carson 1985; Spradbery and Tozer 1996). These data suggest that OP and possibly other nonpersistent pesticides may be found in breast milk, although available data are extremely limited. The CDC and the Center for Children's Environmental Health at the University of California, Berkeley, are conducting a study to develop laboratory methods to measure nonpersistent pesticides in human breast milk. Results for several OPs, carbamates, pyrethroids, phthalates, fungicides, and dicarboximides are promising. Numerous research studies indicate that persistent organic pollutants [e.g., 1,1,1-trichloro-2-(*o*-chlorophenyl)-2,2(*p*-chlorophenyl)ethane (DDT), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers] bioaccumulate in fat and are transferred to breast milk, thereby exposing breast-feeding infants (Landrigan et al. 2002).

Environmental Monitoring

Measurements of pesticides in environmental media can be used to augment biomonitoring and, additionally, can provide information about routes of exposure. In cases when no biomarker is available, the environmental measure may provide the only dosimeter of exposure. For example, no laboratory methods are available for measuring either the parent compound or chemical-specific metabolite of the OP oxydemeton methyl in biologic media.

Air monitoring. Many pesticides are semivolatile (Lewis 2001; Lewis et al. 2001) and are readily detectable in indoor and personal air samples. These include the OPs and carbamate insecticides; many of the older organochlorine compounds; herbicides such as alachlor, atrazine, 2,4-dichlorophenoxyacetic acid (2,4-D) and dicamba; and several fungicides (e.g., folpet and *o*-phenylphenol) (Geno et al. 1995; Hsu et al. 1988). The pyrethroids are less volatile, and some of the newer insecticides (e.g., abamectin) are basically nonvolatile. Air sampling may thus not be the best protocol for these less volatile compounds; however, both semi- and nonvolatile pesticides can be resuspended into air on particles by human and pet activity (Lewis et al. 2001; Nishioka et al. 1999, 2001). Pesticides can reach indoor air as a result of volatilization off of treated surfaces within the home or from pesticides tracked into the house from outdoor uses or from occupational take-home exposures (Lewis et al. 2001; Lu et al. 2000; Nishioka et al. 2001; Simcox et al. 1995). There have been numerous prior studies of pesticide levels in indoor air (Clayton et al. 2003; Esteban et al. 1996; Fenske et al. 1990; Lewis et al. 1994, 2001; Pang et al. 2002; Whitmore et al. 1994) and personal air (Clayton et al. 2003; Whitmore et al. 1994; Whyatt et al. 2002, 2003). Indoor air sampling has been conducted over hours to weeks at flow rates ranging from 0.5 to 4 L/min. Sampler height needs to be considered, as pesticide air concentrations may vary with height, being greatest near the floor after indoor application (Fenske et al. 1991; Lewis et al. 1994). Because of participant burden, personal air samples have generally been collected over shorter time periods (24–48 hr) at the higher flow rates (e.g., 4 L/min). However, a recent study collected 6-day integrated average personal air samples at a flow rate of 1.25 L/min from 74 children in Minnesota (Clayton et al. 2003; Quackenboss et al. 2000). Pesticide detection limits depend on the analytical technique and amount of air sampled but are generally in the low nanogram per cubic meter range (Clayton et al. 2003; Whitmore et al. 1994; Whyatt et al. 2003).

Prior studies have shown that inhalation exposure to semivolatile pesticides in indoor air can be substantial and may be a primary route of exposure after residential use among homes using insecticides (Fenske et al. 1990; Whitmore et al. 1994; Whyatt et al. 2002, 2003). However, for any given pesticide/exposure scenario, the primary route of exposure (inhalation vs. ingestion or dermal) will depend both on use patterns and on the volatility of the pesticides. For example, an aggregate exposure assessment of chlorpyrifos found that inhalation exposures accounted for approximately 85% of total daily dose (Pang et al. 2002). Similarly, results from the U.S. Environmental Protection Agency (EPA) Nonoccupational Pesticide Exposure Study indicate that 85% of the total daily exposure of adults to airborne pesticides is from breathing air inside the home (Whitmore et al. 1994). By contrast, a recent assessment of children's exposure to chlorpyrifos, diazinon, malathion, and atrazine determined that ingestion rather than inhalation was the dominant route (Clayton et al. 2003). Indoor air pesticides levels have been shown to be considerably higher than outdoor air levels.

Dust monitoring. Several researchers have concluded that the majority of household pesticides are better detected by dust sampling than by air sampling (Butte and Heinzow 2002; Fenske et al. 2002b; Roberts et al. 1991; Whitmore et al. 1994). Multiple organic chemicals (both persistent and nonpersistent) can be measured in a single house dust sample, and samples without detectable pesticides are rare. For example, laboratory methods are available for measuring pesticides (both semivolatile and nonvolatile), PCBs and other organochlorine compounds, dioxin, dibenzofurans, polycyclic aromatic hydrocarbons, and phthalates in house dust (Butte and Heinzow 2002; Chuang et al. 1995; Lewis et al. 1999; Moate et al. 2002; Rudel et al. 2003). Studies designed to characterize children's exposure to pesticides indicate that the largest number of pesticides and the highest concentrations are found in household dust compared with air, soil, and food (Lewis et al. 1994; Simcox et al. 1995). Finally, whereas air levels of semivolatile pesticides decline rapidly after use, residues are more constant in house dust and can still be detected for months or years after use (Lewis et al. 1994; Roinestad et al. 1993; Rudel et al. 2003). Because of hand-to-mouth activities, house dust may be a significant pesticide exposure pathway for young children.

Table 2. Recommended sample collection for nonpersistent pesticide analysis during early childhood.

	Months					Years			
Samples	3	6	9	12	18	2	3	4	5
Urine[a,b,c]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood[a,c,d]				✓		✓		✓	
Breast milk[a,e]	✓	✓	✓	✓					
Saliva[e,f]					✓		✓	✓	✓
Dietary assessment[e,g]		✓		✓	✓	✓	✓	✓	✓
Home air sample[a,c,h]	←	←	←	Each home/year		→	→	→	→
Home dust or wipe samples[a,c,h]	←	←	←	Each home/year		→	→	→	→
Other home samples[c,h,i]	←	←	←	Special studies		→	→	→	→
Outdoor samples[c,j]	←	←	←	Special studies		→	→	→	→
Questionnaire[a]		✓		✓	✓	✓	✓	✓	✓
Ecologic analysis (e.g., GIS)[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓, sample collection recommended.
[a]Metrics that have been used in prior epidemiologic studies. [b]Pediatric urine bag or diaper sample for non–toilet-trained children. If not diaper, spot samples or multiple spots. Methods to measure pesticides in diapers under development. [c]Media with existing laboratory methods for likely target pesticides (e.g., urine, dust, air). [d]Blood collection at young ages should coincide with CDC-recommended lead screen at 12 and 24 months. Ongoing research has also established that blood collection at 4–5 years of age is feasible. [e]Metrics that are more experimental or costly. [f]Choking hazard for saliva collection for children younger than 3 years with current protocol. [g]Duplicate diet sampling, food frequency questionnaire, or other method (see text). [h]We recommend that air and/or composite dust or wipe samples be collected for each home lived in. Other environmental samples should be considered for special studies of selected participants. [i]For example, clothing dosimeter, hand wipe. [j]For example, ambient air samples in agricultural area (see text).

Most prior studies have collected a sample of house dust from carpets or rugs with the high-volume, small-surface HVS-3 sampler (Cascade Stamp Sampling Systems, Bend, OR) (Lewis et al. 1994; Roberts and Dickey 1995; Simcox et al. 1995). Dust has also been collected using other vacuuming devices (Thompson et al. 2003), and several studies have sampled noncarpeted areas, although dust loading levels are much lower. In all cases, the protocols are labor intensive because they require that the sample be collected by the study team. Studies have also collected dust samples by asking the participants themselves to save the bag from a vacuum cleaner (Roinestad et al. 1993). Colt et al. (1998) compared levels of pesticides and other compounds in dust obtained from used vacuum cleaner bags with those collected by the HVS-3 among 15 homes and found reasonably comparable results. This approach has the advantage of relatively low cost of sample collection. However, disadvantages include the fact that participation is limited to those subjects who own a vacuum cleaner. Further, although the protocol allows determination of contaminant concentrations per gram of dust, pesticide loading (amount of pesticide/floor area) cannot be assessed.

A limitation of dust sampling is that the timing of application is not known, and levels in the dust may reflect use months to years before the sampling. Also, dust on hard surfaces may be readily available to transfer to children's skin and result in nondietary ingestion or dermal exposures, whereas dust lodged deeply in carpets may not be available to children. Carpet dust and dust from other surfaces may function as a reservoir for household pesticide contamination, recontaminating surfaces and air after cleaning depending on the physical and chemical properties ("fugacity") of the specific compounds. Additionally, studies on the inter-relationships of environmental and personal exposures can be difficult to interpret.

Wipe samples. Initial attempts to look at direct child exposures have included the use of hand wipes to collect pesticides directly from children's hands. These methods include wiping the child's hand with sterile gauze dressing pads that have been moistened with propanol or asking the child to place his/her hand in a bag containing propanol (Bradman et al. 1997; Geno et al. 1996; Lioy et al. 2000). Gordon et al. (1999) found excellent correlations between chlorpyrifos in indoor air and corresponding dermal wipes but poor correlations between chlorpyrifos in dust and dermal wipes. Another study reported a weak association between concentrations of OP pesticides in house dust, loadings in house dust, and concentration on hands, hand surface area, and urinary levels of OP metabolites (Shalat et al. 2003). However, hand loadings of OP pesticides were more strongly associated with urinary OP metabolite levels. This finding suggests that on a cross-sectional basis, pesticides on hands may be more strongly correlated with exposure biomarkers. On a longitudinal basis, however, the dust measure may provide better classification of potential and actual exposure. Dust wipe samples have also been collected using the Edwards and Lioy (EL) press sampler and the Lioy, Wainman, and Weisel (LWW) surface wipe sampler (Lioy et al. 2000). The EL sampler has been designed to collect surface concentrations of dust and pesticides that are representative of those adhering to the human hand (Edwards and Lioy 1999). A significant correlation was seen between chlorpyrifos levels in EL surface and carpet samplers (Lioy et al. 2000). The LWW sampler has been used to obtained dust samples from smooth surfaces in the home (Lioy et al. 2000). A protocol that is currently being validated involves mailing study participants an alcohol wipe with instruction for wiping dust on the top of a specified doorframe. The sample is then placed in a Ziploc bag and mailed back to the study team. Advantages include low cost of sample collection and low participant burden. However, research is currently ongoing to determine detection limits and detection frequencies using this method. Other techniques include use of clothing dosimeters such as cotton gloves, union suits, and socks, as well as alternative surface wipe techniques, to quantify exposures (Fenske 1993; Lewis 2005).

Dietary sampling. Diet is a potentially significant pathway of exposure to pesticides for children (Clayton et al. 2003; Fenske et al. 2002a; National Academy of Sciences 1993). Numerous studies have detected OP and organochlorine insecticides and herbicides in food, including chlorpyrifos, malathion, dichlorodiphenyldichloroethylene (DDE), diazinon, and atrazine (Clayton et al. 2003; MacIntosh et al. 2001; Pang et al. 2002). Market-basket surveys by the U.S. Department of Agriculture (USDA) indicate that most food types contain some pesticide residues (USDA 2002). For example, 65 and 82% of conventionally grown vegetables and fresh fruits tested by the USDA Pesticide Data Program (PDP) from 1994 through 1999 contained one or more pesticide residues (Baker et al. 2002). However, pesticide concentrations vary significantly across foods (Gunderson 1995). Low detection frequencies, combined with highly variable individual diets, make it difficult to estimate individual dietary exposures using food consumption questionnaires (MacIntosh et al. 2001). Instead, studies have generally estimated dietary exposures by measuring pesticides in duplicate diet samples, in which study participants prepare and collect duplicate portions of all foods and beverages consumed (Quackenboss et al. 2000; Wilson et al. 2004). These studies are considered the gold standard; however, they are extremely time intensive and costly and place substantial burdens on participants. Duplicate diet studies may also underestimate dietary exposure if study designs do not account for contamination of foods from indoor sources, such as handling of food by children who also contact contaminated surfaces or dust (Melnyk et al. 2000). Finally, duplicate diet studies are valid for the period over which the samples were collected (e.g., 24 hr) but may not reflect chronic exposures. Laboratory methods for food often require extensive cleanup steps to address fatty and nonfatty foods. Some researchers recommend that acidic foods (e.g., fruit) be collected separately from nonacidic foods (e.g., bread), potentially increasing participant burden and the possibility of error.

Questionnaire-based evaluations have also been used to assess dietary exposures. The key questions that these methods address are how much and what types of food are being eaten and what are the pesticide levels in these foods when eaten (after preparation and handling). Questionnaire methods including 24-hr food recall and food-frequency questionnaires, and diaries can be used to estimate the types and amounts of food individuals are eating. This information can then be linked to national food pesticide residue data (e.g., California Department of Pesticide Regulation 2005a; USDA 2005) to estimate the range of individual exposures. Finally, questionnaires can also be used to classify food consumption patterns that relate to exposure (and nutrition). Examples include the timing of the transition in young children from liquid to solid foods (at 4–6 months) and the consequent increase in consumption of potentially contaminated grains or produce. Before 4–6 months, virtually all dietary exposures, if present, will be due to contamination of formula (powder or water) and possibly breast milk (discussed above).

Infant formula. Several studies have investigated pesticide contamination in milk- or soy-based infant formula. In the United States, Gelardi and Mountford (1993) reviewed tests on 2,043 milk-derived samples and 1,141 soy-derived samples by formula manufacturers. Thirty-four target pesticides included OPs, carbamates, herbicides, and several fungicides (National Academy of Sciences 1993) (persistent organic pollutants were not included). No detectable results were reported. All detection limits were < 1.0 ppm, with most detection limits < 0.005 ppm. We did not find any U.S. studies funded by nonindustry sources. In Canada, Newsome et al. (2000) tested six composite milk-based and six composite soy-based formula samples for a wide array of pesticides, including OPs, carbamates, herbicides, and persistent organic compounds (i.e., DDT,

etc.). The sampling scheme was designed to represent the Canadian infant diet. No pesticides were detected in these composite samples. Studies in New Zealand, India, and Spain report positive detections for several pesticides, including DDT and derivatives, hexachlorobenzene, hexachlorocyclohexane, heptachlor, aldrin, endrin, azinphos-methyl, pirimiphos-methyl, dimethoate, and malathion. Overall, these studies suggest that pesticide contamination in infant formula in North American and other developed countries is low and unlikely to be a major source of infant exposure.

Drinking water. Drinking water may also be a source of pesticide exposure, particularly in agricultural communities. In the late 1980s the U.S. EPA undertook a nationwide survey of pesticide contamination in groundwater (Nadakavukaren 2000). The study found that 14% of all public and private drinking-water well samples had measurable levels of at least one pesticide. Subsequent analyses showed that nearly one-third of rural wells sampled had pesticide contamination, with aldicarb and the herbicides atrazine and alachlor being the most widespread. Agricultural pesticide use was the main source (Nadakavukaren 2000). The PDP recently initiated monitoring of finished waters at drinking water treatment plants in New York and California states as a pilot program for a nationally representative drinking water assessment program (USDA 2001). New York and California were initially chosen because they represent diverse climate, geology, and land use and are highly populated. In the near future, monitoring sites will be expanded to include Texas, Kansas, and Colorado. The PDP screens for more than 150 pesticides and metabolites, with detection limits in the part-per-trillion range; 297 samples were tested in 2001, the most recent year with published data. Overall, "positive detections were reported in 145 (40%) of the samples"; the detects were primarily of widely used herbicides. Atrazine or its metabolites were detected in 42–60% of the samples tested (concentration range = 5–500 ppt). Simazine was detected in 15% of samples (concentration range = 13–93 ppt). Metolachlor, metolachlor ethanesulfonic acid, or metolachlor oxanilic acid (OA) was detected in 10–50% of samples, with concentrations ranging up to 4,420 ppt (OA). Alachlor or metabolites were detected in 4% of samples. Detection frequencies for other compounds were all below 1%, including bentazon, diazinon, malaoxon, metribuzin, or propanil.

The California Department of Pesticide Regulation monitors surface and well waters statewide. Diazinon, dimethoate, chlorpyrifos, carbaryl, DDE, DDT, diuron, and oxamyl have been detected in surface water (concentration range = 0.1–2.8 µg/L), and 1,2-dichloropropane, 2,4-D, atrazine, dibromochloropropane, ethylene dibromide, heptachlor, simazine, bromacil, diuron, and hexazinone in well waters (California Department of Pesticide Regulation 2005b). Overall, detection frequencies are low (9%, with ultimately 0.5% verified in 2001). Melnyk et al. (1997) tested drinking water in Iowa and North Carolina for 32 pesticides, including OPs, carbamates, herbicides, and organochlorines; none were detected. Zaki et al. (1982) reported aldicarb in 52% of groundwater samples collected in Suffolk County, New York (concentration range up to > 75 µg/L). Little or no pesticides were found in municipal drinking water in the Nonoccupational Pesticide Exposure Study (Whitmore et al. 1994). In summary, available data suggest that widespread contamination of drinking water by herbicides may contribute to chronic exposures in some parts of the United States. Although other compounds have been detected in surface and well waters, available data suggest that contamination is limited to isolated communities or households and does not result in population-wide exposures. Although the core NCS hypotheses do not focus on nonpersistent herbicides, laboratory methods for measuring herbicides in biologic samples are available for future studies of archived material.

Questionnaire Data and Ecologic Analyses

It is unlikely that questionnaires alone will prove adequate data for pesticide exposure classification (Sexton et al. 2003). However, questionnaires can provide an important supplement to environmental and biologic monitoring. For example, results from ongoing studies by the Children's Environmental Health Centers funded by the U.S. EPA and National Institute of Environmental Health Sciences have found that questionnaires are able to provide information about residential use habits but are rarely able to obtain more detailed information on specific chemicals (Fenske et al. 2005). In preliminary analyses of questionnaires administered by the Columbia Center for Children's Environmental Health, women provided a pesticide product name for fewer than half the pest control methods reported to be used in the home during pregnancy and, in particular, were rarely able to identify the pesticide products used by an exterminator (Fenske et al. 2005). Further, pesticide products can have the same brand name but contain different active ingredients, further complicating use of questionnaire data in pesticide exposure assessment. A visual inspection of active ingredients in pesticide products in the home can be used to supplement questionnaire data. Questionnaires can also provide information about exposure-related events in a household that would not be captured by biomonitoring. For example, a short-term exposure related to a single pesticide application, such as a "bomb" fumigant, may not result in a detectable exposure in a biologic sample collected several weeks later. Finally, questionnaires can provide basic information about milestones in child behavior that explain changes in exposure, such as the transition to solid foods noted above or the onset of crawling and walking that may lead to increased dermal contact with their environment.

Geographic information systems (GIS) provide a tool to evaluate information on pesticide use or landscape features to classify exposure. For GIS analyses, pesticide use reporting (PUR) data must be geographically coded. Several states compile data on agricultural pesticide use. In California 100% of all agricultural pesticide use is reported to the state and geocoded to one-square-mile sections based on the Public Lands Survey System (PLSS). In several epidemiologic studies, researchers have then linked these data to residential addresses to classify exposure based on the amount of nearby pesticide use (Bell et al. 2001; Gunier et al. 2001; Reynolds et al. 2002, 2004). In a case–control study of stillbirths, Ihrig et al. (1998) linked residential address to geographically based estimates of arsenic exposure from an agricultural chemical manufacturing facility. This approach could be a model for nested case–control studies within the NCS. Other researchers have used GIS and land-use data to classify residential proximity to croplands as an exposure metric (Ward et al. 2000a, 2000b; Xiang et al. 2000).

Classifying pesticide exposure using these types of ecologic analyses has many limitations. For example, nearby pesticide use does not necessarily result in exposure, and if it does, exposure may vary depending on proximity to a given application (which can vary greatly within a PLSS section), weather conditions, daily activity patterns, and so forth. In a simulation study of exposure misclassification and bias using PUR data, Rull and Ritz (2003) found that accounting for nearby cropping patterns, seasonality, mobility, and other factors was necessary to improve the "spatiotemporal resolution of pesticide exposure models." Researchers in Washington State have found higher pesticide levels in house dust and urinary metabolite levels in children for households living close to fields compared with those living farther away (Lu et al. 2000; Simcox et al. 1995). Other researchers have not found these relationships (Royster et al. 2002). Differences in crop (orchard vs. row crop), pesticide application methods, climate, sampling methods, etc., could explain these findings. Clearly, additional studies are needed to determine whether ecologic exposure measurements are valid for large-scale epidemiologic studies.

Discussion

Quantifying exposure to nonpersistent pesticides in the NCS will be challenging (Needham et al. 2005). Exposures are likely to be variable, can occur simultaneously from multiple routes (dietary and nonintentional ingestion, inhalation, and dermal absorption), and can vary dramatically within a particular group or across populations depending on use patterns. These circumstances will require intensive sampling and a repeat-measurement design and will likely necessitate use of a combination of both environmental and biologic monitoring supported by questionnaire information. Özkaynak et al. (2005) provide an overview of the steps necessary in selecting appropriate exposure assessment methods in the NCS. The framework presented in Tables 1 and 2 outlines assessment methods specific for characterizing pesticide exposures for a longitudinal epidemiologic study of neurodevelopmental outcomes in children. Experimental evidence indicates that the window of susceptibility for neurotoxic pesticides is likely during nervous system development (Slotkin 1999). Thus, the prenatal and early postnatal periods are the key critical life stages during which pesticide exposure must be carefully assessed. The initial step in selecting the exposure assessment methods will include an evaluation of whether the exposure at the critical life stage can be reliably estimated using questionnaire data alone or another indirect low-cost, low-burden measure of exposure. In most instances these measurements alone will not provide reliable dosimeters for pesticide exposures and will need to be supplemented by other methods. However, the survey instruments will be useful to assess household information directly related to pesticide exposures, including household practices such as home pesticide use, food consumption trends, address changes, and so forth. Where feasible, GIS and other ecologic methods should be used. At the very least, the latitude and longitude coordinates of each home should be determined for future studies of pesticides or other environmental exposures. It is also important that questionnaires and other indirect exposure measurements be validated against more direct measures (e.g., biologic or environmental monitoring).

In selecting the direct measurements, the researcher must decide whether to collect a biologic or an environmental sample, or some combination of both. Given the complexity of assessing exposure to nonpersistent pesticides, it is likely that both environmental and biologic sampling will be needed for many compounds. It is important to realize, however, that although efforts to assess children's pesticide exposures have increased dramatically in the last decade, most exposure assessment methods are not fully validated for use in an epidemiologic study. Despite these limitations, a strong case can be made for collecting biologic and environmental samples to characterize children's exposure for the NCS. Tables 1 and 2 include the primary media we believe should be collected to assess pesticide exposure: *a*) urine from mothers and children, *b*) maternal and child blood with blood collection linked to scheduled medical tests, *c*) cord blood, and *d*) air and/or house dust or wipe samples. Meconium, breast milk, and saliva should also be collected and stored for future use. Validation studies are currently in progress that will provide key information about pesticide exposure assessment methods (Bradman et al. 2003; Fenske et al. 2005; Kieszak et al. 2002; Kissel et al. 2005; Whyatt and Barr 2001; Whyatt et al. 2003). Additionally, several birth cohort studies have successfully used blood and urinary metabolite exposure markers to assess relationships between nonpersistent pesticide exposure and adverse health outcomes in newborns (Berkowitz et al. 2004; Eskenazi et al. 2004; Whyatt et al. 2004b). In some cases the findings of these studies are not consistent. However, these studies have demonstrated the feasibility of collecting environmental and biologic samples, including blood and urine, for large cohort studies. Finally, each project has also stored a variety of samples that will ultimately allow replication of each study and direct assessment of key criteria necessary to judge causal relationships. Planning for the NCS should be forward-looking and include resources to bank a variety of sample types to ensure that new or improved laboratory methods can be applied when they become available. Other exposure assessment methods should be considered for specialized exposure or health outcome studies that involve a subset of participants. These methods could include measuring pesticides in duplicate diet or breast milk samples, or other media (reviewed above). Information from new validation studies should be continuously monitored to improve exposure assessment protocols for this long-term prospective study. For example, exploratory studies of semipermeable membranes that absorb pesticides or wipe and settled dust-sampling techniques may provide less expensive strategies to assess exposure (Robertson et al. 2003). Participant incentives should also be carefully chosen to maintain retention and encourage cooperation. For example, some participants could be provided with vacuum samplers to collect house dust. Participant burden will be a key factor to consider when choosing exposure assessment methods. Initial pilot studies for the NCS should determine what is feasible for participants and tailor protocols to accommodate participant needs. Recent birth cohort studies have implemented protocols approximating the sampling framework presented in Tables 1 and 2. These efforts, however, require intensive staff time to collect the information and samples and to maintain retention. They also require a major time commitment by participants and are logistically challenging, especially when different visit types (e.g., prenatal, delivery, child) with different women are occurring simultaneously.

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