Exposure Assessment in the National Children's Study: Introduction

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The science of exposure assessment is relatively new and evolving rapidly with the advancement of sophisticated methods for specific measurements at the picogram per gram level or lower in a variety of environmental and biologic matrices. Without this measurement capability, environmental health studies rely on questionnaires or other indirect means as the primary method to assess individual exposures. Although we use indirect methods, they are seldom used as stand-alone tools. Analyses of environmental and biologic samples have allowed us to get more precise data on exposure pathways, from sources to concentrations, to routes, to exposure, to doses. They also often allow a better estimation of the absorbed dose and its relation to potential adverse health outcomes in individuals and in populations. Here, we make note of various environmental agents and how best to assess exposure to them in the National Children's Study—a longitudinal epidemiologic study of children's health. Criteria for the analytical method of choice are discussed with particular emphasis on the need for long-term quality control and quality assurance measures.
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According to the National Center for Health Statistics (NCHS), in the year 2000 more than 4 million children were born in the United States (NCHS 2002), and according to the U.S. Census Bureau, 72 million children younger than 18 years were living in the United States, accounting for approximately one-fourth of its population (U.S. Census Bureau 2000). Children are our future; however, in 2001 more than 27,000 children died in the United States. The leading causes of deaths among children varied with the age group; for example, the leading causes of death among infants were birth defects and conditions associated with premature births. Approximately 3% of children in the United States were born with a major birth defect; approximately 17% of children had some type of developmental disorder; and an estimated 31% had a chronic health problem (Arias et al. 2003). The reasons for many of these adverse health conditions are not known, although some can be linked to known environmental exposures.

In 1997 the President's Task Force on Environmental Health Risks and Safety Risks to Children was charged with developing strategies to reduce or eliminate adverse effects on children (up to 21 years of age) caused by environmental exposures. The task force proposed a longitudinal cohort study of the effects of environmental exposure (broadly defined) on the health and development of children. Subsequently, the Children's Health Act of 2000 (2000) authorized the National Institute of Child Health and Human Development (NICHD) to conduct a national longitudinal study of environmental influences (including physical, chemical, biologic, and psychological) on children's health and development. To lead the planning and implementation of the study, staff and funds have been allocated by the NICHD, National Institute of Environmental Health Sciences (NIEHS), Centers for Disease Control and Prevention (CDC), and the U.S. Environmental Protection Agency (EPA). Investigators from each of these four entities serve on the National Children's Study (NCS) Interagency Coordinating Committee, which has further developed the conceptual framework for the NCS (NCS 2001). Various work groups are charged with providing technical guidance to the federal advisory committee of the NCS. Our work group, the Exposure to Chemical Agents Working Group, is charged with characterizing various means of assessing exposure for those hypotheses requiring exposure assessment (NCS Interagency Coordinating Committee 2003). Our work group primarily considered exposures to chemicals found in the environment that we may have contact with in our daily lives (environmental chemicals) and to selected biologic and physical agents.

Exposure Pathways

When examining a population for adverse health impacts that result, in part, from environmental insults, it is essential to try to link those impacts with exposures to selected chemical, biologic, and physical agents that occur in our daily environment. We consider not only the known toxicity and the concentration of a given agent to which an individual or a population is exposed but also the frequency, duration, pathways, and routes of these exposures. In addition the developmental life stage of the person(s) exposed is of fundamental importance (U.S. EPA 2001). For example, many researchers believe that some health end points that manifest at various stages of development are a result of exposures that occurred soon after conception. They also deem the critical or most susceptible time period for environmental exposures as *in utero* through 2 years of age, especially for some neurobehavioral outcomes. Other research suggests prepubertal exposures are significant; for example, prepubertal males highly exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin later fathered predominantly female children (Mocarelli et al. 2000). There are various means for assessing children's exposures to environmental agents (Needham and Sexton 2000). However, before discussing these methods, we must examine the pathways of these agents that lead to exposure and ultimately to dose.

Exposure is defined as contact between an agent and a target; contact takes place at an exposure surface over an exposure period [World Health Organization (WHO) 2002; Zartarian et al. 1997). In the NCS various hypotheses linking exposures and health end points will be tested. The agents of concern to certain hypotheses are selected environmental

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chemical, biologic, and physical agents; the targets are children; the exposure surfaces are the external surfaces of the children (i.e., skin, mouth, and nasal passage); and the exposure period is the child's lifetime or a defined portion of that lifetime. The continuum (Figure 1) often used to describe the human exposure assessment pathway starts with the agent at its origin or its source, which, for example, can be a chemical manufacturing plant, automobile exhaust, or a chemical waste site. The agent can undergo various fate (e.g., transformation to another chemical) and transport (e.g., long-range air transport or leaching from soil into groundwater) steps in the environment. This may lead to multiple intermediate sources in the pathway for a given agent; eventually, humans may have contact with the environmental media that contain the agent or its environmental transformation products. The exposure mass may pass through membranes and enter into the body's circulatory system by three routes: ingestion, inhalation, and dermal absorption. Depending on the membrane absorption coefficients and other bioavailability factors, the agent (or its metabolite) can be absorbed into the bloodstream. This absorbed dose of the agent or metabolite [or its reaction product (adduct)] is also known as the internal dose. This internal dose can be directly eliminated (usually a minor route); distributed within the body to other organs including the target organ(s); metabolized and eliminated (usually in urine); metabolized and distributed within the body to other organs including the target organ; or some combination of these (Needham et al. 2004). A portion of the dose at the target organ may be biologically effective (biologically effective dose) (Needham et al. 1992). The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed, is called an exposure assessment (WHO 2002; Zartarian et al. 1997); certainly for health studies the term "exposure assessment" includes assessing the dose within the body (Figure 1).

Exposure Assessment Methods and Their Uses

Exposures to the general population of the United States may be very difficult to accurately assess because we are generally exposed to low levels of environmental chemicals, and the exposure scenario may be episodic (occurring only occasionally). The exposures may occur in different settings (e.g., occupational) through various pathways (including air and dietary) and routes (inhalation, ingestion, dermal absorption). For assessing exposures to environmental agents (e.g., chemicals), there is no single method that will capture all the needed exposure information all the time. Because the NCS will assess exposures of children at various ages and life stages (Figures 1,2), impact or burden to the study participants is a factor, especially when attempting to assess exposures during the *in utero* and early childhood life stages. Therefore, a method that is "best" for assessing exposure to a given chemical at one life stage may not be the "best" method for assessing exposure to that same chemical at a different life stage.

Three main methods are used to assess human exposures to chemical and biologic agents: questionnaires and other indirect means, environmental monitoring including personal monitoring, and biomonitoring. All these methods seek to gain information on the concentrations of the agent(s) to which the person(s) may have been exposed, the duration and frequency of that exposure, and an estimation of their internal dose. Other data that should be factored into the assessment, especially when the human population being studied contains fetuses and children, are the timing of the exposure (or when the exposure took place) during those critical susceptible periods of development. The three means of assessing exposures to these agents are discussed below.

Questionnaires help researchers acquire needed individual exposure and potential effect information such as demographic characteristics, lifestyle activities including nutritional status and exercise regimen, and medical history including medications that is unavailable through other methods. These factors can affect the environmental chemical's pharmacokinetics [absorption, distribution, metabolism (biotransformation), and elimination], which can influence the biologically effective dose, and pharmacodynamics, which can influence the health effects. Therefore, this information is crucial for the NCS. Questionnaires have also been used for developing exposure indices for study participants. These exposure classification indices consist of two types of information: the concentrations of the chemical with which participants have contact (exposure) and the frequency/duration of that exposure. In general, questionnaires provide more accurate data on the frequency/duration aspect of the index compared with the concentration component. Once developed, these exposure indices must be validated by using a more direct exposure assessment method such as biologic or environmental monitoring. However, questionnaires are more frequently used to give complementary data to the actual exposure assessment. One example of where exposure indices developed by questionnaires may be of most use is in estimating the dose of certain ingredients in personal care products that are applied directly to the skin (Figure 1). However, for reasons given below, it is still preferred to validate these estimates through biomonitoring if possible.

Questionnaires can be self-administered or interviewer administered. Both require a high level of expertise in writing the questionnaire and, for the latter, in administering the

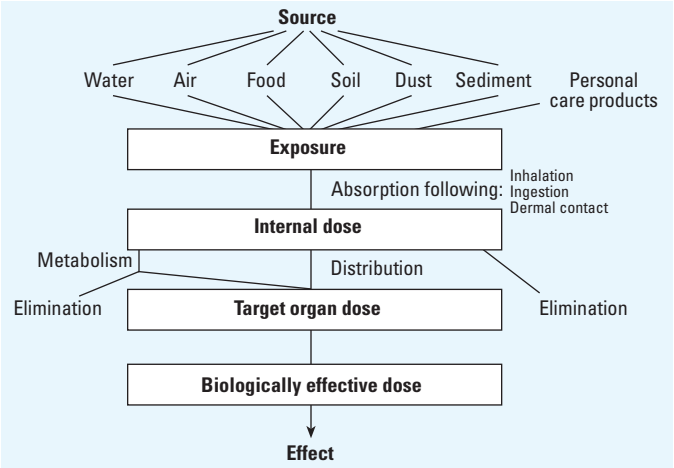

Figure 1. Source to exposure to health effects pathway.

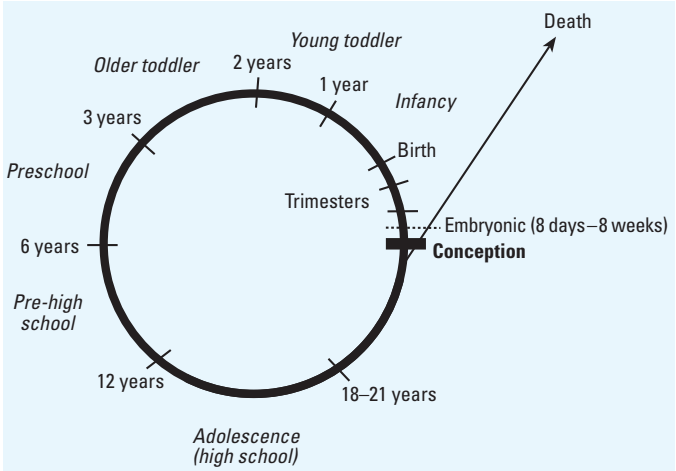

Figure 2. Life stages of interest in the NCS.

questionnaire. The questionnaire must acquire the necessary information in a clear, unbiased manner but yet not be so lengthy that it presents an undue burden (which leads to boredom and to inaccurate information) to the study participant. Questionnaire data may suffer from the disadvantage of information bias, especially recall bias, which can lead to inaccurate exposure and outcome classifications. The use of questionnaires is discussed in more detail in our work group's white paper (NCS 2004).

Information from other indirect methods such as geographic information systems (GIS) and videotaping is also limited by not providing actual concentration data for the agent in environmental and human specimens. Videotaping has the advantages of tracing a given individual throughout his/her activities in daily life and observing potential contacts with the agent of concern and the frequency/ duration of these contacts. Videotaping is particularly useful for recording the potential for transferring an agent from the outer surfaces of the body into, for example, the mouth, for recording such actions as hand-to-mouth activity. GIS uses computerized maps to integrate potential exposure data (e.g., from estimated pollution data) into a spatial form so that the data can be analyzed geographically. GIS data are often used when more direct monitoring data are not available. In the future GIS information on both potential exposures and the occurrence of disease will be mapped globally, nationally, regionally and locally. One of the more important issues in using GIS information is how to integrate data gathered at different levels of spatial resolution (e.g., ZIP code, city, county, and region) into a final data analysis (Viner et al. 1997). As for exposure data gathered by questionnaires, we urge that for the NCS, measurements in environmental or biologic samples be performed to validate exposure assessments.

Environmental measurements, that is, the measurement of a chemical agent or its transformation product in an environmental medium, provide information that can be used to track the chemical from its source throughout the environment—air, water, food, soil, dust, etc.—up to its human contact. Consequently, environmental measurements are especially useful in risk management, where one is concerned about interrupting the pathway to exposure and preventing further environmental contamination and human exposure. In addition these measurements have been used as the metric for risk assessment. For example, reference concentrations/doses and cancer unit risks are expressed as an environmental concentration that can then be compared with an exposure estimate to determine whether an adverse health risk is likely. Environmental data are of most use when there is a single predominant environmental matrix such as air involved in the exposure pathway. If the environmental pathway is multimedia, then the number of potential measurements (and hence costs) to assess this cumulative exposure increases dramatically, and the data are more difficult to model for the purpose of predicting human exposures and particularly the internal doses. In the exposure index paradigm, environmental monitoring provides us with information about the concentration of the chemical(s) to which humans are potentially exposed and potential routes of exposure, whereas questionnaire information provides the data on the duration and frequency of exposure and the timing of the exposures. Thus, this combination of environmental monitoring and questionnaire information provides needed information on the potential dose, which may be useful for regulatory purposes. However, for health studies, we are most concerned with the biologically effective dose at the target organ of the exposed individual; therefore, models must be developed to estimate the amount of the chemical to which the population is exposed and furthermore, the amount that is absorbed into the body and becomes the internal dose and ultimately the biologically effective dose (Burke et al. 2001; MacIntosh et al. 1995; Ott 1985; Özkaynak 1999; Ryan 1991; Zartarian et al. 2000). These models, if possible, should be calibrated and validated before being used.

Air pollutants are some of the most measured environmental chemicals. They can be measured in the air itself or by personal exposure monitors. Depending on several factors, including the chemicals to be monitored, active or passive sampling may be used. Active sampling involves drawing the air into the collection unit with a sampling pump, whereas passive sampling relies upon diffusion. In both sampling processes, the collection unit should be located within 30 cm of the nose and mouth (i.e., in the "breathing zone"). Personal air monitoring is an important component in estimating exposure concentrations in certain exposure scenarios, but again the uptake data for the chemical and pharmacokinetic data have to be modeled for the exposed individual. Disadvantages of personal air monitoring and environmental air monitoring include the lack of accounting for differences of breathing rates and volumes of air inhaled among people or within a person, for example, during physical exercise.

A concern in all methods used for human exposure assessment is the burden on the study population. However, the use of environmental monitoring plus questionnaire information may present no more burden on the study population than the questionnaire itself, but this is usually not the case. For example, if indoor air is monitored, equipment must be installed in the home; if food is monitored, then duplicate diets may be taken; and if personal air monitors are used, they must be installed on the individual. However, many developments in monitoring personal exposures to airborne chemicals and particulates are ongoing. These developments include portable chemical sensors and clothing ranging from bracelets to smart shirts that will allow the assessment not only of chemicals in the air but also of chemicals coming into contact with clothing; furthermore, the clothing devices can denote physiologic changes such as heart rate.

Assessing personal exposures in health studies such as the NCS often relies upon partial information on measured concentrations of chemicals in various microenvironments of concern. Consequently, the use of limited outdoor or indoor monitoring information can lead to exposure misclassification biases that in turn may result in loss of statistical power or potential for obtaining a null result when actually an association between exposure and disease exists (Özkaynak et al. 1986; Özkaynak and Spengler 1996). To minimize errors in estimating personal exposures, researchers identify key sources, media, routes, and pathways of concern for each environmental pollutant and then determine an optimum sampling and analysis plan. These plans should consider the stability of the chemical in the environment as well as if and how it is bound, suspended, or in solution. In practice both budgetary and technical constraints often limit the extent of an environmental monitoring program. Such a program's actual cost depends on the chemical, the number of matrices to be monitored, which matrices are monitored, frequency of monitoring, and the cost of the questionnaire.

One advantage of environmental monitoring that is often overlooked is that it identifies the route of exposure that is important information for chemicals whose toxicities differ depending upon the route of exposure. For example, chemicals such as manganese and polycyclic aromatic hydrocarbons that are bound to particulate matter are potentially more toxic when inhaled than when ingested. Monitoring methods that do not account for this might incorrectly assess the toxicity of such an exposure.

The primary goal of an environmental epidemiologic study such as the NCS is to link the biologically effective dose with the adverse health outcome of interest. However, measurements of the biologically effective dose are most often impossible because the target organ may not be known or, if known, cannot be sampled. As a result, researchers most often regress (work back from biologically effective dose toward the source) on the exposure continuum (Figure 1) and attempt to measure the absorbed dose or internal dose. Such measurements are called biologic monitoring or

biomonitoring and provide information on the internal dose integrated across environmental pathways and routes of exposure; thus, an advantage of biomonitoring is that it directly considers the amount of the chemical that is absorbed into the body's systemic circulatory system. These concentrations can then be entered into models such as physiologically based pharmacokinetic models in order to estimate the biologically effective dose (Mason and Wilson 1999).

Procedures for collecting biologic samples range from those that are invasive, such as the drawing of blood, to those with little intrusion, such as collecting urine samples from older children. If one neglects the burden on the person and the amount of blood that can be collected, blood has inherent advantages for biomonitoring, for regardless of the route of exposure, the chemical must be absorbed into the bloodstream and circulate to the tissues to have an effect (exceptions would include direct inhalation effects on the lung and also blistering agents on skin). Blood is also a "regulated" matrix; therefore, there is a constant amount of blood for a given body weight, so measurements can be "normalized" to this amount. The other most commonly monitored biologic matrix is urine, which serves as a "sink" for many chemicals, especially the nonpersistent chemicals (i.e., chemicals with short biologic half-lives); the persistent chemicals are eliminated primarily through the feces. The nonpersistent chemicals are generally found in the urine not only as their original "parent" structure but more frequently as metabolites. Measuring these metabolites to assess exposure, however, may be problematic because multiple chemicals may form the same metabolite and because the environmental transformation product (e.g., for organophosphorous pesticides) may be the same chemical as the metabolite, thereby confounding interpretation. Nonetheless, urinary measurements can play a vital role in assessing human exposure to many environmental chemicals. To gain specificity, these nonpersistent chemicals, such as chlorpyrifos and many volatile organic chemicals, have been measured as the parent compound in blood (Needham 2005; Whyatt et al. 2004). Another way to gain specificity and increase the time window for the exposure assessment for certain nonpersistent chemicals is to measure their reaction products or adducts, such as with hemoglobin, albumin, or DNA.

For persistent chemicals (those that have "long" half-lives on the order of months or years in the environment and in humans), biomonitoring data provide information as to what chemical and how much actually enters into people and accumulates; however, in most cases, biologic monitoring data do not provide information on the timing, the sources, or routes of exposures. Persistent chemicals are generally measured in blood or its components (e.g., serum and plasma), in adipose tissue, or in human milk. After exposure to persistent chemicals, differences in pharmacokinetics among various people will affect the internal dose levels to some degree but not to the extent of misclassification for the purposes of epidemiologic studies. Thus, biomonitoring is generally considered to be the "gold standard" for assessing human exposure to persistent chemicals, provided the sample collection medium is feasible. In the event that biomonitoring is not feasible (e.g., collection of 100 mL blood from an infant for a dioxin measurement is not feasible), an exposure index derived by other methods for persistent chemicals, such as environmental sampling combined with questionnaires, should be considered.

For chemicals that have short half-lives, biomonitoring data may become much more difficult to interpret. If the exposure situation is continuous or even continual, then the exposure situation (not the chemical) could be deemed "persistent" or "chronic" and biomonitoring plays a vital role in assessing human exposure (Needham et al. 2004); however, if the exposure is predominantly from one environmental medium, then environmental monitoring and questionnaire data should also be considered for assessing a child's exposure. Whenever exposures are inconsistent or episodic, then biomonitoring, like other techniques such as environmental monitoring, loses much of its ability to track these exposures. In this scenario the frequency of sampling and hence the comparison of data from these samplings and their associated costs are extremely important issues.

For some chemicals or physical agents, we have little or no means to assess their exposure via biomonitoring. These include particulate matter, asbestos, some of the air criteria pollutants (e.g., oxides of nitrogen), and allergens. Also, for some chemicals the nonspecificity of the metabolite biomarker (depending on the chemical and the biologic matrix used) may make it difficult to determine the actual chemical to which the population was exposed. Another important point, especially for inorganic chemicals, is that both environmental and biologic monitoring include the biologically active specie(s) of the chemical, for example, methyl mercury for assessing exposure to mercury after fish consumption (Needham et al. 2005a).

Regardless of whether data from questionnaires, environmental monitoring, biomonitoring, or a combination of these techniques are used for exposure assessment, these data need to be modeled and linked to the biologically effective dose (Figure 1) and beyond to adverse effect (disease) data. Another approach that can potentially be used is to move through the exposure continuum (Figure 1) and into the effect portion of the continuum. This approach involves monitoring for endogenous changes (an effect) in the body [e.g., by using molecular profiling to note changes in messenger RNA (transcriptomics), proteins (proteinomics), and endogenous metabolites (metabolomics)] (Wilson and Suk 2003). Once these changes are noted, we again regress on the exposure continuum to focus on the agent(s) that can be linked to these changes. This approach has advantages, but certainly the specificity of linking certain stressors (e.g., psychosocial and nutritional) in addition to exposures to environmental chemicals with such changes is unclear at this time.

Analytical Methods Used in Environmental and Biologic Monitoring

Monitoring data on a global, national, and regional basis are generally organized by media. For example, the U.S. EPA lists several programs on its website (U.S. EPA 2004) that monitor the United States or portions of the United States for persistent bioaccumulative toxicants in emission inventories, ambient air and air deposition, water and ecosystem, food monitoring, human exposure, and databases. Another recent U.S. exposure monitoring example of interest to the NCS is the National Allergen Survey, which is being conducted by the NIEHS and the Department of Housing and Urban Development (NIEHS 2005). Such survey data benefit the study designers of the NCS. However, as mentioned above, we think that for the NCS, monitoring individuals should be the basis for the exposure assessment. This means that the monitoring is conducted primarily with environmental, biologic, or personal samplers, questionnaires, or a combination of these tools. The analytical methods for actually measuring the amount of the chemical or degraded product/metabolite in an environmental or biologic sample are quite similar. The method consists of three major steps: sample preparation, which generally involves the separation of the chemicals of interest from other chemicals in the matrix; analysis, which may involve further separation by, for example, chromatography, but does involve detection and quantification; and data handling. Generally, the major step that has the most matrix-dependent differences is the sample preparation step. During method development, we seek methods that allow us to monitor multiple chemicals, which may have many different chemical/physical properties but yet maintain the features of accuracy, precision, specificity, linearity and range, limit of detection (LOD), and ruggedness/robustness. We must also think of cost and throughput. No analytical chemical procedure optimally meets all these criteria (Needham et al. 2002). For the measurement of chemicals present in a

matrix at extremely low concentrations (e.g., dioxin in blood at parts per quadrillion levels), the method of choice is one that uses specific cleanup procedures and high-resolution gas chromatography/high-resolution mass spectrometry with isotope dilution technique for quantification. This method is very expensive (~ $750–1,000 per sample) and has relatively low throughput. Other methods have less sample preparation and use less expensive equipment and thus are available in more laboratories and have higher throughput. This is the case for the monitoring of most environmental chemicals. However, even then the methods are expensive, with costs in the range of low hundreds of dollars per sample. For the NCS we should consider the use of lower-cost screening procedures such as immunoassays; however, if extensive sample preparation steps are needed, immunoassay methods can also be quite expensive. Generally, these procedures have higher throughputs (dependent on the degree of sample preparation) and require less expensive equipment but suffer from problems associated with cross-reactivity and hence specificity.

Once the analytical data have been generated, one topic of particular concern in environmental and biologic analyses is how to report and statistically treat concentration levels below the LOD. The LOD is defined by the lowest concentration of a chemical that the analytical method can measure and is determined by the measured value that differs in a statistically significant manner from having "zero" amount of the chemical in the sample (Taylor 1990). Concentrations below the LOD are an issue because of lack of analyte in a sample or a high method LOD, which can be the result of the efficiency of the analytical method to prepare extracts free of potential interferents (but still recover a high percentage of the analytes of interest) and the sensitivity of the instrumental system. Other factors such as insufficient sample size or characteristics of the analytical method can affect the method LOD; for example, we often measure multiple analytes in an analytical run, and the more analytes that we measure in an analytical run, the lower the sensitivity (and higher the LOD) for the measurement process of all the analytes, because of instrumental, recovery, or interference reasons. Therefore, the use of multianalyte methods has many advantages, but generally they have higher LODs than single-analyte methods (Needham and Wang 2002). In the NCS, multianalyte methods and small amounts of sample matrix will be issues for biomonitoring. Also in the NCS, multiple instruments in multiple laboratories may well be measuring the same chemicals in the same matrices. The LOD should be determined in each laboratory for each instrument (instrumental LOD) and for each method (method LOD); frequently, the method LOD is calculated for each and every sample analyzed. Certainly, if multiple laboratories are used, it is best if they use the same, or at least comparable, methods so that the LODs and other analytical criteria are similar; also, the sample weight of all samples of the same metric should be similar so that the LODs will be similar.

When measurements are calculated to be less than the LOD, the concentrations are generally reported as "nondetectable" with the LOD given. However, for parametric statistics, a number must be assigned for each sample. To circumvent this problem, single-value approaches using fixed values ranging from the most conservative value of zero, to one-half the detection limit concentration, to the detection limit divided by the square root of 2, to the most "liberal" value—the detection limit itself—have been used. However, Lubin et al. (2004) generally recommend the use of multiple imputations of missing data instead of single-value approaches, which use either fixed or randomly selected fill-in values. However, the question remains as to how to report concentrations when they are below the LOD but the computer produces a concentration number. Is this computer number more accurate than any number(s) generated by the imputation methods? Many scientists would argue that it is, especially when a detector such as a mass spectrometer, which gives structural information of the analyte, is used. If so, then how are concentrations in samples that give no signal or actually quantify as less than zero, after subtracting out blank values, reported? In these cases most would agree that the concentration value of zero should be used for statistical purposes. Certainly, this area of confluence between chemistry and statistics calls for more work.

The analytical laboratory must be able to demonstrate the method's accuracy, precision, specificity, linearity and range, LOD, and ruggedness/robustness. Once this has been done, a quality assurance/quality control program must be established and enforced to easily allow the detection of systematic failures in the methodology and to ensure that these defined requirements are being maintained over time and among laboratories (Needham et al. 2002). The testing procedures used can include proficiency testing to ensure accuracy as measured against a known reference material, repeat measurements of known materials to confirm the validity of an analytical run and to measure analytical precision, "round robin" or interlaboratory studies to confirm reproducible measurement values among laboratories, regular verification of instrument calibration, daily assurance of minimal laboratory contamination by analyzing "blank" samples, and cross-validations to ensure that multiple analysts and instruments obtain similar analytical values. Fortified and unfortified sample media can also be used to assess potential contamination and analytes losses through the collection, transportation, and storage of samples. In addition some public health laboratories in the United States have been certified by the Center for Medicare and Medicaid Services to comply with all quality assurance/quality control parameters outlined in the Clinical Laboratories Improvement Amendment (1988). Quality assurance/quality control measures are applicable not just to the analytical method but also to all aspects of the measurement process—from sampling design to sample collection (need to ensure no or a defined amount of contamination), transport and storage of samples, analytical method, and data reporting; therefore, all aspects of the measurement process must be subject to a stringent quality assurance/quality control protocol. Often overlooked in longitudinal studies, which require the collection and long-term storage of environmental and biologic samples, is the effect of long-term storage on the sample and the agent. Matrix-based quality control samples containing the agent at known or "analytically assigned" concentrations should be stored under the exact conditions as the study samples and periodically monitored. Also, any new analytical method or any change in the measurement process must be documented and validated against the method being used. Many parameters for implementing or improving a quality assurance program have been published (Schaller et al. 1991; Taylor 1990).

Conclusions

The exact strategy for exposure monitoring directly depends on the study design; for example, if the study design is a long-term longitudinal cohort study of 100,000 children, fewer direct (e.g., biomonitoring) exposure measures may be collected for each child; but if it is a series of smaller nested case–control studies, more direct exposure measures can be made. Regardless of the design, individual exposure assessment will play a vital role because one important, if not the most important, aspect of many of the hypotheses is to associate individual exposures with adverse health outcomes. Therefore, exposure and the resulting dose concentrations must be assessed as accurately and as totally as possible. For assessing exposure and dose information to the participants in the NCS, we encourage the use of data sets and methods used from many sources, including questionnaire and general population nutritional and environmental chemical biomonitoring data from the National Health and Nutrition and Examination Survey (NHANES) (CDC 2003; NCHS 2003; Needham et al. 2005b); food intake from the U.S. Department of Agriculture's Continuing Survey of Food Intake by Individuals (CSFII), which has now been combined with

Table 1. Chemicals and chemical classes of potential interest to the NCS.

Persistent organic chemicals
- Polychlorinated biphenyls (PCBs)
- Hydroxy PCBs
- Polychlorinated dibenzo-*p*-dioxins
- Polychlorinated dibenzofurans
- Organochlorine pesticides
  - Chlordane and metabolites
  - DDT and metabolites (DDE, DDD)
  - Dieldrin
  - Aldrin
  - Endrin
  - Kepone
  - Heptachlor and metabolites
  - Hexachlorobenzene
  - Hexachlorocyclohexanes (including α, β, and γ isomers)
  - Mirex
  - Octachlorostyrene
  - Pentachlorobenzene
  - Pentachloronitrobenzene
  - *trans*-Nonachlor
  - Toxaphene
- Perfluorinated chemicals
  - Perfluorooctanoic sulfonic acid
  - Perfluorooctanoic acid
- Brominated flame retardants
  - Polybrominated diphenyl ethers (PBDEs)
  - Hexabromocyclododecane (β, δ, and γ isomers)
  - Polybrominated biphenyls (PBBs)

Nonpersistent nonvolatile chemicals
- Pyrethroid insecticides
  - Permethrin
  - Cypermethrin
  - Deltamethrin
  - Resmethrin
  - Allethrin
  - Bioallethrin
  - Cyfluthrin
  - Fenvalerate
  - Esfenvalerate
  - Sumithrin
- Miscellaneous pesticides
  - Hydramethanone
  - Phenoxycarb
  - Sulfluramide
  - Imidacloprid
  - Abimectin
  - Amitrol
  - Fipronil
  - Paraquat
  - Diquat
  - Pendamethalin
- Phytoestrogens
  - Isoflavones
    - Daidzein
    - Genistein
    - Formononetin
    - Glycitein
    - Biochanin-A
  - Lignans
    - Secoisolariciresinol
    - Matairesinol
    - Pinoresinol
    - Lariciresinol
    - Syringaresinol

Nonpersistent semivolatile organic chemicals
- Organophosphorous insecticides
  - Azinphos methyl
  - Chlorethoxyphos
  - Chlorpyrifos
  - Chlorpyrifos methyl
  - Coumaphos
  - Dichlorvos
  - Diazinon
  - Dicrotophos
  - Dimethoate
  - Disulfoton
  - Ethion
  - Fenitrothion
  - Fenthion
  - Isazaphos-methyl
  - Malathion
  - Methidathion
  - Methyl parathion
  - Naled
  - Nitrofen
  - Oxydemeton-methyl
  - Parathion
  - Phorate
  - Phosmet
  - Pirimiphos-methyl
  - Sulfotep
  - Temephos
  - Terbufos
  - Tetrachlorviphos
- Carbamate insecticides
  - Carbaryl
  - Propoxur
  - Carbofuran
  - Benfuracarb
  - Carbosulfan
  - Furathiocarb
  - Pirimicarb
  - Bendiocarb
  - Aldicarb
  - Methomyl
- Herbicides
  - Salts and esters of 2,4,5-triclorophenoxyacetic acid
  - Salts and esters of 2,4-dichlorophenoxyacetic acid
  - Atrazine and other chlorotriazines
  - Alachlor
  - Acetachlor
  - Butachlor
  - Metolachlor
- Other pesticides
  - Endosulfan I and II
  - Methoxychlor
  - Bis-dithiocarbamates and metabolites
  - Sulfonyl ureas
  - Ureas
  - DEET
  - Dicofol
  - Iprodione
  - Vinclozolin
  - Trifluralin
  - Naphthalene
- Halogenated phenols
  - Dichlorophenols
  - Trichlorophenols
  - Pentachlorophenol
  - Triclosan
  - Tetrabromobisphenol A
- Polycyclic aromatic hydrocarbons
  - Benzo[*a*]pyrene
  - Benzo[*a*]anthracene
  - Benzo[*c*]phenanthrene
  - Chrysene
  - Fluoranthene
  - Fluorene
  - Phenanthrene
  - Pyrene
  - Naphthalene
- Phthalates
  - Dimethyl phthalate
  - Diethyl phthalate
  - Dibutyl phthalate
  - Dibenzylbutyl phthalate
  - Di-2-ethylhexyl phthalate
  - Di-*n*-octyl phthalate
  - Di-isononyl phthalate
- Alkyl phenols
  - Bisphenol A
  - Nonylphenol
  - Octylphenol
  - *tert*-Butylphenol
- Tobacco smoke
  - Cotinine
  - Naphthalene

Nonpersistent volatile organic chemicals (boiling point < 250°C at 1 atm)
- Acrylamide
- 1,1,1-Trichloroethane
- 1,4-Dichlorobenzene
- 1,3-Butadiene
- 2-Butanone
- Acetone
- Acetaldehyde
- Acrolein
- Benzaldehyde
- Benzene
- Chloroform
- Crotonaldehyde
- Ethylbenzene
- Formaldehyde
- Hexanal
- Hexane
- Isobutyraldehyde
- Methylene chloride
- Methyl ethyl ketone
- Methyl-*tert*-butylether
- Pentanal
- Propanol
- *m,p*-Xylene
- *o*-Xylene
- Styrene
- Tetrachloroethene
- Toluene
- *o*-Tolualdehyde
- *m*-Tolualdehyde
- *p*-Tolualdehyde
- Trichloroethylene
- Vinyl chloride

Bioaccumulative inorganic chemicals
- Lead
- Mercury
- Cadmium

Nonbioaccumulative inorganic chemicals
- Antimony
- Arsenic
- Barium
- Beryllium
- Cesium
- Chromium
- Cobalt
- Manganese
- Molybdenum
- Platinum
- Thallium
- Tungsten
- Iron
- Nickel
- Vanadium
- Perchlorate

Criteria pollutants
- NO_x
- SO_x
- CO
- Lead
- Ozone
- Particulate matter

Bioallergens
- Dust mites
- Arthropods/rodents
- Endotoxins
- Pollen
- Mold/mildew
- Pet dander

NHANES (*Journal of Nutrition* 2003); activity patterns from the U.S. EPA's National Human Activity Pattern Survey (NHAPS) (Klepeis et al. 2001); and many environmental monitoring programs conducted by the U.S. EPA (2005a). Even though these resources are helpful and provide guidance, the NCS should assess exposure on an individual basis such as was done in NHANES and in the pilot phase of the National Human Exposure Assessment Survey (U.S. EPA 2005b). The use of questionnaires will play a vital role, and the use of videotaping and GIS may be considered in certain scenarios. If the exposure pathway is primarily via one environmental medium, then generally that matrix should be monitored; however, the importance of route to potency of the exposure must be considered. Biomonitoring should be used when possible in order to assess total exposure to an individual or to validate and calibrate any exposure index that is derived by other means. If biomonitoring data reveal high exposures within a segment of the population, certainly environmental monitoring and questionnaire information should be used in an attempt to determine the key sources and pathways of exposure and to mitigate the exposure.

To move the process forward, we have compiled a list of chemical classes containing individual substances of potential interest to address the various hypotheses of the NCS (Table 1). In subsequent tables presented in accompanying article, we have determined and prioritized for each life stage (age group), which environmental metric or biologic matrix would be preferred for assessing exposure to these environmental chemicals (Barr et al. 2005; Bradman and Whyatt 2005). The biologic samples and the amount of sample available for sampling are variable and depend on the life stage of the child up to the point that the child nears adulthood, at which time that child is capable of reproducing and continuing the generations in the life cycle. Whenever a person is not involved in reproduction, that person exits the cycle, as shown in Figure 2. Questionnaire data would generally be used to augment this exposure assessment. Other issues we have addressed include storage and analytical methods. We recognize the need to determine the gaps in exposure measures and to determine cheaper methods for accomplishing the end goal, for example, the use of personal air monitors, the use of tap water as a matrix if drinking water is the primary pathway, biosensor technology, etc. Thus, there is little doubt that exposure assessment techniques will improve during the course of this study.

In summary, our Exposure to Chemical Agents Working Group has presented and prioritized the various means of assessing human exposure to a variety of environmental chemical/biologic agents that will assist study designers to develop exposure indices for accurately estimating exposures during the life stages of interest. We strongly suggest that the outcome and study design work groups work closely with us to ensure the highest quality data possible.

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