Examining the influence of environmental exposures on various health indices is a critical component of the planned National Children’s Study (NCS). An ideal strategy for the exposure monitoring component of the NCS is to measure indoor and outdoor concentrations and personal exposures of children to a variety of pollutants, including ambient particulate and gaseous pollutants, biologic agents, persistent organics, nonpersistent organics (e.g., pesticides), inorganic chemicals (e.g., metals), and others. However, because of the large sample size of the study (~100,000 children), it is not feasible to assess every possible exposure of each child. We envision that cost-effective strategies for gathering the necessary exposure-related information with minimum burden to participants, such as broad administration of product-use questionnaires and diaries, would likely be considered in designing the exposure component of the NCS. In general a biologic (e.g., blood, urine, hair, saliva) measure could be the dosimeter of choice for many of the persistent and for some of the nonpersistent organic pollutants. Biologic specimens, such as blood, can also indicate long-term internal dose to various metals, including lead and mercury. Environmental measures, on the other hand, provide pathway/source-specific exposure estimates to many of the environmental agents, including those where biologic measurements are not currently feasible (e.g., for particulate matter and for some gaseous criteria pollutants). However, these may be burdensome and costly to either collect or analyze and may not actually indicate the absorbed dose. Thus, an important technical and logistical challenge for the NCS is to develop an appropriate study design with adequate statistical power that will permit detection of exposure-related health effects, based on an optimum set of exposure measurement methods. We anticipate that low-cost, low-burden methods such as questionnaires and screening type assessments of environmental and biologic samples could be employed, when exposures at different critical life stages of vulnerability can be reliably estimated by these simpler methods. However, when reliability and statistical power considerations dictate the need for collecting more specific exposure information, more extensive environmental, biologic, and personal exposure measurements should be obtained from various “validation” subsets of the NCS population that include children who are in different life stages. This strategy of differential exposure measurement design may allow the exposure–response relationships to be tested on the whole cohort by incorporating the information on the relationship between different types of exposure measures (i.e., ranging from simple to more complex) derived from the detailed validation subsamples. Key words: biomonitoring, environmental, epidemiologic study design, exposure assessment, measurement, National Children’s Study, questionnaires. Environ Health Perspect 113:1108–1115 (2005). doi:10.1289/ehp.7616 available via http://dx.doi.org/ [Online 12 May 2005]

Role of Exposure Assessment in the National Children’s Study

Examining the influence of environmental exposures on various health indices is a critical component of the National Children’s Study (NCS), one that will require determining a) the likely chemical and biologic agents of interest, b) the most cost-effective approaches to measure these chemicals in environmental and biologic matrices, c) how to best design and administer questionnaires, and d) cost-effective statistical sampling strategies for gathering the necessary environmental and personal exposure-related information with minimum burden to the participants. The Chemical Exposure Work Group of the NCS has been evaluating the available information on exposure monitoring in the context of an epidemiologic study design. In this article we synthesize the recent findings from this NCS-sponsored work group activity, which is presented in a comprehensive white paper (NCS 2004a), regarding potential alternatives for assessing subject-specific exposures in the context of an epidemiologic study design.

In general, children and adults are exposed to a wide variety of persistent and nonpersistent chemicals in the environment, some of which are either known or suspected to cause health effects and/or exacerbate health conditions. The NCS hypotheses attempt to link certain types of exposures with specific health effects. For example, one NCS hypothesis holds that exposure to several indoor and outdoor air pollutants, including particulate matter (PM), ozone, and certain volatile organic compounds (VOCs), and bioaerosols (including allergens, endotoxin, and mold) is associated with an increased incidence of asthma in children. Much of the epidemiologic asthma research to date has focused on the acute effects of air pollution and allergen exposures and on housing and personal factors that may trigger asthma attacks. For example, researchers have shown that acute air pollution, including fine PM and sulfur dioxide (SO2), exacerbates asthma and also may increase its incidence (Dockery and Pope 1994; Schwartz et al. 1993; Tolbert et al. 2000). Additionally, children who live near a busy road and are exposed to motor vehicle emissions have been shown to be at increased risk of wheezing, a symptom of asthma (Venn et al. 2001). Researchers have also shown associations between wheezing or asthma incidence and exposure to indoor allergens such as dust mites or cockroach-related allergens (Finn et al. 2000; Platts-Mills et al. 1996; Pekkanen et al. 2001)

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these chemicals such as outdoor concentrations of fine particulates or pollen are more widespread, but concentrations of many other pollutants such as combustion-related pollutants (e.g., NOx, air toxics from motor vehicles) are higher near roadways or in cars or buses. Exposures to pesticides are highly variable, depending on the proximity to agricultural fields or during times of indoor or outdoor residential application. Consequently, concentrations of most of the chemicals may vary considerably over time, geographic locations, and seasons. As a result, quantifying exposures to short-term or intermittent acute exposures requires a measurement system that incorporates periodic monitoring (perhaps triggered by reported chemical use, e.g., a residential-use pesticide or consumer products) as well as more routine surveillance-type monitoring. However, measurements collected as a result of a particular event constitute a type of adaptive sampling, and those data are likely to result in biased estimates of the distribution of exposures if great care is not used to analyze them properly (i.e., researchers need to consider the frequency of use events over time as well as the magnitude of exposure per event).

Environmental sampling methods vary by analytical sophistication and level of precision. Unfortunately, increased sensitivity, accuracy, precision, and temporal resolution often come at the cost of more expense (including both instrumental and operating costs) and larger instrument size. Personal monitoring is not always possible for all the environmental agents because of sample volume constraints dictated by analytical requirements. Moreover, active personal samplers are often heavy and bulky and are not suited for use by children younger than 7 years. Passive samplers such as the 3M (3M, St. Paul, MN) or Ogawa (Ogawa & Co., USA, Inc., Pompano Beach, FL) badges are lightweight and may be used by small children for monitoring VOCs and NOx or SO2, respectively. However, all types of personal samplers require parental supervision and collection of accurate activity and instrument use information. Active or passive devices can be used for fixed-site indoor or outdoor environmental monitoring applications. Use of these sampling devices, especially active samplers, requires technician visits to homes, schools, and other selected micro-environments of the study subjects. Less detailed measurements may be more feasible to collect from many homes. Passive or active devices could be shipped by mail or installed by a field technician in homes. The parents of the study subjects can return these devices on a prespecified schedule. Results from the analysis of these monitors can then be used to determine if additional more accurate or shorter-term sampling is recommended for a given household. Many biologic specimens will most likely be collected during technician home visits or during checkups at doctors’ offices. However, biologic measures collected in a noninvasive manner (e.g., hair, nail, saliva, lost teeth, and perhaps urine samples) could be collected directly by the parents without a technician visit. Where and how these samples are collected depend on the biologic sample, the chemical of interest, and the age of the participant. Unfortunately, there are still no practical low-cost technologies for determining exposures to indoor allergens of concern (e.g., dust mites, mold, endotoxin) that are linked with the asthma hypothesis. Because indoor bioaerosols levels of allergens and their viability can vary seasonally, it is desirable to collect indoor air, dust, and furniture, mattress, and stuffed toy samples frequently over the course of a year. Ideally, quarterly samples, starting with preconception and through 3 years of age, are recommended. Fewer annual samples collected after 3 years of age may be considered (NCS 2004a).

In addition to collecting environmental and biologic measurements, collecting questionnaire and time–activity diary data is also important. This information will be used not only to augment any measurement data collected but also can be used to estimate exposures in the absence of direct monitoring data because of subsampling of participants or time periods to be measured. In essence, such indirect data may provide surrogate or indirect estimates of exposures to environmental agents. Furthermore, questionnaires will be used to obtain background information from the study population cohort—so that inferences are strengthened when subsampling is required—and to adjust for item nonresponse. Questionnaire information will also be cross-compared with other survey information where appropriate to relate item response and generate a measure of representativeness of the cohort (e.g., to compare participant and household characteristics with census data).

Given the size and long-term duration of the NCS, questionnaires are expected to be a key component of any planned exposure study design for the NCS. They will be used to enroll the participants and gain understanding about the family, family structure and relationships, education, occupational and residential history, type and nature of potential exposures, activity and behavioral profiles, and medical and health-related information. The content of the questionnaires and the frequency and mode of administering them will vary depending on the nature of the chemical or chemical class, the hypothesis of concern, and the age of the child (or fetus). Also, questionnaires may provide some information on past exposures to the fetus, especially during the first trimester when knowledge of conception at least for part of the trimester is unknown to the parent. Nevertheless, recruiting women before they are pregnant and obtaining early pregnancy (e.g., first 20–30 days of gestation) exposure measures can be possible under a national probabilistic sample of households (NCS 2004b). Collecting both questionnaire information and early pregnancy exposure and biologic measures for a sample of women should also provide a way to check for potential recall bias.

Questionnaires regarding the presence of, or contact with, potential sources of exposures to chemicals in homes, schools, and other key locations (e.g., to PM, NOx, VOCs) where a child spends his or her time each day have been used in various community health studies. However, the reliability of these survey instruments in predicting exposures to chemicals of concern in the absence of actual exposure measurements is uncertain, and they should be used cautiously. All survey instruments in the NCS should be pilot tested and used in conjunction with direct exposure-related measurements for a sample of participants to obtain some measure of validity.

Technologic advancements may reduce the time burden of obtaining questionnaire information. For example, wireless-coupled infrared technologies (e.g., radio frequency identification (RFID) chips or sensors) may provide information on updated consumer source inventory or usage, by collecting and transmitting product information via RF spectrum, which would be more accurate and useful for exposure modeling, and without participant burden. Greater use of web-based technology may improve data collection and data processing, generating savings for the participants and the researchers. Accuracy and completeness of the item response can be improved with automation of responses via personal digital assistants (PDAs) or similar devices because the data checking could be done very quickly. Questionable responses could be verified in a timely manner via human or machine interaction.

The discussion presented thus far has addressed the important strengths and weaknesses of alternative exposure measurement methods. However, an important operational question for the NCS is how to determine an optimum strategy for a measurement program (i.e., one that uses environmental monitoring, personal monitoring, biomonitoring, questionnaires, or other indirect methods in a most cost-effective, reliable, and minimally burdensome manner) for the selected health hypothesis. We have examined this complex issue and developed a recommended approach for selecting an appropriate exposure measurement method (or methods) for different classes of chemicals and exposure situations.

Figure 1 provides an overview of the steps in selecting the appropriate exposure measure(s). Initially, the researcher must identify
Selecting an appropriate exposure measure.

Figure 1. Selecting an appropriate exposure measure.
can be burdensome or costly to collect or analyze depending on the chemical or biologic agent of interest. Often, biologic and environmental samples provide a snapshot of exposures and may require repeat measurements when exposure conditions are not stable over time. Combining biologic and environmental measures allows comparison of the relative contribution of different routes and media to internal dose, facilitates the identification of missing exposure measurements (e.g., locations that were not sampled), and provides a link to identify locations and sources of exposure, all of which help researchers to determine how to reduce exposures and risks.

In general, a biologic measure, for example, serum levels of polychlorinated biphenyls (PCBs), could be a dosimeter of choice for many of the persistent organic pollutants and certain metals (e.g., Pb, mercury) measured in blood (see Table 1 in Needham et al. 2005). In addition, biologic measures can provide reliable dosimeters for some of the nonpersistent compounds listed in Table 1 in Needham et al. (2005), particularly when exposures are constant, intrindividual variability is low, and pathway-specific information is not needed or exposure occurs principally from one pathway, such as in the measurement of plasma or urinary cotinine as a dosimeter of cigarette smoke exposure. In some instances, however, collecting one or more types of biologic measures from a very young child may not always be easy (e.g., from newborn or young infants). In some of these situations, questionnaires and low-cost direct environmental measurements may be used instead, when feasibility and other factors limit the use of biomonitoring. For example, questionnaire information has been shown to be a good indicator of exposure for environmental tobacco smoke. There are low-cost methods for measuring cotinine on a filter that has been shown to have very high association with biomarker levels. Also, depending on other information needed about the environment or the exposure, researchers may choose an alternative type of an environmental sampling approach. For example, collection of dust samples (e.g., house dust, carpet dust, attic dust) over 2–3 months before removal and analysis or long-term passive monitoring with existing or emerging technologies might provide good indicators for a number of potential or historical exposures to the infant/fetus, especially when concurrent biologic or environmental measures are not available.

An environmental measure will be necessary when no biologic measure is available, as is the case for most of the criteria air pollutants and bioallergens. In addition, an environmental sample may be the measurement of choice for exposures that occur predominantly by one route. For example, inhalation exposures to many of the VOCs listed in Table 1 in Needham et al. (2005) may be measured with the lowest cost and participant burden by using passive diffusion badges. The internal dose is then estimated based on models. In general, whenever possible, collection of both biologic and environmental measurements are encouraged because together they provide a much more complete picture of media, routes, pathways, and physiologic factors that influence exposures of a child.

Quantifying exposures to the nonpersistent compounds listed in Table 1 in Needham et al. (2005) will be difficult, particularly in instances of multimedia sources and sporadic exposures such as the nonpersistent pesticides when exposures are variable. These exposures can occur simultaneously from multiple routes (dietary and nonintentional ingestion, inhalation, and dermal absorption), can vary dramatically within a particular group or across populations depending on use patterns, and are difficult to quantify by questionnaires only. These situations will likely require intensive sampling and a repeat-measures design, and they may require a combination of both environmental and biologic monitoring supported by questionnaire information. Questionnaires or checklists have been used in past exposure studies to estimate/classify individuals by frequency of exposures to household products.

**Epidemiologic Study Design Considerations**

In addition to determining what measurement methods to use, NCS researchers must also determine optimum sample sizes for obtaining measurement data. Sample size determinations should be made on an epidemiologic basis. More common health outcomes or relative risks > 1.3 can be readily tested on a large portion of or on the full NCS cohort. However, rarer outcomes (e.g., autism, certain birth defects, or reproductive health outcomes) or exposures that are unique to certain subgroups may be more efficiently tested using a case–control or a nested case–control study design involving fewer subjects. For example, in studying the cases of autism, researchers might use a nested case–control design in which a large screening sample is used to identify the cases and a subsample of the non-case sample members is selected for the control sample. However, some environmental or exposure samples must still be collected for the entire cohort because case status will be unknown until later in the study. Properly analyzing the exposure and outcome data from this type of design will require considerable care.

The large sample size and longitudinal nature of the NCS raise unique statistical issues, such as obtaining sufficient samples to provide adequate statistical power to detect health effects attributable to environmental and personal exposures with a minimum amount of burden, while still being cost-effective and staying within the study’s overall budget. Rather than measuring the full cohort for every hypothesis, researchers could draw a sample randomly using a stratified or matrix sampling approach to minimize overlap and burden. The sample could then be assigned to subsamples covering critical life stages targeted to answering specific hypotheses or having common measurement requirements (e.g., hypotheses requiring similar exposure measures, collected at similar time points, might be grouped together). Unrestricted randomization may not be practical for this purpose, but academic medical centers, primary sampling units, or other geographic sample areas can be randomly assigned to test specific hypotheses or collect more detailed exposure measures so that no sample household is overburdened with excessive numbers of environmental measurements, biologic samples, or questionnaire items.

In developing an exposure assessment strategy for the NCS, researchers should carefully analyze each hypothesis to determine the various appropriate measures of exposure, including both basic (or core) and more detailed direct measures, as well as indirect measures (e.g., ambient monitoring data, time-activity diaries). The resulting measurement design and statistical analysis plan should consider cost, burden, and level of detail (i.e., accuracy, precision, sensitivity, specificity, temporal resolution). Given the measurement design, statistical analysis plan, and the basic features of the sampling design for recruiting participants (e.g., multistage probability-based sample), researchers should determine the required sample size for the full cohort and possibly for a subsample in which more detailed measures are collected. If the full NCS cohort is not required to answer the questions of interest, researchers should develop a plan for random assignment of NCS cohort members to a subsample to support the specific hypothesis. With this main objective in mind, researchers at the U.S. Environmental Protection Agency, Battelle, and Harvard University have undertaken a project to develop cost-effective statistical sampling strategies and optimal design considerations for the NCS. The following material regarding the design strategy for collecting exposure-related information is derived from the recent Battelle/Harvard report (Strauss et al. 2005).

The low-cost, low-burden methods such as questionnaires, emissions inventories, and ambient pollution surveillance data could easily be applied to a large cross section of the NCS. However, these methods are not likely to be sufficient for completely characterizing the participants’ actual exposures, and even
questionnaires do not have a low burden unless they are very short, which is not likely to be the case for the NCS. The lower level of detail and quality (i.e., accuracy, precision, specificity, and temporal resolution) associated with these methods can be problematic in generating data across the entire cohort. However, biologic samples or low-burden environmental samples that can be collected in a noninvasive manner (e.g., urine or passive air samples) may be appropriate in some instances for the entire cohort. Participants are more likely to understand the value of these measures, and, for certain chemicals, these samples are likely to be more informative than the survey data alone. In general, questionnaire data should be restricted to items directly related to exposures of interest, or they should cover time periods that are not included in monitoring (e.g., retrospective or changes over time between monitoring visits). Surveys could include some core items and other items that may be used only for subsamples addressing specific hypotheses. In addition, if numerous questionnaire items are relevant to certain hypotheses, a short version for the primary sample and a long version for the subsample participating in more detailed monitoring may be appropriate. However, questionnaires and other surrogate exposure assessment tools should be revised periodically to reflect changes in lifestyle factors, sources, and societal conditions over time.

Although recruiting study subjects may be difficult, keeping them in the study throughout the full period of 21 years may be even more difficult. Because of the study’s length, both nonresponse over the course of a monitoring period (i.e., wave nonresponse) and attrition or dropout are concerns. Wave nonresponse refers to a study subject missing data for one or more planned sampling events but remaining in the study. Strauss et al. (2003) evaluated the influence of both factors seem to have minimal effect on the study samples. The studies conducted on a small yet representative subsets of the NCS cohort may also include additional repeated sampling for biologic specimens to capture temporal variability in biomarker chemical concentrations; concurrent analysis of a subset of biologic and environmental samples to measure VOCs, semivolatile organic compounds, and biologic pathogens to characterize measurement error in questionnaires and other methods used to act as surrogates for these types of exposures; and higher-technology methods to capture exposure-related behavior (e.g., global positioning systems, accelerometer, or heart-rate monitor to capture physical activity) with a higher degree of precision. In most cases, according to Strauss et al. (2003), these carefully designed subsamples provide adequate power and precision for characterizing the relationship between health outcomes and measures of exposure using sample sizes in some cases as low as a few thousand respondents, with exceptions typically occurring when the prevalence of the health outcome is very low (e.g., autism) and the relationship between the core and detailed measures of exposure is very weak.

Because some of the efficient design options for linking health outcomes to exposure metrics are outcome dependent, collecting basic (or core) exposure measures from all study subjects in a consistent manner with a sampling plan that provides coverage across life stages will be critical. Having exposure-related information available for all study subjects at different stages of development for the subject child will also be critical to support health-outcome-oriented research in which the biologic cause of disease is not well understood and the disease is rare. The collection and archiving of biologic specimens (e.g., blood, hair, or urine) could serve as a foundation for some but not all exposure-related research. To provide coverage across exposures that cannot be assessed retrospectively using archived environmental or biologic specimens, the NCS will likely need to employ the prospective collection of less-detailed exposure-related information, including the use of questionnaires to capture exposure-related behavior information on activity, diet, and consumer product use; collection of house dust samples; abstraction of medical records and/or diaries during pregnancy to capture fever and exposure to biologic pathogens; and reliance on independent data sources such as ambient air monitoring data obtained from the U.S. Environmental Protection Agency Aerometric Information Retrieval System (AIRS).

The hypothesis on neurobehavioral or neurocognitive health effects from exposures to environmental pesticides highlights how combined biomarker, environmental, and questionnaire information can be used in the NCS. Some health effects might be related to long-term average pesticide exposure, in which case an environmental measure (e.g., a house-dust or passive air sample) might be an appropriate measure of exposure for use in these studies. Alternatively, if an adverse health effect is related to an acute pesticide exposure event, questionnaire information regarding consumer product use and other exposure-related behavior combined with periodic biologic monitoring (e.g., for urinary pesticide metabolites triggered by the occurrence of periodic events) might be better suited to estimate the impact from these episodic events. Generally the urinary metabolite measurements represent roughly only a 24- to 72-hr exposure time frame, whereas dust or semipermeable membrane diffusion would cover weeks or months.

One possible sampling strategy proposed in Strauss et al. (2003) for the detailed exposure study is randomly selecting and recruiting a subsample of participants < 10% of the full cohort, say, about 1,000–5,000 participants among women planning pregnancy or in early stages of pregnancy. However, the actual sample size necessary to provide detailed exposure assessment information to the NCS and to serve as a basis for adjusting relationships for measurement error in basic measures of exposure may, in fact, be different than the 1,000–5,000 subjects chosen here as an example at each stage of life. The sample size and timing of detailed measurements will be important topics of research, especially if the recommended approach is adopted as part of the overall strategy for exposure assessment. Of these 1,000–5,000 women who participate in the aggregate exposure study during this first stage (e.g., the first year of study), 40% (or 400–2,000 women) could be selected at random to participate in the aggregate exposure study during the first two stages of vulnerability, and 16% (or 160–800 women) would be encouraged to participate in the aggregate exposure study for the first three stages of vulnerability. At each subsequent stage of vulnerability covered by the NCS, the aggregate exposure study would be replenished to achieve a total sample size of 1,000–5,000 study subjects by enrolling 600–3,000 study subjects for the aggregate exposure study from a pool of available NCS study participants who previously had not participated in the aggregate exposure study. Of the 600–3,000 study subjects chosen for participation in each subsequent stage or year, 240–1,200 would participate in two consecutive phases, of which 160–800 would participate in three consecutive phases. This hierarchical sampling or recruitment strategy offers the advantage of both samples (i.e., the
The associations between children’s environmental exposures to chemical and biologic agents and various health outcomes is an important component of the planned National Children’s Study. The health outcomes of interest to the NCS include such conditions as asthma, neurobehavioral and neurocognitive disorders (e.g., autism and ADD), adverse birth outcomes, and alteration of age of puberty. Current epidemiologic evidence suggests an important role of environmental and genetic factors in the development or incidence of these conditions. However, it has not yet been possible to identify the nature and magnitude of exposures to specific pollutants or allergens that could lead to these undesirable health outcomes during critical life stages of either development or vulnerability. Because of the large sample size of the NCS study (~100,000 children), it is now feasible to formulate and implement a study design that would examine the influence of acute and chronic exposures to many indoor and outdoor pollutants and bioaerosols in the development of many of the health conditions noted above. It is important, however, to recognize that the study protocols for exposure measurement and analysis have to be flexible enough to address changes in our understanding of pollutants, personal factors, and societal conditions that could play a role in influencing exposures and health status of children. The magnitude and frequency of potential exposures to children during various life stages of concern (ranging from preconception to prenatal and from postnatal to infancy) have to be considered first. Technical and practical considerations dictate that the NCS employ both direct and indirect (e.g., survey-based) monitoring methodologies. Direct monitoring methods include environmental and personal exposure monitoring methods using either passive or active sampling techniques, or biomonitoring of appropriate matrices, such as meconium, placenta, blood, urine, saliva, hair, nail, tooth. Indirect measurement methods may include household and personal questionnaires, time–activity diaries, dietary and consumer product surveys, and existing ambient pollution and emissions surveillance databases, among others.

In selecting the direct measures, the researcher must decide whether to collect a biologic or an environmental measure, or some combination of both, as summarized in Figure 1. In addition to technical factors such as the timing of exposures, participant burden and cost are among the key issues to consider in selecting one or both of these sample types. Ideally, whenever feasible, collection of both environmental and biomonitoring samples is recommended. Combining biomonitoring and environmental exposure measurements allows for the comparison of the relative contribution of different routes and media to internal dose, facilitates the identification of missing exposure measurements (e.g., locations that were not sampled), and provides a link to identify locations and sources of exposure, all of which help researchers to determine how to reduce exposures and risks.

Given the large sample size and long duration of the planned NCS and the potentially high costs and burden associated with environmental sampling, collecting detailed longitudinal exposure information across the cohort and at all time periods to support multiple hypotheses relating environmental exposure to potential adverse health outcomes will be difficult. Well-designed substudies, however, can be carried out within the NCS cohort—using only a small fraction of the sample size (possibly <10% of the study sample)—to estimate and adjust for exposure measurement errors, with sufficient power to characterize the relationship between exposure and health outcome for most hypotheses. We envision that low-cost, low-burden methods, such as the use of questionnaires and screening type environmental and/or biologic measurements, may be employed across the entire (i.e., core) NCS cohort, with smaller subsets of respondents (i.e., the detailed study subcohort) undergoing more extensive environmental exposure assessment using more expensive and detailed environmental, biologic, and other sophisticated exposure measurements. This strategy allows the exposure–response relationship to be tested on the whole cohort, while the detailed validation subsamples provide the relationship between different exposure measures. Finally, the results from these partially overlapping studies can then be used for conducting more specific epidemiologic analyses or for identifying optimum exposure mitigation strategies, the ultimate aim of the planned NCS.

### Table 1. A conceptual example on rolling enrollment.

| Sampling event | Cohorta | Total participants |
|----------------|---------|--------------------|
| 1              | 1,000   |                    |
| 2              | 400     | 1,000              |
| 3              | 160     | 600                |
| 4              | 160     | 240                |
| 5              | 160     | 240                |
| 6              | 160     | 240                |
| 7              | 160     | 240                |
| 8              |         | 1,000              |

aCohort 1: 1,000 recruited for first sampling event; 400 of 1,000 (40%) retained for second sampling event; 160 of 400 (40%) retained for third sampling event. Cohort n: 600 recruited for nth sampling event; 240 of 600 (40%) retained for (n + 1)th sampling event; 160 of 240 (66%) retained for (n + 2)th sampling event (assume n > 1).

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