FINAL REPORT
National Children's Study (NCS)
Estimating Subject Burden for Potential NCS Measurements

Prepared for:

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Work Assignment Number: 01-06

RTI Project No. 08601.000.006

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Executive Summary

The National Children's Study (NCS), a large longitudinal cohort study of environmental exposures among children, is currently in the planning stage. Prior to enrollment of 100,000 pre-pregnant and pregnant women across the United Sates for this study, a better understanding of the participant burden involved is essential. Due to the number and range of hypotheses being tested in the NCS, the families participating could face some significant burdens. Even though individually the burden associated with specific measurements may not be very taxing, the subject's effort increases with multiple measurements. Currently, research in the area of participant burden is limited. This project examined aspects of participant burden beyond the time expenditure and direct cost to the subject.

The main objectives of this work assignment included: estimating subject burden associated with the potential measurements proposed for the NCS, developing a method to estimate burden, and providing suggestions on strategies that can be used to increase or decrease participant burden.

The tasks specified to complete this work were:

- Produce a work plan,
- Develop a definition of participant burden,
- Propose a quantitative method and develop an MS Excel spreadsheet,
- Estimate the burden for each participant for the measures proposed, and
- Propose strategies to maximize data collection for the proposed hypotheses with reasonable minimal subject burden.

Calculations of burden are accomplished using the burden database developed for this Work Assignment. (The database is sent as a separate file attachment to the final report.) The database, which is an Excel spreadsheet, contains rows for measurements included in a list that accompanied the Work Assignment. (The list of measurements is sent as a separate file attachment to the final report.) Each row of the spreadsheet contains information for a specific measurement and method of assessment. The participants assessed and the visits during which the assessment is conducted are indicated, along with all the hypotheses that utilize data from the assessment. Each row also contains information on the estimated burden and factors that affect the burden (referred to as multiplier variables), such as the participant's response rate for the assessment and the proportion of the participant population assessed. Burden is then calculated by identifying all the relevant rows for a specific calculation and summing the estimated burden that is modified by the multiplier variables. In summary, the calculation of burden depends on three types of variables:

- *Indicator variables*: Indicator variables include the values of "0" or "1" that designate inclusion of the measurement in the calculation, visits, participants, and hypotheses. Together, these define what measurements are conducted in all possible visit-participant combinations and how the data from the measurements are used.

- *Multiplier variables*: The multiplier variables adjust the estimate of burden by various factors that account for acceptability, relevance (e.g., gender-specific measurements), and study design options (e.g., measurements conducted only for certain substudies or additional assessments for persons with disabilities).

- *Burden estimates*: These variables, taken together, describe the range of possible burden for the specific measurement-method combination.

Estimation equations are provided in the database for measurement method-specific, hypothesis-specific, and visit-specific participant burden. All burden estimates are shown for each participant separately and then totaled. Method-specific and hypothesis-specific are presented for each visit and total study. Worksheets are provided for all hypotheses separately and eight of the most common measurement methods.

The database spreadsheet includes all measurements included in the list provided by EPA (682 rows). The number of rows is fewer than the number of hypothesis-visit-measurement-participant listings included in the list. A number of assumptions were made to code this list, which is the compilation of several independently developed lists, into the common database format. As a result of the assumptions, measurements assessed at multiple visits on the same participant and utilized by several hypotheses are combined in one, or a few, rows. Those assumptions are documented in this report. Burden estimates are provided for 456 rows (67 percent). Clarification for some of the measurements will enable the completion of the burden estimates.

This report also includes instructions for making modifications to the database and suggestions for using the database to evaluate NCS alternative assessment scenarios. Care should be taken when making changes. Because multiple hypotheses may be indicated on a single row of the spreadsheet, a change to the assessment schedule may affect several hypotheses. The user should determine whether this impact on multiple hypotheses is desirable. Further, the complete assessment schedule for a measurement of a participant is often coded in several rows due to the different requirements of the hypotheses. The user should be sure all relevant rows have been changed.

The database can be used to view the burden impact of the proposed measurements in a variety of ways:

- By measurement method, e.g., view all measurements included in the preconception visit of the mother,

- By specific measurements, e.g., view the assessment schedule for occupation of the parents which is utilized by multiple hypotheses to determine whether there are similarities,

- By hypothesis, e.g., view all measurements conducted on the index child for Hypothesis 3.2,

- By visit, e.g., view the total burden for the mother at the trimester 1 office visit, or

- By participant, e.g., view the total number of visits that the father will participate in the assessment process.

There are a number of enhancements that are recommended for the database that will enable the database to handle unusual situations, such as hospitalization, sick child visits, or primary care givers other than the mother and father.

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Exhibits

Introduction

In this section, we present the objectives, tasks and activities that were undertaken to carry out the work assignment (WA) entitled ***Estimating Subject Burden for Potential NCS Measurements***. This final report has two attachments, sent as separate files: the list of measurements sent to RTI with the WA and the Excel spreadsheet database.

1.1 Purpose

The National Children's Study (NCS), a large longitudinal cohort study of environmental exposures among children, is currently in the planning stage. Prior to enrollment of 100,000 pregnant women across the United Sates for this study, a better understanding of the participant burden involved is essential. Due to the number and range of hypotheses being tested in the NCS, the families participating could face some significant burdens. Even though individually the burden associated with specific measurements are not very taxing, the subject's effort increases with multiple measurements. Currently, research in the area of participant burden is limited.

The purpose of this work assignment (WA) was to:

- Develop a definition of "participant burden",
- Provide the U.S. EPA with an Excel spreadsheet, i.e., the burden database, that can be used to calculate burden under a number of scenarios,
- Begin compiling estimates of burden for specific measurements from a list provided by EPA in the spreadsheet, and
- Provide suggestions on strategies that can be used to increase or decrease participant burden.

1.2 Specific Objectives

The main objectives of this work assignment were to:

(1) Develop a quantitative method with the following characteristics:

- Develop a quantitative method of calculating participant burden that could be used for the following calculations:
    - o Total visit-specific burden for specific participants,
    - o Total hypothesis-related burden for specific participants,
    - o Total hypothesis-related burden by specific visit,

- - Hypothesis-related burden by specific participant for specific visits,
  - Assessment method-specific burden for specific participant, and
  - Assessment method-specific burden for specific visit.
- Develop a quantitative method that would accommodate:
  - Acceptability of assessment by the participant,
  - A different testing pattern for people with a disability, and
  - Sub-study burden estimation.

(2) Develop a database in the form of an MS Excel spreadsheet that:

- Includes information relevant to all the measurements, visits, participants, and hypotheses in the list provided by EPA,
- Contains notes regarding sources of burden estimates, and
- Includes example calculations of burden estimates.

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Quantitative Method

This chapter describes the variables and equations used to calculate burden. A quantitative method was proposed by RTI in the deliverable entitled *Transmittal of Quantitative Method Plan for Work Assignment No. 01-06* dated July 21, 2003. That method was used to develop and populate a database. A number of refinements were made to the method to accommodate specific characteristics of the measurements. Those refinements are indicated below in italicized text.

2.1 Definition of Burden

According to the Office of Management and Budget[1], the term "burden" means:

"the value of time, effort and financial resources expended by persons to generate, maintain, retain, disclose or provide information to or for a Federal agency. This includes reviewing instructions; developing, acquiring, installing and utilizing technology and systems for any of these purposes, training personnel to respond to or otherwise take action needed to respond to a collection of information; searching data sources; collecting data; completing and reviewing information collections; and transmitting or otherwise disclosing information. "Burden" covers the time and other resources expended to fulfill specific one-time information requests as well as recurring information requests, including to obtain data and develop, procure and operate information systems necessary or desirable to retain such data in fulfillment of statutory or regulatory requirements, whether or not they are applicable only to the period of a specific information collection request."

This definition has a number of implications for the calculation of burden for the National Children's Study.

- For the environmental monitoring measurements, participant burden for responsible household members will be incurred if any training, monitoring, or set up is required.
- For record reviews, burden may be incurred for agency staff— e.g., clinic staff or local environmental protection agency staff— who either need to identify the records or assist the data abstraction process in any way.

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[1] Office of Management and Budget. *The Paperwork Reduction Act of 1995: Implementing Guidance for OMB Review of Agency Information Collection.* Available at www.omb.gov .

- Burden is incurred by a primary care giver who must accompany the child to an assessment.

In this work assignment, a method was developed to estimate participant burden that can be used to provide estimates for OMB. The tool will have an additional use to evaluate and prioritize components for the survey. For that use, other issues that affect the conduct of the study, such as the willingness of the person to participate, become important.

2.2   General Description of Variables

In this section we describe the variables used in the calculations and discuss some specific coding issues.

2.2.1 Variable Nomenclature

EPA provided RTI with a 123-page list of possible measurements for the National Children's Study. These measurements were identified in the course of evaluating 22 possible hypotheses. Each measurement is associated with information on when the measurement will be assessed (i.e., which visit), which participant(s) is the subject of the assessment, the method of measurement, and which hypothesis(s) will utilize the information from the measurement. All of this information is required to evaluate participant burden. In some cases, however, the participant being evaluated is not the participant incurring burden. For instance, an interview about an infant is conducted with either the mother, father, or primary caregiver. In this situation, for the purposes of estimating burden, burden is incurred for the respondent, not the infant.

Exhibit 2-1 lists the variables included in the database spreadsheet that we developed. On the first worksheet of the spreadsheet file, designated "Inputs", each measurement, N_j, is assigned one or more rows, depending on the unique combination of when the measurement is conducted, who it impacts, which method is being considered, and what hypotheses are involved. We use the following subscripts to index the variables:

i designates the hypothesis (separate columns)
j designates the measurement (separate rows)
m designates the method of measurement
v designates the visit (separate columns)

Exhibit 2.1- List of Variables Included in Burden Database

Variable	Definition	Comments
N_j	Measurement name	This variable provides the measurement name. In some cases the person being evaluated is not the participant incurring burden, e.g., interviews about infants. Therefore, the measurement name often indicates the person being evaluated.
B_j	Inclusion multiplier	This indicator flag denotes whether the specific measurement is to be included in the calculation. The default setting for this flag is 1. Set this to 0 (or blank) if the measurement is excluded.
M_m	Method of measurement	This variable provides the method of assessment. This variable is presented in text and in a numerical recode. See *Appendix A* for recodes.
$V_{v,j}$	Visit	This indicator flag denotes whether a specific measurement, j, is conducted on visit, v. 1=yes, (0 or blank)=no.
I_j	Participant impacted	This indicator flag denotes which participant(s) incur burden due to the measurement, j. 1=yes, (0 or blank)=no.
$H_{i,j}$	Hypothesis	This indicator flag denotes the hypotheses, i, that will utilize the measurement, j. 1=yes, (0 or blank)=no.
$MINT_j$	Minimum time burden	This variable is the estimated minimum time burden to perform the measurement, j.
$MAXT_j$	Maximum time burden	This variable is the estimated maximum time burden to perform the measurement, j.
BT_j	Likely baseline time burden	This variable is the estimated most-likely burden to perform the measurement, j, if it is performed without other measurements using the same method.
MT_j	Marginal time burden	This variable is the estimated marginal time associated with the measurement, j, if it is performed in conjunction with other measurements using the same method.
BC_j	Baseline cost burden	This variable is the estimated most-likely cost burden associated with the measurement, j, if the measurement is performed without other measurements using the same method. These costs do not include the cost associated with time burden.
A_j	Acceptability	Estimates the response rates of participants to the measurement, j, using method, m.
P_j	Population frequency multiplier	For those measurements, j, that are conducted on individuals having certain characteristic, such as specific gender, or having a specific health condition, such as asthma, this variable is the population frequency of individuals with those characteristics. The default value for this variable is 1.
S_j	Substudy multiplier	For those measurements, j, which are only conducted as a substudy, this variable is the percent of the entire study population that is included in the substudy. The default setting for this variable is 1.

Variable	Definition	Comments
$D_{v,j}$	Disability multiplier	Participants with disability are likely to receive twice the number of contacts for specific visits, v, for some measurements, j. For other measurements, participants with disability may not be tested or tested less frequently. This variable is the frequency of participants with disability. The default setting for this variable is 0. This multiplier may be either positive or negative.

A variable for the marginal cost estimates was not included in this version of the database because there were no marginal costs.

2.2.2 Coding of Visits

The visits were defined relative to conception of the index child, time during pregnancy, and age of the index child. Some measurements can be done in an office setting and others require a home setting. To allow for maximum flexibility of this database for the incorporation of new measurements, the scheme shown in *Exhibit 2.2* was used to designate a comprehensive list of all possible visit formats, $i = 1, \ldots, 57$.

Exhibit 2.2- Designation of Visits

Index	Visit	Index	Visit	Index	Visit
1	Preconception, Office	20	Months 19-24, Office	39	Year 12, Home
2	First Trimester Pregnancy, Office	21	Months 19-24, Home	40	Year 13, Office
3	First Trimester Pregnancy, Home	22	Year 3, Office	41	Year 13, Home
4	Second Trimester Pregnancy, Office	23	Year 3, Home	42	Year 14, Office
5	Second Trimester Pregnancy, Home	24	Year 4, Office	43	Year 14, Home
6	Third Trimester Pregnancy, Office	25	Year 4, Home	44	Year 15, Office
7	Third Trimester Pregnancy, Home	26	Year 5, Office	45	Year 15, Home
8	Birth, Office or Health Care Setting	27	Year 5, Home	46	Year 16, Office
9	Birth, Home	28	Year 6, Office	47	Year 16, Home
10	Months 0-3, Office	29	Year 7, Home	48	Year 17, Office
11	Months 0-3, Home	30	Year 8, Office	49	Year 17, Home
12	Months 4-6, Office	31	Year 8, Home	50	Year 18, Office
13	Months 4-6, Home	32	Year 9, Office	51	Year 18, Home
14	Months 7-9, Office	33	Year 9, Home	52	Year 19, Office
15	Months 7-9, Home	34	Year 10, Office	53	Year 19, Home
16	Months 10-12, Office	35	Year 10, Home	54	Year 20, Office
17	Months 10-12, Home	36	Year 11, Office	55	Year 20, Home
18	Months 13-18, Office	37	Year 11, Home	56	Year 21, Office
19	Months 13-18, Home	38	Year 12, Office	57	Year 21, Home

For a given hypothesis and for a given participant, assessments may not be conducted at all possible visits. For instance, race of the mother would be assessed only once.

2.2.3 Participants

Although the National Children's Study is about index children, the measurements are not limited to the children. Characteristics of family members and, later, teacher/day care professionals are important to understanding the development and health status of the child. Also, environmental assessments at the home, local, and even regional level are important to describe the exposures of the growing child. Consequently, each of these assessments involves participants who may have burden associated with the conduct of this study.

Further, some participants have burden, although they are not directly being evaluated. Certainly, when children are young, a primary caregiver may be intimately involved in the measurement activities of the study as a participant in the assessment. For example, the adult may be present, or at least available, when venipuncture is being conducted on young children.

Exhibit 2-3 shows a list of all participants identified in the list of measurements provided by EPA. Ten classes of participants were identified.

Exhibit 2.3- List of Potential Participants

Participant	Notes
Index child	
Mother	
Father	
Sibling	In burden calculations, this is assumed to be a single person.
Primary Caregiver	In burden calculations, this can be designated to be the mother, father, or teacher/day caregiver. Age-dependent designations may be apportioned between all three responsible adults.
Household	This designation was used for several "interview" measurements. In the burden calculations, this is assumed to be a single person. In the quantitative calculations, this can be apportioned between the mother and father.
Teacher/Day Care Provider	In the burden calculations, this is assumed to be a single person.
Staff	This is meant to include staff from any institution that will be utilized for record checks. This may be health care staff, school staff, or staff of local agencies.
Community-Regional	This is undefined. However, there were several "interview" measurements that designated this as the participant.
Community-Local	This is undefined. However, there were several "interview" measurements that designated this as the participant.

The designation of a participant on the list of potential measurements provided by EPA differs slightly from the designation of participant in the database. On the potential

measurement list, the "participant" is the subject of the measurement. In the spreadsheet, the "participant" is the individual who is impacted in terms of time or cost as a result of the assessment. The most common situation for which the designation was different occurred when measurements on the EPA list designated the "index child". In this situation, the impacted participant—i.e., the participant coded in the spreadsheet—was coded in one of two ways, depending on the measurement.

- If the measurement did not involve interactions with the child, such as an interview with the primary care giver about the child, burden was only designated for the primary care giver or responsible parent.

- If the measurement did involve interactions with the child under age 18, such as a biological or neuropsychological assessment, both the child and the primary care giver were designated. This necessarily assumes that the primary care giver either participates in, observes, or waits for the assessment of the index child to be completed.

Because the age of the sibling was not provided, no similar assumptions regarding primary care giver burden were assumed for assessments of the sibling.

2.2.4 Hypotheses

A total of 22 specific hypotheses were specified in the information provided by EPA. All of these could be considered as subcategories under five primary hypotheses, see *Exhibit 2.4*. (The subscript i is assigned in the following order from 1 to 22.)

Exhibit 2.4- List of Hypotheses

Undesirable Pregnancy Outcomes	Neurobehavioral Development	Injury	Asthma	Obesity/ Altered Physical Development
1.1	2.1	3.1	4.1	5.1
1.2	2.2	3.2	4.2	5.2
	2.3	3.3	4.3	5.3
	2.4		4.4	5.4
			4.5	5.5
			4.6	5.6
				5.7

2.2.5 Coding Time and Cost Burden

Most of the measurements were general descriptions of domains of information deemed relevant to the hypotheses. As such, there are often several ways to obtain the information, either in terms of detail for specific measurements (such as "smoking"

which might be assessed as current smoking or smoking history) or in terms of domains (such as "neuropsychological testing" which could include mental, behavioral, or motor measurements). To accommodate the uncertainty at this point in the development of the NCS, estimates of burden are provided for a minimum burden (such as a single question about current smoking status) and a maximum burden (such as a detailed smoking history). A further estimate was made for the most-likely burden. (See details of the determination of burden below.)

For the case of venipuncture, another burden estimate (marginal burden) was defined. A number of specific measurements, for instance clinical chemistry or DNA, were specified that all utilized venipuncture as the method of measurement. The evaluation of multiple analytes at a single visit does not require multiple venipunctures. It may, however, require that different vacutainers be used in a single draw. To accommodate the minimal added burden of additional vacutainers, a marginal burden is defined. The actual time, T_j, then is the baseline time (for instance) for the first measurement in a calculation that utilizes venipuncture as the measurement method and marginal time for the remainder of measurements in the calculation that utilize venipuncture.

2.3   General Description of Quantitative Method

For the calculation of burden there are three types of variables that are considered:

- *Indicator variables*: Indicator variables include the values of 0 or 1 that designate inclusion, visits, participants, and hypotheses. Together, these define what measurements are conducted in all possible visit-participant combinations and how the data from the measurements are used.

- *Multiplier variables*: The multiplier variables adjust the estimate of burden by various factors that account for acceptability, relevance (i.e., gender-specific measurements), and study design options (such as measurements conducted only for certain substudies or additional assessments for persons with disabilities).

- *Burden estimates*: These variables, taken together, describe the range of possible burden for the specific measurement-method combination.

In the following equations, it is assumed that burden is calculated for a single class of participant, i.e., index child, mother, or father. This can be adjusted to calculate the burden for a different set of participants, such as mother and father, by summing these estimates over all included participants.

To estimate the impact of excluding specific measurements, burden is estimated using the default setting of $B_j = 1$ and then recalculated setting the appropriate $B_j = 0$. The difference between the two estimates is the impact of excluding these measurements.

For this version of the spreadsheet, it is assumed that the only measurement method that has the characteristic of burden efficiency, i.e., the addition of other measurements using the same method at the same visit incurs only marginal time burden, is venipuncture. That is, it is assumed that adding additional assessments requires, at most, collection of blood in an additional vacutainer; it does not require an additional venipuncture.

Calculation of burden involves separate calculations of venipuncture, for which there is an efficiency with regard to burden, and all other measurement methods. The total burden across all measurement methods, such as visit-specific calculations and hypothesis-specific calculations, is the sum of both calculations.

All calculations can be conducted using burden defined as the minimum, maximum or most likely burden. For purpose of generalization, we use the designation T_j below to represent the minimum, maximum, or most likely time burden or the baseline cost burden.

2.3.1 Method-specific (M_m) Participant Burden for Individual I at Visit V_v

Calculations for non-venipuncture methods of assessment: Define the variable

$$H_j = \quad 0 \text{ if } (\Sigma_i H_{i,j}) = 0, \text{ or}$$
$$1 \text{ if } (\Sigma_i H_{i,j}) > 0 \; .$$

Then, for a given individual, I, the method-specific (m) adjusted time burden at visit V_v is given by:

Adjusted burden for individual I= $\Sigma_j(I_j B_j T_j H_j P_j S_j V_{j,v} A_j(1+D_j))$,

where j indexes all non-venipuncture measurements in the burden database. This burden is adjusted for substudy, acceptability and disability considerations. These multipliers have been set to 1.0 (for substudy and acceptability) or 0.0 (for disability) in the spreadsheet provided with this final report to calculate the total burden.

Calculations for venipuncture methods of assessment: For a given individual, I, the venipuncture adjusted-time burden at visit V_v is given by:

Adjusted burden for Individual I = $[BT + MT*((\Sigma_{jj}(I_{jj}B_{jj}H_{jj}V_{jj,v})-1)] *$ $\Sigma_{jj}(I_{jj}B_{jj}T_{jj}H_{jj}P_{jj}S_{jj}V_{jj,v}A_{jj}(1+D_{jj}))$

where BT is the baseline time for venipuncture and MT is the marginal time, and jj indexes all venipuncture-related measurements.

2.3.2 Hypothesis-specific (H_i) Participant Burden for Individual I

For a given individual, I, the hypothesis-specific (i) time burden for all visits is given by two possible equations:

Adjusted burden for individual I= $\Sigma_j(I_jB_jT_jH_{j,i}P_jS_j(\Sigma_vV_{j,v})(A_j(1+D_j)))$ +{[BT +
MT*(($\Sigma_{jj}(I_{jj}B_{jj}H_{jj,i}V_{jj,v})$-1)] * $\Sigma_{jj}(I_{jj}B_{jj}T_{jj}H_{jj,i}P_{jj}S_{jj}V_{jj,v}A_{jj}(1+D_{jj}))$},

where j indexes all measurements except venipuncture, jj indexes all venipuncture-related measurements, and v indexes all visits.

The burden can be calculated for only a subset of visits, for instance all pregnancy visits, by restricting the subscript, v, to the appropriate subset.

2.3.3 Visit-specific (V_v) Participant Burden for Individual I

For a given individual, I, the visit-specific (v) time burden for all hypotheses is given by:

Adjusted burden for individual I= $\Sigma_i(\Sigma_jI_jB_jT_jH_jV_{j,v}A_jP_jS_j(1+D_j))$ +{[BT +
MT*(($\Sigma_{jj}(I_{jj}B_{jj}H_{jj}V_{jj,v})$-1)] * $\Sigma_{jj}(I_{jj}B_{jj}T_{jj}H_{jj}P_{jj}S_{jj}V_{jj,v}A_{jj}(1+D_{jj}))$}   ,

where BT is the baseline time for venipuncture and MT is the marginal time, i indexes all hypotheses, j indexes all non-venipuncture measurements, and jj indexes all venipuncture measurements.

The burden can be calculated for only a subset of hypotheses, for instance the burden associated with all asthma hypotheses, by restricting the subscript, i, to the appropriate subset in the first and second steps.

Project Procedures

In this section we describe the procedures used to develop the Excel spreadsheet for this WA.

3.1   Developing the Spreadsheet

The WA requested development of a database using Microsoft Excel. A prototype shell was developed that included the measurement name, method of measurement, and all the indicator variables. Staff were then assigned specific domains of collection methodology to populate the database. The purpose of specializing was to:

- Use staff with expertise in the specific survey methodology so they would be able to evaluate the proposed measurements and identify collection issues;
- Enable staff to become familiar with the full range of measurements utilizing the specific collection methodology so they could develop an effective strategy for obtaining burden estimates; and,
- Help staff identify measurement commonalities across hypotheses, visits, and participants.

Staff were assigned to: interview and self-assessment; biological and physiological assessments; environmental measurements; and, record checks and neuropsychological testing. Interview and biological assessments were undoubtedly the most frequent method of measurement.

A number of issues required resolution before populating the database. First, the visits included in the summary sheet specified only office visits. Because some of the assessments, such as environmental monitoring in the home, required home visits (as noted in *Section 2.2.2*), the database was formatted to accommodate all possible combinations of time and place. (In the final database, all visits, except a preconception home visit, included at least one measurement.) Second, standard definitions were required for visit designations. Some hypotheses were specified in terms of specific visits and other hypotheses were specified using general time groupings, such as pregnancy, early childhood, or adolescence. The standard definitions shown in *Exhibit 3.1* were proposed in the quantitative method plan and approved by EPA.

Exhibit 3.1- Standard Definitions for Visits

General Description	Specific Visits
Preconception	Preconception (office and home)
Pregnancy	1st, 2nd, and 3rd Trimester (office and home)
Birth	Live, stillbirths, and abortions
Perinatal	Birth and Months 0-3 (office and home)
Infant, Year 1, or Nursing	Months 0-3, Months 4-6, Months 7-9, and Month 10-12 (office and home)
Year 2	Months 13-18 and Months 19-24 (office and home)
Early Childhood	Year 3 through Year 6 (office and home)
Later Childhood	Year 7 through Year 12 (office and home)
Adolescence	Year 13 through Year 19 (office and home)
Adults	Year 20 and Year 21 (office and home)

We then began to assign measurements to four separate spreadsheets. A number of clarifications were required to specify the indicator variables. Through a series of iterations with the EPA and National Institutes of Health program staff, most of the issues were clarified. (See *Sections 5.4* for further issues that require clarification to enable the complete estimation of burden.)

For each measurement, all listings in the list of measurements were identified that used the same assessment method for the specific measurement. In some instances different methods were used to assess the same measurement, such as "Environmental – Indoor air" which could be assessed using "For Environmental Sources: Filter + XAD" or "For Environmental Sources: Sensor". When different methods were used, measurements were coded in the database for each method. In many instances, there were several duplications of the measurement, using the same method within a specific hypothesis-visit-participant event. These duplications were not entered into the database.

Staff entered the assessment pattern (in terms of visits and participants) as a separate row for each hypothesis. The database was then sorted and rows with the same measurement were compared to determine similarities in the assessment pattern. When different hypotheses utilized data from the same measurement, there was usually overlap in the assessment patterns. These rows were then recoded into the minimum number of rows such that there was only one assessment coded per each visit-participant combination. For specific measurements, each row could contain multiple hypotheses, but visit columns only included one assessment per participant.

Once the file was completed, another staff member then conducted a 100% check. The process was iterated until final files were developed.

3.2 Estimating Burden

To estimate burden four approaches were attempted. First, burden estimates from other, existing large national Federal data collection systems were contacted to determine whether burden estimates were available for similar measurements. Specifically, staff of the National Health and Nutrition Examination Survey and the National Survey of Drug

Use and Health were contacted. However, data were not available in a format sufficiently disaggregated to be used in this exercise.

Second, published literature were considered. Many of the measurements considered for this work assignment are used extensively, such as demographic data. These were unlikely to be highlighted in published literature. Therefore, we searched for literature on some of the specialized measurements. However, none of the articles identified noted the time required to conduct the assessment.

Third, principal investigators of large surveys were contacted regarding burden estimates for specific measurements. As time allowed, multiple investigators were contacted.

Finally, for questionnaire modules, a variety of resources were used to determine the range of the number of questions included in the modules, in addition to information obtained from principal investigators. The National Cancer Institute has a number of standard questionnaire modules available through the Internet at http://dceg2.cancer.gov/QMOD/ . In addition, the questionnaires utilized by national studies such as the National Health Interview Survey, National Health and Nutrition Examination Survey, National Survey of Drug Use and Health, Behavioral Risk Factor Surveillance System, National Immunization Survey, US Census, and others that were available on the Internet were evaluated. For interview formats (self-administered and interview), a burden estimate of 4 questions per minute was used.

4

Burden Database

The burden database is an Excel spreadsheet file that contains:
- Specifications of the measurement assessment times and person affected,
- Uses for the data generated by the measurement,
- Estimates of the burden, and
- Adjustments to accommodate acceptability, relevance, and special situations.

The database delivered with this report contains 682 rows, each row corresponding to a unique assessment schedule for a specific measurement, measurement method, and participant. Each row may contain multiple hypotheses, if appropriate.

4.1 Description of Worksheets

4.1.1 Input Worksheet

The worksheet named "Input" contains the measurements with their associated attributes, e.g., visits, which are listed as variables in ***Exhibit 2.1***. Each row of the file contains information for one measurement on a given individual. Multiple rows have been consolidated into a single row when the measurement is assessed at several visits or when multiple hypotheses utilize the data from the measurement. Consequently, each row is a unique pattern of assessments that is utilized by at least one measurement.

Exhibit 4.1 is a listing of the variables and the corresponding columns in the spreadsheet.

Exhibit 4.1- Variable and Column Correspondence for Input Worksheet

Variable	Column
Measurement Name	A
Measurement Method	B
Method Recode	C
Inclusion Indicator	D
Visits (v= 1, 57)	E – BL
Participants (1 to 10)	BM – BV

Variable	Column
Hypotheses (I=1, 22)	BW – CR
Minimum Time Burden	CS
Maximum Time Burden	CT
Likely Time Burden	CU
Marginal Time Burden	CV
Baseline Cost Burden	CW
Marginal Cost Burden	CX
Acceptability Multiplier	CY
Population Frequency Multiplier	CZ
Substudy Multiplier	DA
Disability Multiplier	CB

The following are views of the Inputs worksheet using hypothetical data. The first view shows the measurement, method, and visit schedules for the visits that occur early in the NCS.

Scrolling to the right in the spreadsheet reveals the participants who incur burden as a result of the assessments.

Measurement Name = Nj	Year 20 Office	Year 21 Office	Home	Index Child	Mother	Father	Sibling	Primary Caregiver	Community-Regional	Teacher/Daycare Provider	Household	Staff	Community-Local
Environmental					1	1		1					
Environmental - Indoor Air					1	1		1					
Time Activity Patterns					1	1		1					
Demographic Survey - Residential environment				1	1			1					
Environmental - Dermal (sock)			1	1				1					
Environmental - Indoor Air			1	1				1					
Time Activity Patterns			1	1				1					
Environmental - Indoor Air			1	1				1					
Environmental - Indoor Air					1			1					
Environmental - Indoor Air				1				1					
Environmental - Outdoor air								1					1
Environmental - Allergen								1			1		
Environmental - Diesel exhaust/traffic								1					1
Environmental - Endotoxin						1		1			1		
Environmental - Tobacco smoke								1			1		
Environmental - Indoor Air						1		1			1		
Environmental - Mold		1				1					1		
Environmental - PAHs		1		1		1							
Housing Survey		1					1						
Environmental - Outdoor air		1		1			1						
Environmental - Allergen	1	1		1			1						
Environmental - Tobacco smoke									1		1		
Environmental - Indoor Air									1		1		
Environmental - Pet census									1		1		
Environmental - Allergen				1					1				
Environmental - Allergen				1									
Environmental			1	1									

Continuing in the spreadsheet, the hypotheses utilizing these measurement data are indicated, followed by burden estimates, and the multiplier variables.

Measurement Name = Nj	Hypothesis	5.1	5.	5.	5.	5.!	5.	5.	Minimum Time Burden	Maximum Time Burden	Baseline Time Burden	Marginal Time Burden	Baseline Cost Burden	Marginal Cost Burden	Acceptability Ajm	Population Frequency Multiplier Pi	Study Frequency Multiplier Si	Disability Multiplier r = D Dvi	(1+D)
Environmental									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Time Activity Patterns									10	70	30	10	0	0	1	1	1	0	1
Demographic Survey - Residential environment									10	70	30	10	0	0	1	1	1	0	1
Environmental - Dermal (sock)									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Time Activity Patterns									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Outdoor air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Allergen									10	70	30	10	0	0	1	1	1	0	1
Environmental - Diesel exhaust/traffic									10	70	30	10	0	0	1	1	1	0	1
Environmental - Endotoxin									10	70	30	10	0	0	1	1	1	0	1
Environmental - Tobacco smoke									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Mold									10	70	30	10	0	0	1	1	1	0	1
Environmental - PAHs									10	70	30	10	0	0	1	1	1	0	1
Housing Survey									10	70	30	10	0	0	1	1	1	0	1
Environmental - Outdoor air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Allergen									10	70	30	10	0	0	1	1	1	0	1
Environmental - Tobacco smoke									10	70	30	10	0	0	1	1	1	0	1
Environmental - Indoor Air									10	70	30	10	0	0	1	1	1	0	1
Environmental - Pet census									10	70	30	10	0	0	1	1	1	0	1
Environmental - Allergen									10	70	30	10	0	0	1	1	1	0	1
Environmental - Allergen									10	70	30	10	0	0	1	1	1	0	1
Environmental							1		10	70	30	10	0	0	1	1	1	0	1

4.1.2 Notes Worksheet

The second worksheet in the Excel file, "Notes", contains notes about the measurements. Each measurement-method combination is represented by a row with notes about:

- Decisions that were made while translating the list of measurements to the spreadsheet, such as how the method of measurement was determined if no method was noted in the original list of measurements, and

- Source of burden estimates.

4.1.3 Calculations Worksheets

The worksheets that follow contain the burden estimates. Calculations are provided for the three different types of burden calculations: visit-specific, hypothesis-specific, and method-specific. Because of the large number of measurement methods, calculation pages are provided only for those methods associated with at least 10 rows in the database. Burdens for the many measurement methods that are associated with 10 or

fewer rows can be calculated as needed.

Each calculation worksheet contains titles describing the calculation, the range of parameters included, and values for specific parameters. The calculations are then shown for each participant type. Total burden is also calculated in two ways: for each participant and for the "primary caregiver" reapportioned to the "mother" and "father" according to the percentages listed at the bottom of the table (denoted the Reapportioned burden). Specifically, the worksheets include the following:

Visit-specific calculations (calculation includes measurements for all hypotheses)
- Burden for each participant at each visit
- Total burden for each participant
- Reapportioned burden for each participant

Hypothesis-specific calculations
- Burden for each participant at each visit
- Total burden for each participant
- Reapportioned burden for each participant

Method-specific calculations
- Burden for each participant at each visit
- Total burden for each participant
- Reapportioned burden for each participant

The following is a portion of one of the calculation worksheets using hypothetical data:

Calculations of Visit-specific Participant Burden for Specified Individuals

Title: *Basic calculation of all hypotheses, all measures, and all visits (office and home)*
Specific Settings: *All visits (office and home)*
                   All hypotheses

NOTE: when copied to live workbook, all ranges for column length will need to be edited

NOTE: Burden measured by Time

Visit	Index Child	Mother	Father	Sibling	Primary Caregiver	Commun ity- Regional	Teacher /Daycare Provider	Hous ehol d	Staff	Commun ity - Local	Total	Re-Apportionment** (see footnotes) Primary Caregiv er	Mother	Father	Total
Year 5	150	0	0	0	150	0	0	0	0	60	360	0	127.5	22.5	360
Year 6	150	0	0	0	90	60	0	60	0	0	360	0	76.5	13.5	360
Year 7	180	0	60	90	210	0	0	90	0	60	690	0	178.5	91.5	690
Year 8	30	0	60	0	60	30	0	120	0	0	300	0	51	69	300
Year 9	30	0	60	0	60	30	0	120	0	0	300	0	51	69	300
Year 10	30	0	60	0	60	30	0	120	0	0	300	0	51	69	300
Year 11	60	0	60	30	60	0	0	90	0	0	300	0	51	69	300
Year 12	30	0	60	0	60	0	0	90	0	0	240	0	51	69	240
Year 13	150	60	30	60	90	0	0	0	0	0	390	0	136.5	43.5	390
Year 14	30	0	0	30	0	0	0	0	0	0	60	0	0	0	60
Year 15	30	30	60	30	0	0	0	30	0	0	180	0	30	60	180
Year 16	30	0	30	0	0	0	0	30	0	0	90	0	0	30	90
Year 17	120	30	0	0	90	0	0	0	0	0	240	0	106.5	13.5	240
Year 18	30	0	0	0	0	0	0	0	0	0	30	0	0	0	30
Year 19	30	0	0	0	0	0	0	0	0	0	30	0	0	0	30
Year 20	60	0	0	30	0	0	0	0	0	0	90	0	0	0	90
Year 21	210	30	60	90	120	0	0	30	0	0	540	0	132	78	540
Total	3090	780	1440	720	3390	570	0	1860	0	480	**12330**	0	4012.5	1597.5	**12330**

** Apportionment rates:
   For birth through year 4: Primary caregiver = mother 100% father 0%
   For year 5 through year 17: Primary caregiver = mother 85% father 15%

*** Not applicable

The preconception through year 4 visits are not shown in this example to enable the totals and footnotes to be visible on this screen view. In the example, the screen shows that the index child will spend 3090 minutes over the 21-year period providing data for all the hypotheses in this hypothetical prototype example; the mother will spend 780 minutes and the primary care giver 3390 minutes. Because the mother is often also the primary care giver, the burden is also shown reapportioned using the rates shown in the footnote. When the rates are reapportioned, the mother's burden increases to 4012.5 minutes.

Because the burden estimates were only available for about two-thirds of the rows in the version of the database that accompanies this report, the estimates presented in the calculation worksheets are incomplete.

4.2   Making Additions or Changes to the Database

It is recommended that a locked master file copy be kept that is not altered. Copies of the master file can be used to explore various options.

The calculations include a number of indicator flags, with values (0 or blank) and 1. Stated in the most succinct fashion, these flags designate which measurements are conducted at specific visit incurring burden for designated participants. Further, the hypothesis flags indicate how the data derived from the measurement is used. The flags are defined in the Input worksheet. If these flags are changed, the calculations will change accordingly. For instance, if an option to delete a measurement at the preconception visit is considered, the appropriate indicator flags can be set to 0 and the calculations will reflect the new burden. If, however, an option to delete a measurement from all visits is considered, the inclusion flag should be set to 0, rather than setting each of the individual visit indicator flags. Care should be taken when the inclusion flag is changed because the data may be used by more than one hypothesis. Setting the inclusion flag to 0 will affect all hypotheses that utilized the specific measurement.

Data for most of the measurements are utilized by multiple hypotheses. Consequently, changes to the assessment schedule for a measurement may impact several hypotheses. Further, there may be multiple rows for a specific measurement. Care should be taken when making changes to measurements to evaluate whether it is acceptable to affect a change to all hypotheses. Some hypotheses may require the original assessment schedule.

The principal variables for making changes or exploring this database is the combination of measurement (column A) and method (column B). We will refer to this combination as MM. Most operations on the database are based on MM. The variable of next importance is the participant (I_j). (Note: For simplicity, it is easiest to "view" the MM-P combination by adding the name of the participant to the measurement name, such as "Psychosocial stress (mother)" or "Psychosocial stress (index child)".)

Adjustments to burden estimates or multiplier variables. If adjustments are made to the multiplier variables for a specific measurement, care should be taken to change all relevant rows that contain the specific measurement. The rows can be identified by using the filters on columns A and B, which together define MM. Then all possible relevant rows will be clustered. Be sure to change all relevant rows. In some instances the burden is age dependent. Consequently, it is important to consider the age of the participant when assigning new burden estimates.

Adding new measurements. The first step to adding a new measurement is to determine whether the MM combination currently exists in the database. If it does not exist, then new rows should be added to the database. If multiple rows are added for the new MM, care should be taken to avoid duplicate assessments for the same participant and a specific visit. That is, the data from an assessment may be used by multiple hypotheses (i.e., multiple hypotheses can be coded as "1" for a given row), but for a given participant, the assessment should only be coded in the visit column as "1" in only one row.[2]

Adding new hypotheses or assessments for existing MM (measurement-methods). If a new hypothesis is added that includes a MM currently existing in the database, the filters of columns A and B can be utilized to view all the relevant MM rows. For a given participant, determine whether the assessment schedule, as indicated by the indicator flags in the visit columns, is identical. If so, simply add the hypothesis by setting the flag to "1" in the appropriate hypothesis column.

If there is no overlap in the assessment schedule, a new row should be specified. To assure that the multiplier variables and burden estimates are retained, the optimal way of adding a row for an existing MM is the following:

1) Create a new row in the database,

2) Copy the existing row to the new row,

3) Clear all the visits and hypotheses and make the appropriate changes to the participant,

4) Set the indicator flags to "1" for the new hypothesis and for all visits in the assessment schedule.

If there is partial overlap of the new hypothesis assessment schedule and existing schedules, the following steps should be taken to add a new row that contains the common visits, yet retain the unique visits of the existing hypothesis and the new hypothesis.

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[2] For example, data on the height of a participant may be utilized by multiple hypotheses, but it is measured only once per visit. Therefore, only one row of the measurement "height" for a specific individual should have the indicator flag for a given visit set to "1".

1) Add a new row to the database, copy the existing row into the new row, and delete visits that are not common to both hypotheses. In the original row, delete the common visits.

2) Consider the remaining visits for the new hypothesis. If some of the visits overlap with another row having the same MM for the participant, repeat step 1. If the remaining assessment schedule does not overlap with other existing rows,
   a. create a new row in the database,
   b. copy the existing row into the new row,
   c. clear all visits and hypotheses, and
   d. add the new hypothesis and any remaining visits that have not been previously designated in other rows.

5

Findings and Recommendations

This report describes the work that has been completed on this project as of August 25, 2003. This is a work in progress. Restructuring the information into the database format has identified issues that need to be clarified. Further, the list of measures from which this database was developed is changing. As a consequence, the database that accompanies this report contains all of the measurements with sufficient information to code into the database. Almost two-thirds of these measurements are associated with specific burden estimates. Some clarifications have been identified that will enable the development of estimates for many of the remaining measurements. A full range of possible calculations are provided to demonstrate the use of this tool for evaluation of various study scenarios. If the hypotheses for the NCS are revised or new ones added, then additional changes to the database may be needed.

This section of the report describes the data contained in this version of the database, assumptions that were incorporated in the structuring of the database, limitations to the calculations, clarifications required, and suggestions for enhancements. In this section we also discuss suggestions on a strategy to maximize the data collection of the NCS.

5.1   Assumptions and Their Implications for the Spreadsheet

The list of measurements provided by EPA is a working document compiled from suggestions of multiple NCS Working Groups deliberating both separately and in joint meetings. As such, the content and definitions vary between the sections developed by different groups, i.e., between hypotheses. Some assumptions were necessary to develop standard definitions. Further, duplications of measurements in the list—see, for instance, "Medical Hx-Asthma Symptoms" for Index child in Year 2 under Hypothesis 4.3—were coded as single measurements, rather than duplicate measurements, in the database.

In the discussion below several examples are cited to illustrate the need for the assumption. These are not the only examples and are not intended to highlight one situation over another.

Assumptions regarding participants:
- It was assumed that the primary care giver, rather than children, participated in

interviews until the child was the age of 20.[3] On the other hand, for biological or direct observation assessments, the child as well as the primary care giver were assumed to incur burden.

- For all record checks, it has been assumed that "staff" incur burden. In fact, release forms must be signed by the responsible participant. However, this is likely to generate very little time burden. Hence, it was not included in the database.

- The "primary care giver" or "household" is the designated participant for multiple assessments. This is usually the mother or father, but may be another relative. To incorporate these assessments in the total burden estimates for a specified individual, for instance for the mother, the new total burden (i.e., the "reapportioned burden") is calculated by adding a specified portion of the "primary care giver" burden to the calculated maternal burden. The proportions can be changed in the database. Similar assumptions have not been made for "household", but could be added to the database.

- In some visits, there was an apparent duplication of measurements. These multiple listings were deleted from the list before entering into the database. In at least one instance, the participant listed was not logical, "offspring of index child" at year 7. This was also deleted.

Assumptions regarding visits:
- Non-specific times, such as "infant", required definitions. Therefore, the definitions shown in ***Exhibit 3-1*** were developed. However, these definitions were not available to the planners who assembled the list. Consequently, there are refinements that need to be made with the Working Groups to assure that the assessment schedule is accurate. It is possible that some Groups indicated developmental periods, such as "infant", to specifically address all visits in that period, whereas other Groups may have meant that the one visit should occur at some point in the developmental period. For instance, physical examination of "infants" may in fact be intended for all four visits of the infant period. However, genetic markers collected during the "infant" period is presumably only conducted at one visit during that period. However, without clarification, all measurements indicating "infant" were assigned to all four visits. A standard definition needs to be developed and shared with the Working Groups to enable

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[3] This assumption can be relaxed in two ways. On overall general estimate of the proportion of interview time for the index child can be incorporated using the reapportionment scheme for the interview method-specific burden estimation. Footnotes at the bottom of the calculation page indicate that the age-specific reapportionment is currently divided between the father and mother. However, this can be further divided with the index child. If the child is added to the reapportionment part of the table, a new column must be added to the reapportionment section of the worksheet and the appropriate equations altered to accommodate a 3-way apportionment of the "primary care giver" burden. Alternatively, certain modules of the questionnaire, in fact, may be answered by children under age 18 years. The burden database can be changed to indicate that for those modules, burden is incurred by the child.

them to verify the assessment schedule.

- The summary list of visits provided with the list of measurement only included office visits. However, because some environmental measurements clearly will be conducted in the home, there will be a need to have home visits, as well as office visits. The current database includes all possible visits. In fact, this version of the database includes measurements that were allocated for all possible encounters except preconception-home visits. The assignment of an assessment was made to the office visit, unless specified otherwise or unless the home environment was required. The burden estimates are made by combining the office and home for the same visit.

Assumptions regarding measurement method:
- When the method was not specified or was specified in non-specific terms—such as, "biological samples" or "container"—in the list of measurements, we consulted with experts who have conducted similar measurements in other studies. The database includes all alternative methods of measurement. If it was unclear whether all or one method would be used, the non-specific term—such as "container"—was retained in addition to the multiple, specific methods. For instance, because allergic sensitization could be evaluated by skin tests or venipuncture, both methods were listed, resulting in two rows in the database for each participant tested. To evaluate the impact of utilizing one or the other method, when making burden estimates, use the inclusion variable to indicate which method should be used.

- Marginal time was defined as the added time over the baseline time required to collect additional information or biosamples enabling the study to evaluate new measurements without additional visits. Marginal time was only utilized for venipuncture-related measurements. For venipuncture, there is some baseline time burden to establish the line. However, the difference in the amount of time to collect 1 vacutainer or 5 vacutainers of blood is minimal compared to the initial burden to establishing the line. That is, there is an efficiency in burden to collect multiple samples. There may be efficiency in medical record checks as additional items are collected. Similarly, there may be additional equipment added to the environmental samples. However, these were not coded because specific information on these possible efficiencies was not available.

- Multiple terms were used that refer to quantitative survey methods: interview, self-administered, and questionnaire. The modes of data collection, however, were not specified, e.g., telephone, mail, Internet, or face-to-face. Total participant burden varies by data collection mode. We assumed time burdens that are consistent with all interviews conducted face-to-face.

Assumptions regarding burden:
- In many instances, the "primary care giver" was designated as the participant

incurring burden. Because personal information and biological tests are being collected, this participant will, in almost all instances, be a guardian—most often the mother or father. Therefore, the total burden for the mother or father is in fact the sum of the assessments being conducted about them plus assessments being conducted about the child with the "primary care giver". Percentages used to reapportion the primary care giver burden to the mother and father. In this version of the database, for computational purposes, we defined the "primary care giver" to be the mother 100% of the time for the infant-related visits. For all other visits until the index child is age 18, the primary care giver is assumed to be the mother 85 % of the time and father 15 % of the time. Other assumptions may be made for this participant. For instance, "other relatives" may be primary care givers. However, "other relatives" will not currently be included in the spreadsheet.

- Travel time is not included in this version of the database. See further discussion below.

- For some assessments, for instance for venipuncture, the time burden depends on the age of the participant. In these instances, there are multiple rows in the database that correspond to specific visits, with the associated burden.

Other assumptions:
- Hypotheses with common assessment schedules were coded together in the same row. The same process was used when there was partial commonality of the schedule. This not only decreases the size of the database; it also enhances the ability to identify measurements for which the assessment schedule is similar, but not identical, between hypotheses. Consequently, each row of the database is a unique assessment schedule with all the hypotheses that utilize data from those assessments. For example, data from the Birth, Months 10-12, and Year 3 visits may be utilized by Hypothesis 2.1, but Hypothesis 4.2 utilizes data from only Months 10-12 and Year 3. The resulting database has two rows, one with the Birth assessment (utilized by only Hypothesis 2.1) and the other with the Months 10-12 and Year 3 assessments (utilized by both hypotheses). Consequently, all the assessments for a specific participant-measure will not appear in one row.

Appendix B lists a number of additional assumptions that were made to facilitate the coding of the measurements in the database.

5.2   Populating the Database: What has been completed

The database delivered with this report contains 682 rows, each row corresponding to a unique assessment schedule for a specific measurement, measurement method, and participant. Each row may contain multiple hypotheses, if appropriate. Burden estimates are provided for 456 rows (67 percent of the entries). Notes on the burden estimation are included in a separate worksheet. Clarification for some of the measurements will enable the completion of the burden estimates (see *Section 5.4*).

Calculation worksheets are provided for all visits, hypotheses, and the measurement methods with at least 10 rows in the database.

Cost estimates are not included. For a majority of the measurements, the cost burden associated with the measurement can be calculated by multiplying the time by the appropriate average wage of the participant. There were no additional costs to the participant for the proposed measurements beyond the time-related costs.

5.3 Limitations of Participant Burden Estimates

There are a number of sources of burden that depend on design-related assumptions. These were not included in the database. For instance, travel time is a potential significant burden, especially for a longitudinal study, that depends on the proximity of the office visit to the participant's residence. Consequently, decisions about the recruitment geography and location of study sites for office visits, such as local, regional, or mobile examination centers, will impact on the average travel time burden. Further, the travel time for the participant is likely to vary over the course of the study because participants are likely to move. These estimates of travel time could be incorporated into the spreadsheet once the design-options have been identified as an additional variable that depends on the measurement and visit. Also, the visit-related travel time burden for the primary caregiver will differ substantially if all assessments can be conducted on all participating individuals in a single visit, as contrasted with multiple visits. Visit-related additional burden, such as travel time, can be added on the calculation pages for each visit separately and then totaled for multiple visits.

It is assumed that questionnaire modules addressing the same measurement do not differ between hypotheses. For instance, it is assumed that the measurement of smoking in the mother is the same for Hypothesis 1.1 and for Hypothesis 4.1.

There are several limitations to the estimation of burden for the responsible adults, which have variously been designated as the mother, father, primary care giver, and household. It is assumed that the measurements for the mother and father are done separately so the time burden for both parents is the same for a given measurement. Further, to enable the greatest flexibility, primary care giver and household are coded separately. However, for some measurements—such as "Demographic survey – Neighborhood characteristics" in Hypothesis 4.6 or "Demographic survey – cultural norms and values on diet and appearance" in Hypothesis 5.5—the measurements are specified at the same visit for the mother, father, and household or mother, father, caregiver-female, and caregiver-male. There is a potential redundancy that is exacerbated by reapportioning the household burden among the parents.

This version of the spreadsheet will assume that all measurements conducted at a specific visit are conducted in the location designated on the cover page of the materials provided by EPA. In fact, it may not be possible to obtain all measurements from all the participants in a single visit. For instance, the mother and index child may be able to attend an office visit, but the father may have to be interviewed in the home or via a

website survey. In this instance, the travel time burden would differ for the mother and father.

5.4   Clarification of Issues to Complete Burden Estimation

Some estimates of burden could not be developed because the specification of the event requires additional clarification. The following are some examples of clarification that is required.

Non-standard visits. Several designations for visits did not translate readily to the proposed schedule. These include:
- Sick child visits (Hypotheses 4.1 and 4.2),
- Periodically (Hypotheses 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 5.2,), and
- Every 3 months (Hypotheses 3.1, 3.2, and 3.3).

Ambiguous measurements. The following are examples of measurements for which focusing the scope of the measurement will enhance the burden estimates.
- Demographic Survey – cultural norms + values on diet + appearance (Hypothesis 5.6),
- Demographic Survey – Residential environment, Community-Local, Interview,
- Environmental – Allergen , Index child, Interview (Hypothesis 4.5)
- Environmental – Environmental Tobacco Smoke, Mother, Interview (Hypothesis 5.7)
- Social function – Social Capital (Hypothesis 3.2),
- Social function – measures (Hypothesis 3.2), and
- Neuropsychological Testing (Hypotheses 2.1). The testing is likely to vary extensively depending on the age of the child and the purpose of the testing. Identifying broadly defined categories, such as mental (cognition and executive function), behavioral (regulation and temperament) and motor (gross and fine) will greatly enhance the ability to make estimates for this measurement.

Clarification of Measurement Methods. For the measurements with no specified method, RTI has made suggestions in the database of appropriate methods. However, there were some measurement and method combinations for which the method may not be suitable. These include the following.

- Periodically, Medical Hx – Asthma, Index Child, Direct Observation – Autopsy data (Hypotheses 4.1, 4.2, 4.3, 4.4, and 4.5). While this may refer to the infrequent occurrence of deaths among the index children, it is unlikely that the study will be able to arrange for staff to observe the autopsy. With regard to asthma, history of asthma might be more completely assessed for a majority of the index children through medical record reviews or interviews. Further, the medical records of an index child who dies would be likely to contain medical histories of asthma and

would not require the conduct of an autopsy.
- Early Childhood, Environmental Allergen, Index Child, Biological Sources (Hypothesis 4.5). This is probably more effectively assessed through environmental sampling.
- Trimester 2, Pregnancy history, Father, "?" (Hypothesis 5.2). While this may refer to the pregnancy history of other wives of the father, it was unclear. This measurement was included in the database.
- Birth, School performance, Index Child, "?" (Hypothesis 5.6). This measurement was not included. However, assessment of school performance beginning in the infant period was included.
- "Collection" and "biological samples" are indicated for several measurements. In most instances there are several alternatives. Narrowing the alternatives will help focus the burden estimation.

Additional Issues. The following are several miscellaneous considerations that may affect the entries in the database.

- In Hypotheses 4.6, there are multiple measurements of "Health care usage – hospitalization". In all but one instance, these were assessed using "Interview"; the one exception being "Medical Records". It is likely that both methods will be used to obtain the information required by the study. In this version of the database, these measurements are listed as utilizing the method "Interview".

- In Hypothesis 5.1, there are multiple "Biological – Glucose tolerance" measurements of the mother during pregnancy. It is recommended that fasting glucose or 2-hour postprandial measurements be utilized instead of the glucose tolerance test.

- The subject of the measurement was not clear in some cases. In general, in the list that was provided, the "who" appeared to refer to the participant who was the subject of the assessment. For instance, there are multiple interview assessments in the infant period about the index child. On this list these were designated as "Who: Index Child". However, there were some measurements that were not clear. For instance, for Hypothesis 4.4 there are multiple measurements of Diet and Nutrition Measures in Years 1 through 6 for which the "Who" is designated as "Primary Caregiver" or "Teacher/Daycare Provider". In these instances, the "Who" is probably referring to the participant who provides the information, rather than the participant who is the subject of the assessment. For the burden database purposes, this does not affect the burden estimates. However, we recommend that future lists include both the designation of who is the subject of the assessment and who provides the information.

- In some instances it was not clear how the measurement method that was specified would be conducted on the specified participant. For instance,

Hypothesis 5.6 specified "interviews" with "community-regional" and "community-local" about "Social/Health Policies". The participant needs to be clarified, e.g., multiple interviews or single interviews and with what agencies. Further "Social/Health Policies" were also specified for interview with father and mother at the same visit. The content of the interview with the parents needs to be specified before burden estimates can be given.

5.5   Strategies to Maximize Data Collection

The process of refining a study as complex as the NCS will necessarily be an iterative process. The assumption of the following discussion is that there will be a need to decrease the burden on the participants. The database has several features that enable this process. The use of filters enable the user to view specific situations and make specialized listings of measurements. The use of indicator flags, such as the inclusion flag, enable the user to alter the assessment schedule. The use of multipliers, such as the substudy or population frequency multipliers, enable the user to design studies in which specific measurements are conducted on subsets of the entire study population. The multiple burden calculations allow the user to evaluate burden from many aspects simultaneously.

The database attached will give the NCS planners a sense of the burden for all the measures, or sets of measures. However, these measures have been identified by several Working Groups acting independently. Most measures probably with equal relative merit. RTI recommends that the process of finalizing the protocol begin with the following steps:

- *Focus on Near-Term Visits.* It is evident given the relative paucity of measurements in the later year visits, the contributors to this list have focused on the near-term visits. Further, the measurements performed in later years may change as research findings from other studies inform the hypotheses of the NCS. This recommendation is discussed further below.

- *Focus on the Core Protocol*, with the recognition that substudies will exist. This assumes the hypotheses have equal relative merit. However, there are several situations for which the hypothesis can be effectively tested on a subset of the total NCS sample. In some instances, the frequency of the outcome if sufficiently common, in which case informative data may be developed from a smaller subpopulation. In other instances, the measurements are most informative on individuals with conditions.

- *Develop Standards* to resolve similar assessments and schedules and have the Working Groups reevaluate their proposals. Standard definitions of visits and developmental periods, standard definitions of responsible adults, and standard definitions of measurements or methods of assessment will substantially clarify the protocol.

- *Set Goals.* RTI recommends that the NCS planners discuss the optimal burden for all the possible participants for near-term visits, as an exercise separate from the use of the burden database. These optimal burden estimates should be based on the collective experience of investigators. Once those goals have been established, the planners are then set to evaluate alternatives using the database.

The following elaborates on these recommendations and develops some further suggestions of ways to use the database can be used to evaluate different study scenarios.

Exploring Existing Scenarios. The Excel spreadsheet is equipped with filters that enable the user to quickly characterize the database. For instance, to identify all questionnaire items assessed with the father, first select "1" from the filter associated with the column designated "father". This will allow the user to view all the measurements that are conducted with the father. Then select "Interview" from the column designated "measurement method". All the interview-related measurements of the father are now displayed on the computer screen. To determine the burden associated with these measurements, the method-specific worksheet will display the total burden by participant as well as visit associated burden.

This feature should be used extensively to gain understanding of various aspects of the proposed measures. For instance, the content of visit-method specific assessments, such as all interview content at the infant visits, will give a better understanding of ways to streamline the assessment. Alternatively, all venipuncture measurements will help determine the types of vacutainers and amount of blood required for each draw. Other useful combinations are hypothesis-participant or hypothesis-method.

Immediate Simplifications. Because the hypotheses have been developed simultaneously, a number of one-time measurements—such as age, race, gender, and DNA—have been assigned to different visits by Working Groups focused on different hypotheses. The first step would be the standardization of the collection schedule for these assessments. Because these measurements are not time sensitive, their assessment will add some flexibility to the study schedule. The optimal time, however, will depend on study design issues.

Another initial step is to visually determine whether the assessment schedules are appropriate. For instance, for Hypothesis 2.3, there were no assessments designated for year 1 and year 2. This probably occurred because the Working Group did not have the standard definition of Early Childhood as Years 3 to 6. The Group may have thought that the ages included Year 2. The adoption of a standard visit nomenclature will facilitate the review by Working Groups of the current recommendations to identify missing or unnecessary assessments.

Another initial step is to produce listings of method-specific measurements for specific participants at each visit. These listings can be developed using the filters and column hide features of the spreadsheet. These lists can be used to identify missing measurements. Developing lists for multiple participants, as for instance for the

"household", "mother", "father", and "primary care giver", will assist in the identification of unnecessary redundancy.

Focus on Near-Term Visits. It is clear from the sparse data in the database for later years that the proposed measurements for the later visits will change. For instance, there are very few biological assessments in the later years. Also, certain measurements are not included that will probably affect the hypotheses and development of the child, such as occupation and economic status of the household adults in later years. Consequently, the total burden, across the multiple years of the study, is likely to be underestimated. Therefore, the study planning should focus on the near-term visits.

An additional consideration for focusing on near-term measurements is that research in other studies is likely to affect the proposed measurements and methods of measuring in later visits. The list, as it currently exists, will change.

Assuming that there will be rolling recruitment and that there is a need to limit the number of revisions requested of review boards, such as Institutional Review Board (IRB) and other approval groups, we recommend focusing on the visits from preconception through Year 3. In a 5-year plan, participants will probably be at all stages of the four- to five-year protocol (including the preconception and pregnancy phases) by the end of the period.

Identifying Nearly Identical Assessment Schedules. The data from a substantial proportion of the measurements are being used by multiple hypotheses. In some instances, however, the schedule for these assessments or the participants differ slightly. For instance, for occupation assessed at the same visits, Hypothesis 2.1 assesses "household", whereas Hypotheses 4.1 and 4.2 assess the father and mother.[4] In another example, Hypothesis 4.1 assesses occupation at birth and during the first year (in addition to other visits), whereas Hypothesis 4.2 only assesses occupation during the first year. This is an example of two assessment schedules that differ by only one visit. This may be an opportunity to delete the additional visit, or an opportunity for the other hypothesis to obtain more information. Identification of these nearly identical assessment schedules is enhanced by the way the database has been structured to code only one assessment per visit per participant and, thereby, indicate all hypotheses utilizing the data from the assessment in a single row. Rows can be selected and viewed together to identify similarities.

Another example of nearly identical assessments are the multiple assessments that utilize different methods, depending on the hypothesis. For instance, "Demographic survey – Race/ethnicity" of the index child is assessed by "Direct observation" in Hypothesis 2.3 and "Interview" in Hypothesis 4.4.[5] This may be an opportunity to make

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[4] Hypothesis 4.1 also assesses "household", which may be an opportunity to reduce the number of measurements by deleting the assessments on father AND mother and retaining only the "household" assessment.

[5] The national vital statistics system has a formula for determining the race of the child, based on the race of the father and mother. This method, however, is more standardized than "direct observation" and is consistent with national statistics. Although this method does not incorporate the social dimensions of

the assessments consistent.

Identifying Broadly Useful Assessments and Specific Assessments. The final protocol is likely to contain measurements whose data will be applicable to multiple hypotheses as well as measurements whose data are applicable to only one hypothesis. That is, selection of measurements solely on the basis of the number of hypothesis that utilize the data is unlikely to produce an optimal study. Nevertheless, it is useful to be aware of those measurements that are broadly useful. Deletion of broadly useful measurements may have a major impact on the utility of the study data. Consequently, it will be useful to identify the 10 percent of proposed measurements with the most number of hypotheses utilizing the data. These are measurements that should be designated as unlikely to change.

Evaluating Substudy Alternatives. The substudy variable, S_j, is currently set to default value "1", indicating that all participants, such as all mothers or all index children, receive the assessment. However, if time-intensive measurements are performed on a subset of the participants, the total participant burden is substantially reduced. This can be evaluated by changing the appropriate S_j to the proportion of participants receiving the measurement, effectively making these assessments a substudy of the larger study.

To decrease the total burden on the entire study population, some detailed interview modules or assessments, including physiologic or neuropsychologic testing, may be performed on participants with specific health conditions or risk factors. That is, skip patterns can be utilized in questionnaires and complicated or time-intensive physiologic or neuropsychologic measurements performed only on individuals with specified attributes. To model this in the database, the population frequency multiplier for the measurements affected should be changed to reflect the percentage of the entire study population that would receive this assessment. For instance, if pulmonary function measurements are only performed on children with asthma symptoms, the population frequency multiplier associated with this measurement can set to the frequency of children with these symptoms.

Evaluating the Addition or Deletion of Specific Measurements. To determine the overall impact of specific measurements on the burden, the inclusion variable can be toggled between 1 and 0.

Identifying Opportunities for Efficiencies. This study necessarily has one aspect that is potentially associated with a substantial level of burden—the need for an adult to accompany the child to office visits. All child-related measurements that involve the child have been coded as incurring burden for both the child and the primary care giver. These measurements can be identified by setting the filters to "1" in both the index child and primary care giver columns. The time burden for the primary care giver can be reduced when the presence of the primary care giver is not required for testing of the child. In these instances, if visit-specific primary care giver-specific assessments are

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defining race and ethnicity, it is recommended that this formula be used at birth and that the race of the index child be asked of the parents at a later visit.

conducted with the adult simultaneously, the total burden for the adult will be reduced. These opportunities can be identified by comparing visit-specific lists (i.e., filter in appropriate visit column has been set to "1") with both the index child and primary care giver columns are set to "1" with lists when only the primary care giver column is set to "1". The additional measurements in the second list are the measurements that can be assessed on the adult simultaneously to testing the child.

5.6   Enhancements to Spreadsheet

The database is currently formulated to depend on a single occurrence of a measurement at a specific visit for the participant. Multiple hypotheses can be specified that utilize data from the measurement, but the measurement is conducted only once for each specified participant-visit combination. This requirement makes the addition of new measurements and hypotheses complicated. Programming the spreadsheet with macros to handle duplications will enable easier manipulation of the data.

Another enhancement to facilitate data entry is to use a database management software for data collection and storage. Some options include:

- MS-Access. This database management software is very powerful in the area of database management and interface development. It can communicate very well with Excel. This combination would allow the development of a robust database and interface with built-in quality control and easy maintenance, as well as the ability to use the power of Excel to do any type of analysis of the data.

- SQL Server-Visual Basic. This software is especially powerful because tools are built for the specific needs of the database. This database could contain tools for data entry, with integration of Excel as a Data Analysis Tool. Development of this system would require more resources.

- Web-based data entry. A web-based interface with the SQL Server for data entry would provide a very flexible, widely accessible tool. However, the options will have some limitations since there are limitations to the control of Excel from a web-based application.

Although this database received a complete review in the course of developing it, we recommend another review of the contents of the database. To make the database efficient, we collapsed rows between hypotheses. However, given the more than 12,000 unique combinations of visits, participants, and hypotheses, the complete verification requires an additional check of the entries.

There are a number of aspects of the database that could not be refined or completed with the level of effort for this task. Additional effort may be needed to:

- Estimate response rates as the acceptability multiplier,
- Determine visit-specific acceptability multipliers that incorporate the age

of the child and length of visit as critical parameters,

- Estimate the impact of disability of the assessment schedule,
- Incorporate a method to recruiting participants at different stages, for instance accommodating recruitment at preconception or prenatal stages,[6]
- Resolve index child, mother, father, household, and primary care giver designations,
- Develop a method to incorporate non-standard visits such as sick child and periodically,
- Obtain additional burden estimates from additional sources,
- Incorporate stage-related burden estimates, that is, follow-up evaluations—such as medical record reviews of specified conditions and smoking history—are less time intensive than the initial assessment,
- Include travel time estimation in burden estimates,
- Incorporate potential for multiple homes that require environmental assessments, as in divorced families,
- Develop a method for identifying opportunities to build in efficiencies, such as interviewing the primary care giver while the index child is being assessed, and
- Incorporate a reapportionment process for "household".

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[6] Recruitment at different stages will affect the assessment schedule because some assessments, particularly the one-time assessments, will require rescheduling for later assessments. That is, the visit-specific burden for the participant entering is not equal to the visit-specific burden of participants already in the study. Further, the calculation of burden when participants join the study at different stages is not simply the sum of the visits that follow the recruitment.

Appendix A: Measurement Method Recodes

Both the measurement name and measurement method are indicated in the burden database. The method is presented in two ways: in text and in a numerical recode. The recoding scheme is defined in *Exhibit A.1* below.

Exhibit A.1 – Measurement Method Numerical Recodes

(Numerical Order)

Code	Measurement Method	Code	Measurement Method
1	For Environmental Sources – Sensor	28	Urine
2	Environmental – Home visit	29	Vaginal Swab
3	Dermal Sock	30	Express/massage (breast milk)
4	For Environmental Sources – Diffusion Badge	31	Container collection (unspecified)
5	For Environmental Sources – Filter + XAD	32	Sperm collection
6	For Environmental Sources – Existing routine monitoring	33	Teeth
7	For Environmental Sources – Vacuum with Filter	34	X-ray fluorescence of bones (in-vivo)
8	Direct Observation – GPS	35	Buccal cells
9	Medical Record Review	36	Catheterization (urine)
10	Direct observation – Autopsy data	37	Collection (unspecified)
11	Direct observation (Multiple assessments in physical examination by health care specialist, assumed to take place at same examination)	38	Cord Blood
12	Direct observation (by interviewer)	39	Digital photography
13	Direct observation (by neuropsychologist)	40	Direct observation
14	School records	41	Chest ausculation
15	Laboratory records (for	42	Dental exam

Code	Measurement Method	Code	Measurement Method
	biological samples)		
16	Interview	43	Pulmonary function
17	Time Activity Patterns	44	Pulse oximetry
18	For Environmental Sources – Ziploc bags	45	Examination (unspecified)
19	Anthropometric measurements	46	Glucose tolerance test
20	Biological sources (unspecified)	47	Other record review
21	Diaper	48	Placenta culture
22	First AM void	49	Skin tests
23	Swab	50	Technical procedure (unspecified)
24	Hair	51	Ultrasound
25	Meconium	52	Amniocentesis
26	Nails	53	Diary
27	Saliva	99	Venipuncture

(Alphabetical Order)

Code	Measurement Method	Code	Measurement Method
52	Amniocentesis	1	For environmental sources – Sensor
19	Anthropometric measures	7	For environmental sources – Vacuum with Filter
20	Biological sources (unspecified)	18	For environmental sources – Ziploc bags
35	Buccal cells	46	Glucose tolerance test
36	Catheterization (urine)	24	Hair
41	Chest ausculation	16	Interview
37	Collection (unspecified)	15	Laboratory records (for biological samples)
31	Container collection (unspecified)	25	Meconium
38	Cord Blood	9	Medical record review
42	Dental exam	47	Other record review
3	Dermal sock	26	Nails
21	Diaper	48	Placenta culture
53	Diary	43	Pulmonary function
39	Digital photography	44	Pulse oximetry
40	Direct observation	27	Saliva
10	Direct observation – Autopsy data	14	School records
8	Direct observation – GPS	49	Skin tests
12	Direct observation (by interviewer)	32	Sperm collection
13	Direct observation (by neuropsychologist)	23	Swab
11	Direct observation (Multiple assessments in physical examination by health care specialist, assumed to take place at same examination)	50	Technical procedure (unspecified)
2	Environmental – Home visit	33	Teeth

Code	Measurement Method	Code	Measurement Method
45	Examination (unspecified)	17	Time activity patterns
30	Express/massage (breast milk)	51	Ultrasound
22	First AM void	28	Urine
4	For environmental sources – Diffusion badge	29	Vaginal swab
6	For environmental sources – Existing routine monitoring	99	Venipuncture
5	For environmental sources –Filter + XAD	34	X-ray fluorescence of bones (in vivo)

Appendix B: Measurement List Changes Incorporated into Database

The following were changes that were made to the designations provided in the list of measurements when these were entered into the database.

Hypothesis 2.1: Birth, Biological Pesticides, Fetus, For Biological Sources: Collection "Fetus" was designated as the "Index Child" for.

"Primary Caregiver" was designated as the "Index Child" for Hypothesis 2.1: Adult – Year 21, Demographic Survey – Residential, Primary Caregiver, Interview. This designation assumes that the adult index child will complete the interview, rather than the primary caregiver. In Hypothesis 2.1, the same designation was made for Diet and Nutrition Measures – Food Frequency Questionnaire at the same visit.

"Index Child" was designated as the "Mother" for multiple measurements in Hypothesis 3.1 at the preconception and prenatal visits.

"For Biological Sources" was designated as "Interview" with the Primary Caregiver for Hypothesis 4.1: multiple infant visits, Lifestyle Factors – Cotinine, Index Child, For Biological Sources.

"Medical Record Review" was designated as "Interview" for Hypothesis 4.6: Birth, Lifestyle Factors, Primary Caregiver, Medical Record Review.

"Medical Records" was designated as "Interview" for Hypothesis 4.6: Early Childhood, Health care usage – Hospitalizations, Index Child, Medical Records. (See *Section 5.4* for a discussion of this change.)

"For Biological Sources – Venipuncture" was designated as "Glucose Tolerance Test" for Hypotheses 1.1 and 5.1. This distinction was made so it was clear why the burden estimates for these measures differed substantially from the standard venipuncture measurements.

"For Biological Sources: Collection" was designated as "Express /massage" for Hypothesis 5.2: Months 1-3, Biological – Breast Milk, Mother (biological), For

Biological Sources: Collection. This distinction was made to clarify the method of collection.

"Biological Source" was designated as "Interview" for Hypothesis 5.7: Trimester 1, Lifestyle Factors – Alcohol consumption, Mother (biological), Biological Source. This change to the measurement method was made to make this entry consistent with the multiple, other visits in which this measurement was assessed.