Supporting Statement Part A
National Birth Defects Prevention Study
OMB 0920-0010
Revision

Project Officer:
Jennita Reefhuis, PhD
Epidemiologist
Centers for Disease Control and Prevention
Phone: (404) 498-3917
Fax: (404) 498-3040
Email: nzr5@cdc.gov

November, 2008

The National Birth Defects Prevention Study

A. Justification

The Division of Birth Defects and Developmental Disabilities is seeking OMB approval of this revision of a currently approved data collection which collects data within the state of Georgia, but to also incorporate the information from the eight other states that currently comprise the Centers of Excellence for Birth Defects Research and Prevention (AR, CA, IA, MA, NC, NY, TX, and UT).

1. Circumstances Making the Collection of Information Necessary

Adverse reproductive outcomes such as birth defects and genetic diseases are associated with substantial morbidity and mortality in the United States. Roughly three to four percent of all newborn babies are affected by some form of serious defect. Seventeen of the most clinically important types of birth defects cost this country approximately $6 billion in 1992. Birth defects are the leading cause of infant mortality and the fifth leading cause of loss of potential years of life before age 65. One in five infant deaths is due to birth defects. Identifying the cause and subsequently controlling birth defects would help bring us closer to reducing infant mortality to 4.5 per 1,000 live births, a Healthy People 2010 objective.

However, to date primary preventive measures are available for only a few birth defects. For example, vaccination programs have reduced the incidence of congenital rubella syndrome, Rh hemolytic disease of the newborn can be prevented by appropriate medical practice, and genetic counseling can provide parents with information about the increased risk of Down Syndrome associated with advanced maternal age. And, perhaps most importantly, folic acid dietary supplements can theoretically prevent up to half of all cases of fatal or permanently disabling neural tube defects such as anencephaly and spina bifida.

For the vast majority of the remaining birth defects, the causes are simply not known, and cases continue to occur. The existence of this continuing burden justifies reasonable attempts to reduce birth defects and genetic diseases. The first step in understanding and controlling adverse health outcomes is always surveillance for those outcomes by public health agencies. The CDC initiated birth defects surveillance in 1967, in the wake of the thalidomide disaster, with the Metropolitan Atlanta Congenital Defects Program (MACDP). This surveillance system was meant to serve as a defense against unnecessary infant mortality and morbidity from teratogenic exposures. It was to be an early warning system for birth defect epidemics as well as the foundation upon which to do the epidemiological analysis needed to discover the cause of such epidemics. In order to achieve these ends, the MACDP has monitored (through medical record abstraction) the occurrence rates of various types of defects in the Atlanta population by recording every major congenital anomaly that has occurred among all children born in the Atlanta metropolitan area. MACDP has carried on this effort without a break since 1967, making it the longest running active surveillance system in the world.

To improve its ability to determine the causes of birth defects, the CDC paired up the Birth Defect Risk Factor Surveillance study (BDRFS) with MACDP in 1993, following OMB

approval. The BDRFS collected additional information on exposure and susceptibility factors for cases of birth defects and for comparison controls. To help reduce birth defects among U.S. babies, in 1996 Congress directed the CDC to establish the Centers of Excellence for Birth Defects Research and Prevention. This was formalized with passage of the Birth Defects Prevention Act of 1998 (see **Attachment A.1** for Public Law 105-168,). This Act authorized CDC to (1) collect, analyze, and make available data on birth defects; (2) operate regional centers that will conduct applied epidemiological research for the prevention of birth defects; and (3) provide the public with information on preventing birth defects. In 1996, CDC awarded cooperative agreements to AR, CA, IA, MA, NY, and TX to establish Centers for Birth Defects Research and Prevention (CBDRP). In September 2002, UT and NC were also funded (**Attachment D**).
Beginning in 1997, the State of Georgia exercised its option to require the reporting of birth defects under the state's disease reporting regulations, which list birth defects as a condition whose reporting is required by law. The Georgia Department of Human Resources (DHR) authorized the CDC to serve as its agent in the collection of these birth defects case report forms. (Authorization from the GA DHR is renewed on a yearly basis. **Attachment A** contains the authorization that will expire on 12/31/2010). MACDP findings are shared with the state. Since birth defects surveillance in Atlanta is a state requirement, OMB approval is not required for this data collection activity, since state-required data collections do not require OMB approval. However, the Division of Birth Defects and Developmental Disabilities is seeking a revision of its OMB clearance for the *additional* data collection, that information that is beyond what is included in the case report forms, that is carried out under the National Birth Defects Prevention Study (NBDPS) (CDC Protocol # 2087, Expiration 1/29/2009 **Attachment C**).

In the past, OMB approval was requested to include only the data that CDC collected within the state of Georgia from the results of a maximum of 400 planned interviews, 300 cases and 100 controls, which resulted in a maximum interview burden of 400 hours. This current request for revision will continue to include the data from within the state of Georgia previously approved by OMB, and will also incorporate the information from the eight other states that currently comprise the Centers of Excellence for Birth Defects Research and Prevention (AR, CA, IA, MA, NC, NY, TX, and UT). Altogether, this inclusion would potentially yield a maximum of 3,600 planned interviews, 2,700 cases and 900 controls from a total of nine states, resulting in a maximum interview of 3,600 hours for all of CBDRP. The reason for these additional states to be added to the ICR is because utilizing a multi-state case–control study to identify potential risk factors for rare birth defects better narrows the prevalence of rare exposures. The article “Risk Factors for Isolated Biliary Atresia, National Birth Defects Prevention Study, 1997-2002” (The, NS, Honein MA, Caton AR, Moore CA, Siega-Riz AM, Druschel CM and the National Birth Defects Prevention Study), the study of a rare defect, biliary atresia, is possible because of the combined data provided by the additional states. Also, the knowledge gained from research done by the expanded CBDRP through this ICR holds great promise in identifying new causes of and strengthening birth defect prevention strategies.

Infants with birth defects are identified through the birth defects surveillance system in each participating state, control infants are randomly selected from electronic birth certificates or birth hospitals in the same population, and mothers of case and control infants are interviewed by phone about their medical history, pregnancies, environmental exposures and lifestyle. Genetic

samples are obtained through the collection of DNA from cheek cells. After completing the interview, participants are sent a packet in the mail and are asked to collect cheek cells from the mother, father, and infant using small brushes. The brushes containing cheek cells are then sent back to the lab by mail.

OMB approval (OMB 0920-0010) for NBDPS was originally obtained in September 1999. The current OMB approval will expire 31 May 2009. This request is for a 3-year revision of that approval, with the expansion of the ICR to include data collected within the state of Georgia as well as the eight states outside Georgia who participate in the CBDRP as described above (AR, CA, IA, MA, NC, NY, TX, and UT). This revision request also proposes minor modifications to the currently approved data collection instrument (described below and in Attachment S)

Privacy Impact Assessment

A Privacy Impact Assessment was done previously for this project in 2004, and a Certificate of Confidentiality was signed by Dr. Tanja Popovic on August 30th, 2004 and will expire on August 31st, 2009. Since this certificate will expire soon, we provide again a PIA overview below:

Overview of the Data Collection System

The data is collected by our state collaborators within the eight states outside of Georgia. For the data collected within the state of Georgia, CDC will contract with Abt Associates to collect the data.

The data will be collected by using a questionnaire within a computer assisted telephone interviews (CATI) format. The average time to complete the CATI is approximately one hour. The interview used in the NBDPS is designed to ascertain only questions that are pertinent and useful in identifying possible risk factors associated with adverse reproductive outcomes. The CATI makes it possible to complete the interview in segments so that participants have the option of completing the interview in several sessions rather than all at once. The CATI was last approved by OMB in May 2006. We now propose minor changes to the last approved CATI, and our proposed version of the CATI for this ICR is shown in **Attachment E**. The description and justification of the proposed changes to the CATI are described in Section A.2. below.

Once the data is collected, it will be securely transmitted to the CDC through the CDC's Secure Data Network (SDN). Abt Associates will transmit the data to CDC in an identifiable format, since CDC is the recognized agent for the State of Georgia to collect and maintain this data. However, the eight other states outside of Georgia will transmit de-identified data through the SDN to the CDC (see Section A.10 below).

Items of Information to be Collected

Using the computer assisted telephone interview (CATI) system, information in identifiable form (IIF) is collected, maintained and passed through the CDC database via a Secure Data Network (SDN) to facilitate the compilation of data for the CBDRP. The following are all categories of IIF collected: name, data of birth of mother, father and baby, mailing address, phone numbers, medical information and notes, biologic specimens, education records and employment status. Other variables of information that will be collected in the CATI include: pregnancy history (i.e. prenatal diagnosis, prenatal care and fertility), maternal conditions and illnesses (i.e. diabetes,

high blood pressure and infections), family history, lifestyle and behavioral factors (including stress, alcohol use and substance abuse), nutrition, multivitamin use, environmental exposures, occupational history and family demographics (i.e. birth place and household income).

Identification of Websites

A website for this project is in very preliminary planning as of this writing. However, the URL that would be assigned to the site is not yet identified. If any website is created, the content would not be directed at children less than 13 years of age.

A.2. Purpose and Use of the Information Collection

The researchers of the CBDRP have collected sufficient information to make meaningful conclusions about the more common birth defects. As a result, CDC and its partners are better able to answer critical questions about the causes of many of these birth defects. Study collaborators have discovered important findings on: 1) nutritional factors, such as B vitamins, and the causes of certain birth defects; 2) chronic conditions, such as thyroid disease and diabetes, and the increased risk of birth defects; 3) medications commonly used to treat depression and the risk for birth defects; and 4) the relationship between risk factors, such as smoking and obesity, and certain birth defects. These findings have been published using the information collected; and there are over 30 other articles available (see list at the end of this document).

The NBDPS will continue to provide the nation with information on potential causes of birth defects and will serve as a mechanism for identifying new substances in the environment that are harmful to fetal development. This information is critical to the mission of the Public Health Service to reduce morbidity and mortality due to congenital malformations. Data from the NBDPS and the earlier version, the BDRFS, also play an important role in the decision-making process that determine federal research agendas, birth defect prevention activities, and the direction of funding programs such as cooperative agreements.

Privacy Impact Assessment

(i) **Why is this information being collected**: The purpose of the NBDPS is to continue to evaluate factors associated with the occurrence of birth defects and to test hypotheses for gene-environment interactions involved in the etiology of birth defects. Data collected in the interview (**Attachment E**) provide data for the evaluation of suspected new teratogens, mutagens, or environmental agents that are not prevalent enough to cause epidemics but which nevertheless may contribute to the occurrence of birth defects.

(ii) **the intended use of the information**: The information on family history of birth defects is useful in assessing the degree to which subsequent children in a family are at risk of having a birth defect or adverse outcome. The data gathered on parental occupation is useful in assessing the impact of the work place on reproductive outcome. The interviews also offer the possibility of identifying protective factors such as diet or vitamin use. The DNA collected from the cheek cells will be used to study genetic susceptibility to the effects of environmental agents. Using a candidate gene approach, it is possible to evaluate the role of genetic differences at specific gene

loci and their interaction with other genes or specific environmental exposures in the etiology of birth defects. Candidate genes are genes that, because of their function or location, are believed to play a role in the embryology and pathophysiology of different organ systems.

Since the last OMB approval in May 2006, we now propose minor changes to the data collection tool. Examples of these changes include: 1) changing the wording for TABs from ("In the 2 months before your pregnancy with [NOIB]/this pregnancy), did you have any other procedures to help you become pregnant?" to "In the 2 months (before your pregnancy with [NOIB]/before you became pregnant with this pregnancy), did you have any other procedures to help you become pregnant?"; 2) Deleted question about brand of cooking oil; and 3) Instead of using "around the time you got pregnant" as a prompt, ad it to the end of the question. Other changes were made similar to these and were implemented to either improve the flow of the interview and/or to simplify some of the questions posed to the participants. The interview time remains at one hour and does not increase burden to the participants. A complete list of requested changes to the CATI from the last version approved by OMB in 2006 can be found in **Attachment S**.

Once the data is collected, it will be shared with CDC via the Secure Data Network in an encrypted format (see http://www.cdc.gov/ncidod/hip/nhsn/members/SDNEnrollmentGuide.pdf). The data collected by Abt Associates from within the state of Georgia will be transmitted to CDC in an identifiable format, since CDC is the recognized agent for the State of Georgia to collect and maintain this data. However, the eight other states outside of Georgia will transmit de-identified data through the SDN to the CDC (see Section A.10 below).

None of the data will be shared with any party outside of the collaborating institutions. All identifiable data collected in this project will be protected by a Certificate of Confidentiality. A Certificate of Confidentiality for the existing OMB-approved ICR is already in place (see Attachment I) and will be modified to include this proposed Revision. Any scientific publications involving this dataset would only include aggregate, de-identified data.

A.3. Use of Improved Information Technology and Burden Reduction

The questionnaire is administered as a computer assisted telephone interview (CATI) methodology to standardize efficiency and therefore maximize burden reduction. All (100%) of the responses will be collected in this manner. The average time to complete the CATI is approximately one hour. The CATI makes it possible to complete the interview in segments so that participants have the option of completing the interview in several sessions rather than all at once.

.

A.4. Efforts to Identify Duplication and Use of Similar Information

This data collection effort is not being duplicated elsewhere in the United States. A search of the scientific literature worldwide reveals the existence of similar efforts in Hungary, Netherlands but no duplicate or similar efforts within the United States. Our CDC scientists have consulted with American Academy of Pediatrics (AAP) and the National Birth Defects Prevention Network (NBDPN) and have attended numerous national and international conferences, such as the National Clearinghouse meeting and Teratology Society conference, and have not identified

similar or duplicate efforts in the U.S. Therefore, the NBDPS is the only case-control study of 30 major selected birth defects (see **Attachment F**) being conducted in the U.S. at this time. The information collected in the NBDPS can only be obtained through maternal interviews. Medical records and physicians do not have information on the wide range of exposures that women experience immediately before and during pregnancy. And the timing and detail that is needed to study these exposures, medication dosage, diet, and prenatal care, for example, can only be obtained from maternal recall of the events.

The NBDPS is being conducted by the Centers for Birth Defects Research and Prevention (CBDRP) in eight states (AR, CA, IA, MA, NC, NY, TX and UT) and by the CDC in the metropolitan Atlanta, Georgia area. All of the sites are using the same processes for identifying eligible cases and controls, participant contact, data collection, and data processing. Collaboration among these sites and CDC is essential for the success of the NBDPS because it allows scientists with differing expertise to work together, substantially improving the ability to better understand birth defect risk factors. Because birth defects are rare, it takes many years to accumulate enough cases of a particular defect to have the power to study risk factors for that defect. This collaborative effort will enable researchers to study the epidemiology of some rare birth defects for the first time. It may also enable researchers to identify rare exposures, such as genetic variations, that are associated with the more common birth defects.

A.5. Impact on Small Businesses or Other Small Entities

No small businesses are or will be involved in this study.

A.6. Consequences of Collecting the Information Less Frequently

For the NBDPS, the mothers of the cases and controls are contacted for a telephone interview and are then sent kits for the collection of cheek cells in the mail. Very rarely a mother may have to be re-contacted if during the quality control process, some information was not clear in her interview or if the cheek cell specimens need to be re-sampled due to lack of DNA or contamination. Otherwise, this is considered a one-time survey.
There are no legal obstacles to reduce the burden.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The project fully complies with all of the guidelines of 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A.8A. 60-Day Federal Register Notice

The 60-day notice was published in the *Federal Register* on April 11, 2008, Vol. 73, No. 71, pp 19853-19854. (**Attachment B**). There were no public comments.

A.8B. Consultation Outside the agency

The principal investigators at each CBDRP work collaboratively with CDC scientists on scientific aspects of study design and analysis, including development of the study protocol, interview instrument design, and study conduct. Committees were formed with representatives from each CBDRP to design the collaborative case-control study. The **coordinating council**

consists of the principal investigators from each CBDRP site and it is the decision making body for the NBDPS and CBDRP. The council prioritized the research projects and determined the scientific direction of the CBDRP. The **standards committee** designed the protocol for the study including standard forms and procedures for identifying, contacting, and interviewing study participants. The **questionnaire and methods committee** revised the BDRFS mother interview instrument and arranged to have the questionnaire placed into a CATI format. The questionnaire committee also evaluated the interview instrument. The **clinicians committee** (geneticists and clinicians from each CBDRP) decided on the case definitions for the 30 birth defects included in the study and developed guidelines to assist with case identification and review, medical record abstraction, and coding. The **biologic committee** designed the protocol for the collection of biologic samples and developed a plan for banking, sharing the biologic specimens, is responsible for the ongoing quality control analysis of the biologic samples and the recommendation of genes for study. The **data sharing committee** has the ongoing task of deciding how the data will be equitably shared for analysis purposes. This committee is responsible for review of all protocols for data analysis as well as addressing human subjects' issues, data access, collaboration, and authorship. The scientists involved in the NBDPS represent the greatest concentration of expertise and experience on birth defects in the United States (please see **Attachment H** for a detailed list of collaborators).
There have been no major problems identified through these consultations.

A.9. Explanation of Any Payment or Gift to Respondents

Research suggests that remuneration results in increased response rates and indicates to respondents that the investigators believe their time is valuable. Remuneration may also help prevent biases introduced by lower participation rates among the economically disadvantaged. Literature examining the benefit of remuneration was summarized by Yu (Yu J, et al. A quantitative review of research design effects on response rates to questionnaires. J Marketing Res 1983;20:36-44). It reviewed 497 response rates found in 93 journal articles and found that response rates increased with monetary and non-monetary incentives.

The NBDPS began remunerating participants for the maternal interview in January 2000. A $20 money order is mailed in the introductory interview packet. Since the $20 money order was added, participation rates for both cases and controls have increased significantly. The average participation rate for the first year of the study was approximately 58% and the current rate is approximately 71%.

The CDC NBDPS also remunerates participants for the biologic specimen collection portion of the study. The cheek cell kits (for Biologicial Specimen Collection in Section A1.12) include $20 as an incentive to complete them and send them back. Overall, 61% of participants completing the interview send in a completed cheek cell kit. While some subjects have stated that they do not wish to provide buccal samples due to their concerns about genetic testing, many subjects state that it is time consuming and difficult to remember to complete the kit and mail it back. In June of 2002, we added an additional $20 incentive in two sites (New York and Atlanta) that is linked to the return of the buccal kits as a pilot study. It is appropriate to have a higher level of compensation for those who spend the additional time to complete the cheek cell collection and return the kit than for those who only receive the kit and invest no time in further participation. A total of $60 (three $20 incentives) is given to subjects who choose to complete

the entire study including the return of the buccal cell samples. The third $20 money order is provided to any mother who returned samples for herself and the baby or for just herself if the baby is deceased. While samples are requested from the father, the third incentive is not dependent on the cooperation of the father since this may pose a hardship to those mothers who are not in regular contact with the father.

Given the time and inconvenience required for the entire study (interview and biologics), a total of $60 is an appropriate level of compensation. The additional $20 money order has increased the number of kits that are completed and returned to the Atlanta Center, particularly among non-White women (Crider et al. submitted to *Epidemiology*, December 2005). Among Black, Non-Hispanic women buccal participation increased from 31.7% to 46.0%. In the logistic model, the additional $20 money order was the only significant factor associated with increased participation among Black, Non-Hispanic women [OR=1.82, (95% CI, 1.22-2.78)]. Among Hispanic women, buccal participation increased from 36.6 to 45.6%. The third $20 money order, along with maternal education greater than 12 years and interview conducted in English were significant factors associated with buccal participation [OR 1.96(1.03-3.72), OR 2.14(1.13-4.07) and OR 3.00(1.56-5.78) respectively]. Although buccal participation among White, Non-Hispanic women increased from 60.7% to 62.7% upon implementation of the third $20 money order, this increase was not significant. The Atlanta Center has a greater proportion of Black women than any other Center participating in the NBDPS it is important we continue the third $20 money order and continue a higher level of participation among this group. By September 2008, all collaborating centers includes the three $20 incentives.

A.10. Assurance of Confidentiality Provided to the Respondents

The Privacy Act Officer reviewed this OMB application and has determined that the Privacy Act is applicable. A contractor is used by NCBDDD to conduct interviews for the Atlanta site. Full names of respondents must be collected to enable the study purposes to be achieved. Records will be covered under the CDC Privacy Act system of records 09-20-0136, Epidemiologic Studies and Surveillance of Disease Problems. The NBDPS is based on the previous experience of the BDRFS, which was initiated at CDC and had 308(d) confidentiality assurance protection. The BDRFS was expanded in 1997 through cooperative agreements. The activities of the NBDPS project are both intramural and extramural, consisting of one CDC operated site in Atlanta, Georgia, and eight CDC-funded cooperative agreements in eight other states. Because all sites (except the CDC's Atlanta site) were funded by cooperative agreements and protection was needed for data at each site, it was determined by the CDC Office of General Counsel and the CDC Confidentiality Officer that a 301(d) Certificate of Confidentiality was the appropriate confidentiality protection. NBDPS received a Certificate of Confidentiality for the eight original study sites in August 1999 (**Attachment I,** expiration 08/01/2009).

The Certificate of Confidentiality, by preventing study staff from being forced under a court order or other legal action to identify study participants or provide individually identified data, supplies additional assurance to both participants and CDC's cooperating researchers that the data collected will be kept confidential and will not be subject to potential release from a wide variety of sources. Because the topics of the study are sensitive, respondents are more likely to participate since they are assured their identity is secure and will not be subject to review by

people outside of the research process (See interview telephone consent script and buccal cell collection written informed consent in **Attachments N and O** respectively).

The data to be covered by 301(d) confidentiality certificate protection include the interviews, clinical data, and results of testing on biological samples collected for the NBDPS. Each site operates a state surveillance program established by law that was operational prior to the Centers study. Surveillance data already in the possession of the sites is not to be included under the certificate. The data are properly safeguarded. Hard copy documents are kept in locked file cabinets. Computer databases are password protected. Data are transferred via the Secure Data Network. Access to individually identified study information is limited to a very small number of authorized study personnel. All personnel with access to study data must sign the NBDPS Confidentiality and Data Use Oath (**Attachment J**).

A.11. Justification for Sensitive Questions

The maternal interview for the NBDPS asks questions about topics that may be considered sensitive: alcohol and drug use, history of sexually transmitted diseases, use of contraceptives, use of fertility medications and procedures, and household income. These topics are included in the study because several reports have linked these factors to birth defects, and these associations need further clarification. The interviewers are trained to emphasize not only the voluntary nature of the entire interview but the respondent's prerogative to not answer specific questions. There are four places before the interview takes place where the mother is informed that her participation is voluntary: the introductory letter, the question and answer pamphlet, the informed consent telephone script that is read to the mother before the interview, and the Human Subjects Fact Sheet.

The initial mailing to mothers about the study includes a pamphlet of questions and answers that includes the following: "*What if I don't want to answer*? You may skip any questions you wish." (see pamphlet, **Attachment K**)

There is also a statement in the introductory letter that reads: "Any information that could identify you will be kept private." (see introductory letter, **Attachment L**).

The Human Subject Fact Sheet informs participants of the following (**Attachment M**):

"As a potential participant in this research study, you have the right to:

- Be informed of the nature and purpose of the study.
- Be given an explanation of the procedures to be followed in the study.
- Be given a description of any discomforts and risks reasonably to be expected from the study procedures.
- Be given an explanation of any benefits you can reasonably expect from participation.

- Be informed of medical treatment, if any, available to you during and after the study if complications should arise.

- Be given an opportunity to ask any questions concerning the study or procedures involved.

- Be informed that you may withdraw from the study at anytime without penalty.

- Be given the opportunity to decide to participate or not without the use of any force or undue influence on your decision.

All information that we gather in this study will be kept private. This is because the study has been given a Certificate of Confidentiality by the Centers for Disease Control and Prevention. This means anything you tell us will not have to be given out to anyone, even if a court orders us to do so, unless you say it's okay. We may share information about you with other researchers but that information will not identify you or anyone else in the study.

The National Birth Defects Prevention Study Question and Answer brochure will give you more information about how your privacy is protected in this study.

If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814, leave a message including your name, phone number, and refer to protocol #2087, and someone will call you back as soon as possible."

The informed consent telephone script (**Attachment N**) also informs the mother that there are some questions about sensitive issues in the interview and that she can choose not to answer any specific questions. The script also emphasizes that the mother's answers are confidential and that her identity will remain private.

The collection of the cheek cells from the mother, father and infant requires written informed consent (**Attachment O**). Again the participants are reminded that all parts of the study are voluntary and all data gathered in the study are stored without names or personal identifiers. The protection afforded by the Certificate of Confidentiality is explained again in the written consent.

The interview data from the NBDPS is compiled on a server at CDC and the cheek cell specimens will be stored at the CDC and ATSDR Specimen Packaging, Inventory, and Repository (CASPIR). The compiled interview data and biologic material do not contain any personal identifiers. The interview data is kept on a password-protected computer in a locked office. The biologic material is stored in rooms that are secured by cardkey access. The physical facilities for both the interview data and biologic material have restricted access with 24-hour security guards.

A.12. Estimates of Annualized Burden Hours and Costs

The interview is estimated to take one hour, which is the same amount of time as the interview which is currently approved by OMB. It is titled "National Birth Defects Prevention Study: Mother Questionnaire, CATI Version 4.0, April 30, 2007" (please see Attachment E). A maximum of thirty-six hundred interviews are planned annually, 2,700 case mothers and 900 control mothers, resulting in a maximum interview burden of 3,600 hours for all Centers per year over three years. Therefore, there is no increase in burden to study participants, only an increase in the number of participants from 400 per year to 3,600 per year. The one hour burden includes the time for the telephone consent script (Attachment N) which is reviewed with the mother at the beginning of the call to collect the information via the CATI interview.

The collection of cheek cells for Biological Specimen Collection from the mother, father, and infant is estimated to take about 10 minutes per person. Each person will be asked to rub 1 brush inside the left cheek and 1 brush inside the right cheek for a total of 2 brushes per person. Collection of the cheek cells takes approximately 1-2 minutes, but the estimate of burden is 10 minutes to account for reading and understanding the written consent form and specimen collection instructions and mailing back the completed kits. The anticipated maximum burden for collection of the cheek cells is 600 hours for the mothers, fathers and infants each, resulting in a total burden of 1,800 hours per year over three years.

The total annual burden hours for all activities for all individuals for all Centers is 5,400 hours.

Table A.12-1 **Estimates of Annualized Burden Hours**

Respondents	Form Name	Number of Respondents	Number of responses per respondent	Avg. burden per response (In hours)	Total Burden Hours
mothers (interview)	1. NBDPS mother questionnaire (CATI V 4.0 (Attach E); 2. Telephone script (Attach N)	3,600 (mothers)	1	1	3,600
mothers, fathers, infants (cheek swabs)	1. letter to families (Attach Q) 2. written informed consent for cheek cell collection (Attach O) 3. instructions for collecting cheek cells (Attach R)	10,800 (mothers + fathers + infants)	1	10/60	1,800
Total					5,400

Table A.12-2 **Estimated Annualized Burden Costs**

Type of Respondents	No. of Respondents	No. Reponses per Respondent	Avg. Burden per Response (in hours)	Total Burden Hours	*Hourly Wage Rate	Total Respondent Costs
Mothers (interview)	3,600	1	1	3,600	$10.00	$36,000
Mothers (cheek swabs)	3,600	1	10/60	600	$10.00	$ 6,000
Infants (cheek swab done by mother	3,600	1	10/60	600	$10.00	$ 6,000
Fathers (cheek swabs)	3,600	1	10/60	600	$10.00	$ 6,000
Total						$54,000

Interview costs: A respondent mother can have time costs for the interview or biological specimen collection. A respondent father and infant can have time costs for the biologic specimen collection only. An interview is estimated to take 1 hour, and an hour of respondent time is estimated to cost $10. A maximum of thirty-six hundred interviews are planned, 2,700 cases and 900 controls, resulting in a maximum interview burden of 3,600 hours for all Centers per year over 3 years ($36,000 per year).

Specimen costs: The anticipated maximum burden for collection of the cheek cells is 1,800 hours per year over 3 years. Since one of the parents will have to collect the cheek cells from the infant, the hourly wage rate was applied to the infant's time burden so the total burden for the biologic specimen collection will be $6,000 per year.

***Approximately 75% of women of child-bearing age do participate in the U.S. workforce (see http://www.bls.gov/opub/ted/2000/feb/wk3/art03.htm). A subset of these child-bearing women are part-time and not full-time workers. We have used the National Compensation Survey to aid in our calculation of the hourly wage rate for our table entitled "Estimated Annualized Burden Costs" (please see the U.S. Department of Labor publication entitled: "National Compensation Survey: Occupational Wages in the United States, June 2006" located at http://www.bls.gov/ncs/ocs/sp/ncbl0910.pdf). We have thus calculated an hourly wage rate of $10.00 for the respondents for this ICR.**

A.13. Estimates of Other Total Annual Cost Burden to Respondents or Recordkeepers
There are neither (a) total capital and start-up costs, nor (b) operation, maintenance, and purchase of services costs for respondents or record keepers resulting from the collection of information.

A.14. Annualized Costs to the Federal Government
See Table A.14-1 for a total annual cost estimate for one year to conduct the entire study of the NBDPS. Funding for the NBDPS at the CBDRP is currently in the last year of Program

Announcement No. 02081. A new five year funding opportunity announcement has been submitted and is scheduled to start on December 1, 2008. It is hoped that the NBDPS will continue indefinitely. Costs in future years will be comparable to those shown in the table with appropriate adjustments for inflation and salary increases.

Table A.14-1: **Estimates of Annual Cost to the Government**

CDC and Contract Personnel*	**FTEs**	**Costs* (dollars)**
Epidemiologist, GS-14	.8	112,000
Epidemiologist, GS-13	.8	85,440
Epidemiologist, GS-14	.25	35,000
Epidemiologist, GS-13	.25	30,000
Epidemiologist, GS-14	.5	69,400
Medical Officer, GS-15	.25	52,750
Programmer (contractor)	1	150,000
Data Collection Supervisor (contractor)	1	150,000
Data Manager (contractor)	1	125,000
Data Manager (contractor)	1	122,000
Data Manager (contractor)	1	140,000
Lab Project Coordinator (contractor)	.5	110,000
Microbiologist GS–15	.25	40,000
Lab Programmer (contractor)	1	150,000
Lab Technicians (contractor) 3		270,000
Laboratory supplies		100,000
Incentives for cheek cell collection		35,000
Cheek cell kits		10,000
Printing		10,000
Postage		5,000
Office Supplies		5,000
Travel		20,000
Computer Equipment		6,000
Interview contract		750,000
TOTAL COSTS		$2,582,590

*CDC personnel cost includes salary, benefits and physicians pay (if applicable). Contractor costs include direct and indirect cost plus profit are fully burdened.

A.15. Explanation for Program Changes or Adjustments

The estimated burden for this study has increased due to data being collected from eight additional states.

A.16. Plans for tabulation and Publication and Project Time Schedule

Data from the NBDPS are currently being analyzed. Data collection for the NBDPS is ongoing and will continue for at least 3 more years. The first coded and cleaned dataset was released to the study Centers in October 2002. Enough interviews have been completed for several birth defects to conduct analyses. Preliminary analyses have begun and over 200 proposals for analyses have been prepared by CDC and the CBDRP.

For the purposes of analysis, individual defects will be categorized into appropriately homogeneous groups, including the presence of single and multiple defects. Analysis of risks from a given exposure will be carried out within broad categories, such as all vascular disruption defects, and be narrowed to a given defect such as gastroschisis.

Because controls are population-based and randomly selected, all controls can be utilized for any of the subgroup analyses which involve interview information. Additionally, other cases can be compared with the case group of interest in certain analyses, when appropriate.

The major analytic tool will be unconditional logistic regression. Relative risk estimates will first be made without consideration of potentially confounding variables. Important covariables such as maternal age and education will then be included.

An important analytic tool will be to look for evidence of gene-environment interaction in the analysis. Genetic information will be obtained using DNA-based polymorphisms. Individuals will be classified according to the presence or absence of specific susceptibility alleles, as well as whether they have those alleles in single (heterozygotes) or double dose (homozygotes). Evidence for interaction will be sought in logistic regression modeling using specific interaction terms. Detectable relative risks using all controls have been calculated based on population exposure frequencies of 10% and 20%, with power (beta) set at 0.80 and significance level (alpha) set at 0.05. For the larger defect categories, after 1 year, detectable relative risks range between 2.7 and 3.9. However, for the rarer defects, detectable relative risks are quite high until 5-year data have accumulated.

The findings published from this study will be published in medical journals and presented at scientific meetings. Information that may be useful in preventing birth defects will be adapted for health education materials. The following NBDPS manuscripts have been published to-date:

Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM for the National Birth Defects Prevention Study. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356:2684-92.

Bitsko, Reefhuis, Louik, Werler, Feldkamp, Waller, Frias, Honein and the National Birth Defects Prevention Study. Periconceptional Use of Weight loss Products Including Ephedra and the Association with Birth Defects. *Birth Defects Res A Clin Mol Teratol* 2008; 82(8): 553-62.

Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A and National Birth Defects Prevention Study. Classifying and evaluating congenital heart defects in etiologic studies: Experience from the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol* 2007;79(10):714-27.

Browne ML, Bell EM, Druschel CM, Gensburg LJ, Mitchell AA, Lin AE, Romitti PA, Correa A, and the National Birth Defects Prevention Study. Maternal caffeine consumption and risk of cardiovascular malformations. *Birth Defects Research Part A* 2007;79(7):533-543.

Carmichael SL, MA C, Rasmussen SA, Honein MA, Lammer EJ, Shaw GM and the National Birth Defects Prevention Study. Craniosynostosis and maternal smoking. *Birth Defects Res A Clin Mol Teratol*. 2008 Feb; 82(2):78-85

Carmichael SL, Shaw GM, Laurent C, Lammer EJ, Olney RS, and the National Birth Defects Prevention Study. Hypospadias and maternal exposures to cigarette smoke. *Paediatric and Perinat Epidemiol.*2005; 19(5):333-404.

Carmichael SL, Shaw GM, Laurent C, Olney RS, Lammer EJ, and the National Birth Defects Prevention Study. Maternal reproductive and demographic characteristics as risk factors for hypospadias. *Paediatric and Perinatal Epidemiology*, 2007;21:210-218.

Carmichael SL, Shaw GM, Laurent C, Olney RS, Lammer EJ, Croughan M. Progestin intake and risk of severe hypospadias. *Archives of Pediatrics & Adolescent Medicine*. 2005; 159:957-962.

Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol*. 2007; 197:585.e1-585.e7.

Carmichael SL, Shaw GM, Yang W, Laurent C, Herring A, Royle MH, Canfield M. National Birth Defects Prevention Study. Correlates of intake of folic acid-containing supplements among pregnant women. *Am J Obstet Gynecol*. 2006 Jan;194(1):203-10.

Carter TC, Druschel CM, Romitti PA, Bell EM, Werler MM, Mitchell AA and the National Birth Defects Prevention Study. Antifungal drugs and the risk of selected birth defects. *Am J Ob Gyn.* 2008;198:191.e1-191.e7

Caton AR, Bell EM, Druschel CM, Werler MM, Mitchell AA, Browne ML, McNutt LA, Romitti PA, Olney RS, Correa A, and the National Birth Defects Prevention Study. Maternal hypertension, antihypertensive medication use and the risk of severe hypospadias. *Birth Defects Research Part A*. 2008; 82:34-40.

Centers for Disease Control and Prevention**.** Evaluation of an Association between Loratadine and Hypospadias. *Morbidity and Mortality Weekly Report (MMWR)* 2004; 53(10):219-221.

Cleves MA, Malik S, Yang S, Carter T, Hobbs CA, the National Birth Defects Prevention Study. Maternal urinary tract infections and selected cardiovascular malformations. *Birth Defects Research (Part A) Clin Mol Teratol* 2008; 82(6): 464-73.

Cleves MA, Savell Jr VH., Raj S, Zhao W, Correa A, Werler MM, Hobbs CA. Maternal use of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and muscular ventricular septal defects. *Birth Defects Research (Part A) Clin Mol Teratol.* 2004; 70:107-113.

Correa A, Gilboa S, Besser LM, Botto L, Moore CA, Hobbs CA, Cleves M, Riehle T, Waller K, Reece AE and the National Birth Defects Prevention Study. Diabetes mellitus and birth defects. *Am J Obstet Gynecol.* 2008 July [epub ahead of print]

Ethen MK, Ramadhani TA, Scheuerle AE, Canfield MA, Wyszynski DF, Druschel CM, Romitti PA and the National Birth Defects Prevention Study. Alcohol consumption by women before and during pregnancy. *Maternal Child Health J*. 2008 Mar 4 [Epub ahead of print]

Feldkamp ML, Reefhuis J, Kucik J, Krikov S, Wilson A, Moore CA, Carey JC, Botto LD. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997-2003. *BMJ* 2008;336(7658):1420 (21 June), doi:10.1136/bmj.39567.509074.25

Green RF, Olney RS, Reefhuis J, Botto LD, Romitti PA. Maternal reports of family history from the National Birth Defects Prevention Study, 1997-2001 *Genet Med* 2008; 10(1): 37-45.

Honein M, Rasmussen SA, Reefhuis J, Romitti PA, Lammer E, Sun L, Correa A. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts, National Birth Defects Prevention Study, 1997-2001. *Epidemiology* 2007; 18(2):226-33.

Lin S, Munsie JP, Herdt-Losavio ML, Bell EM, Druschel C, Romitti PA, Olney RS, and the National Birth Defects Prevention Study. Maternal asthma medication use and the risk of gastroschisis. *Am J Epidemiol.* 2008; 168(1): 73-9.

Malik S, Cleves MA, Honein MA, Romitti PA, Botto LD, Yang S, Hobbs CA and the National Birth Defects Prevention Study. Maternal smoking and congenital heart defects. *Pediatrics.* 2008 Apr;121(4):e810-6.

Malik S, Cleves MA, Zhao W, Correa A, Hobbs CA. Association between congenital heart defects and small for gestational age. *Pediatrics Electronic Pages*; 119:e976-e982. 2007.

Rasmussen SA, Lammer EJ, Shaw GM, Finnell RH, McGehee RE, Gallagher M, Romitti PA, Murray JC and the National Birth Defects Prevention Study. Integration of DNA sample collection into a multi-site birth defects case-control study. *Teratology* 2002; 66:177-84.

Rasmussen SA, Yazdy MM, Carmichael SL, Jamieson DJ, Canfield MA, Honein MA, and the National Birth Defects Prevention Study. Maternal thyroid disease as a risk factor for craniosynostosis. *Obstet Gynecol* 2007; 110:369-77.

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA, and the National Birth Defects Prevention Study. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Research, (Part A)* 2003; 67(3):193-201.

Reefhuis J, Rasmussen SA, Friedman JM. Selective serotonin reuptake inhibitors (SSRIs) and persistent pulmonary hypertension of the newborn [letter] *N Engl J Med* 354:2188-2189, 2006.

Romitti PA, Sun L, Honein MA, Rasmussen SA, Correa A, Reefhuis J, and the National Birth Defects Prevention Study. Maternal periconceptional alcohol consumption and risk of orofacial clefts. *Am J Epidemiol* 2007; 166:775-785.

Shaw GM, Carmichael SL, Laurent C, Louik C, Finnell RH, Lammer EJ and National Birth Defects Prevention Study. Nutrient intakes in women and risks of anophthalmia and microphthalmia in their offspring. *Birth Defects Research (Part A)* 2007; 79;708-713.

Shaw GM, Carmichael SL, Laurent C, Rasmussen SA. Maternal nutrient intakes and risks of orofacial clefts. *Epidemiology* 2006; 17:285-291.

Siega-Riz AM, Olshan AF, Werler MM, Moore C. Fat intake and the risk of gastroschisis. *Birth Defects Research Part A: Clin Mol Terato*. 2006 Apr; 76(4):241-5.

The N, Honein MA, Caton AR, Moore C, Siega-Riz AM, Druschel CM. Risk factors for isolated biliary atresia, National Birth Defects Study, 1997-2002. *American Journal of Medical Genetics.* 2007 Oct; 143(19):2274-84.

Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A. Pre-pregnant obesity: A risk factor for structural birth defects. *Arch of Pediatr Adolesc Med* 2007;161:745-50.

Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *American Journal of Obstetrics and Gynecology*, 2005; 193:771-7.

Yang J, Carmichael SL, Canfield M, Song J, Shaw GM. Socioeconomic status in relation to selected

birth defects in a large multi-centered US case-control study. *American Journal of Epidemiology.* 2008; 167(2):145-154.

Yang W, Shaw GM, Carmichael SL, Rasmussen SA, Waller DK, Pober BR, Anderka M, and the National Birth Defects Prevention Study. Nutrient intakes in women and congenital diaphragmatic hernia in their offspring. *Birth Defects Res A Clin Mol Teratol*. 2008; 82(3): 131-8.

Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, Costa P, Druschel C, Hobbs CA, Romitti PA, Langlois PH, Edmonds LD. The National Birth Defects Prevention Study. *Public Health Reports*. 2001; 116:32-40.

Over 30 abstracts have been published to-date and approximately twenty manuscripts will be submitted for publication in 2008-2009.

Table A.16-1 Project Time Schedule

Activity	**Time Schedule**
Data collection B maternal interviews	1998 - Ongoing
Data collection B cheek cells	1999 – Ongoing
Database coding	2000 - Ongoing
Analysis	Ongoing
Publication	July 2000 - beyond end of study

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

Expiration dates are displayed, so no exemption is sought.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions are sought.