

Supporting Statement A for:

**THE AGRICULTURAL HEALTH STUDY (AHS): A PROSPECTIVE COHORT STUDY
OF CANCER AND OTHER DISEASE AMONG MEN AND WOMEN
IN AGRICULTURE (NIEHS)**

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This is being submitted as Revision.
Yellow highlights indicate changes since the last submission in **2013**.

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The Agricultural Health Study (AHS) program staff is requesting approval of this revision to the Study of Biomarkers of Exposures and Effects in Agriculture (BEEA) to extend the ongoing field period, and add a control respondent group, and a smartphone application (app) component. AHS is a cohort study of 89,568 licensed pesticide applicators (both private and commercial applicators) and the spouses of the private applicators in Iowa and North Carolina that is to be followed for 20 years or more. Information collection for the phase IV follow-up interviews (2013-2015) and buccal cell collections will continue and be completed as requested with the 2013 submission. The primary objective of the AHS study remains to be determination of the health effects resulting from occupational and environmental exposures in agriculture. This revision is to initiate and complete a new control respondent group and a smartphone app component as part of the ongoing Study of Biomarkers of Exposures and Effects in Agriculture (BEEA). Respondents in the new BEEA control group will be selected from lists of registered voters in Iowa and North Carolina and screened to ensure they have not worked in farming. They will receive one BEEA home visit that will be modeled on the protocol received by the other participants, but with a modified computer assisted in-person interview (CAPI) that asks for other occupational exposures instead of farming exposures. Respondents for the pilot smartphone app will be selected from all BEEA participants except controls. They will be asked to download and use a smartphone app to document their daily farm routine on 30 days over a 6-month period. The smartphone app component uses procedures similar to those employed by other NCI studies. Two new specimen types will also be collected from BEEA respondents: buccal cell and airborne dust samples. The buccal cell sample (also called 'saliva') will be collected from all respondents during BEEA home visit specimen collection and will have the same protocol used by the AHS in Phases II, III and IV, except that it will be collected in person during the home visit, instead of using a mailed, self-collection kit. This effort will not increase the participant time burden. For airborne dust monitoring, a subset of the BEEA Recently Exposed group will be selected to receive farm visits at which an industrial hygienist will collect samples near the participant's breathing space. This effort will require an additional consent form, but will otherwise not increase the participant time burden.

A. JUSTIFICATION

A.1 Circumstances Making the Collection of Information Necessary

Under the Public Health Service Act (42 USC § 285l), the Epidemiology Branch of the NIEHS are authorized to collect information to generate and test hypotheses concerning environmental and host determinants of cancer and other chronic disease outcomes. The Agricultural Health Study (AHS) continues to generate and test hypotheses regarding the association of specific agricultural, occupational, dietary, and other exposures and specific cancers and other chronic disease outcomes. This is a request for revision so that the follow-up activities for the phase IV can continue as planned and revisions to the BEEA component (2013-

2018) can be initiated and concluded. The data for Phase IV follow-up of the cohort are collected by using one of three methods of the cohort member's choosing: self-administered computer assisted web survey (CAWI); self-administered paper-and-pen (Paper/pen); or an interviewer administered computer assisted telephone interview (CATI). Proxy interviews for those cohort members unable to complete the follow up will be completed by using one of the three methods as well. This work will continue as previously planned with no additions or changes. In addition, the evaluation of biological markers that may be associated with agricultural exposures and risk of certain types of cancer will continue and some respondents will also be asked to participate in the collection of computer-assisted telephone (CATI) and in-person (CAPI) interviews, and biospecimens (including blood, urine, buccal cells, household dust, and airborne dust). All additional documentation, in the form of attachments, that support this submission are listed in **Attachment 1**.

Since the late 19th century when the use of pesticides in the agricultural community was widely introduced, there has been a growing concern about the relationship between pesticide use and specific health outcomes among agricultural health workers. A number of studies have been conducted in the past with inconsistent results and differences in risk estimates due in part to differences in study design, population heterogeneity, problems with exposure assessment methods, and other limitations (**Attachment 2**). To address some of these limitations, in 1992 the National Cancer Institute (NCI) initiated a prospective cohort study of approximately 90,000 registered pesticide applicators and their families in North Carolina and Iowa titled "The Agricultural Health Study (AHS)".

Cohort enrollment began in the two selected study sites, Iowa and North Carolina, in December 1993 and January 1994 respectively. Under the protocol of the first five years, the

AHS was presented to applicators as they obtained or renewed their pesticide application licenses. During the first five years 89,658 (1993-1998) respondents or approximately 80% of the target population were enrolled into the study; this includes private applicators, spouses of private applicators, and commercial applicators. This enrollment percentage is among the highest for prospective cohort studies conducted to date in the United States (**Attachment 2**).

During phase II (1998-2003) of the study, 60,728 enrolled cohort members were interviewed. Cancer incidence and mortality follow-up was completed on all but 650 (<1%) cohort members who were either lost to follow-up or who requested to be dropped from disease follow-up.

During phase III, the cohort was re-interviewed and continued to be followed to determine disease incidence and mortality. The focus of phase IV is to continue updating the medical history information for respondents enrolled in the Agriculture Health Study. The primary objective of the AHS is to determine the human health effects resulting from occupational and environmental exposures in the agricultural environment. During the remainder of phase IV, updated information on health status will continue to be collected from cohort members to evaluate potential health effects related to exposure information reported in the previous phases of the AHS. In addition, the cohort continues to be followed through the cancer registries within Iowa and North Carolina, the Social Security Administration database, state vital statistics offices, the National Death Index, and various in-state databases, such as the listing of registered pesticide applicators.

Additionally, biomarkers of early biological effect are being assessed to a limited degree to provide indicators of potential alteration in DNA function. Evaluation may include assessment of chromosomal aberrations, telomere shortening and epigenetic effects. The

correlation of early biological effect and subsequent disease is also being assessed. In phase III, buccal cells have been collected from approximately 1,210 additional study subjects, contributing to a total of 36,088 buccal cell collections to date. Buccal cell DNA is now being evaluated for the potential effect of inherited polymorphisms and the interaction of environment and genomic predisposition.

National Institute of Environmental Health Sciences (NIEHS) is interested in other disease outcomes and the National Cancer Institute (NCI) is primarily interested in cancer outcomes and determinants of exposure. NIEHS will be assuming the responsibility for collecting information on medical history from the full cohort. NCI is finalizing the collection of buccal cell information, as well as adding the **control group, smartphone app, and buccal cell and air monitoring samples to the BEEA** study.

The long-term prospective study design offers several advantages over retrospective cohort and case-control investigations including the avoidance of case-recall bias and a comprehensive exposure assessment with periodic updates of occupational exposures, personal health history and lifestyle factors. In addition, the information obtained from questionnaires is being linked to environmental and biologic measures that will strengthen the exposure classification. This study also offers the opportunity to evaluate other exposure-related non-cancer outcomes of interest, such as renal, reproductive, developmental, neurological, and immunologic endpoints.

A.2 Purpose and Use of the Information Collection

The Agricultural Health Study continues to have six major objectives:

1. Identify and quantify cancer risks among men and women, whites, and minorities associated with specific direct pesticide exposures and exposures to other agricultural agents.
2. Evaluate non-cancer health risks associated with exposure to pesticides and other potential agricultural exposures, e.g., neurotoxicity, reproductive hazards, asthma and other respiratory diseases or symptoms, immunological toxicity, kidney disease, birth outcomes, and growth and development among offspring.
3. Evaluate the disease risks among spouses and children of farmers that may arise from ‘indirect’ contact with agricultural chemicals (e.g., ambient air drifts, pesticide residues on rugs, furniture, and other items, transferring chemicals) and ‘non-occupational’ exposures (e.g., applications to pets, in homes, and on gardens).
4. Assess agricultural exposures using periodic interviews and environmental and biological monitoring.
5. Study the relationship between agricultural exposures, the occurrence of biomarkers of exposure, biological effect, and biomarkers of pre-clinical disease and genetic susceptibility factors relevant to carcinogenesis. This objective is enhanced by the continued collection of blood and urine from study subjects from the Study of Biomarkers and Exposures and Effects in Agriculture (BEEA) over the age of 50 years. For more information about BEEA and dust components objectives and background, refer to **Attachment 22.1**.
6. Identify and quantify cancer and other disease risks associated with dietary exposures and cooking practices and chemicals resulting from the cooking process.

A major benefit of a prospective study is that investigators can collect data on exposure and disease as they occur instead of relying entirely on recalled information. This approach reduces errors associated with recall of events that occurred prior to disease onset and will make scientific conclusions more valid. The phase I enrollment questionnaires (1993-1997), phase II telephone interviews (1998-2005) and, phase III telephone interviews (2005-2010) previously administered gathered information on demographic characteristics, pesticide use, general health and health risk factors, diet, buccal cell samples, overall farming characteristics, other agriculture exposures, work practices that modify exposure, as well as on other activities that may affect either exposure or disease risks (e.g., diet, exercise, alcohol consumption, medical conditions, family history of cancer, other occupations and smoking history). Investigators are currently comparing the number of cancer cases expected to the number that are actually identified through linkages with state cancer registries. They are also comparing disease risks in individuals exposed to specific occupational or environmental exposures to risks in unexposed individuals. Phase IV data collection will allow the identification of new cases of adult chronic diseases, not available through disease registries.

Dust **is** collected as part of BEEA for the purpose of evaluating exposures in the rural and agricultural environment, such as endotoxins, and pesticides, which have been shown to settle in dust. These exposures in the dust will be linked both to questionnaire data previously collected to evaluate determinants that influence these levels in the home environment, and to various health outcomes. The questionnaire that accompanies the collection of the dust will allow researchers to evaluate these levels in relationship to home characteristics that may influence the levels, and to ensure that the dust being collected is actually from the home where the participant lives.

To facilitate future cross-sectional molecular epidemiologic investigations of specific agricultural exposures and intermediate biomarkers related to cancer or other chronic diseases, we are enrolling and collecting biospecimens from additional individuals who have not lived or worked on a farm as an adult or held a job applying pesticides. These participants will serve as controls in future cross-sectional biomarker studies. The controls will be identified from state voter registries in Iowa and North Carolina and will be frequency-matched to BEEA participants on age, race, and state and county of residence.

Among a subset of participants in the BEEA study, we will also conduct an evaluation of the use of smartphone technology to record work tasks. The purpose of this effort is to characterize variability in work tasks and to provide insight into the feasibility of using smartphones to collect exposure information for future use in prospective cohort studies. The participants in this effort will be asked to download and use the smartphone app to document their daily farm routine on 30 days over a 6-month period.

To date, there have been over 220 papers published detailing study methods and exposure assessment methods high pesticide exposure events, environmental measures, cancer and other health outcomes, and diet. See **Attachment 2** for a list of all of the current AHS publications.

A.3 Use of Improved Information Technology and Burden Reduction

The phase IV respondents are screened to ensure that the instrument corresponds to the correct respondent, and to obtain informed consent. During phase IV, a questionnaire will be collected by using one of three methods of the cohort members and proxy's choosing: self-administered computer assisted web survey (CAWI)(**Attachments 25.1 and 26.1, respectively**); or self-administered paper-and-pen (Paper/pen)(**Attachments 25.3 and 26.3, respectively**); or

an interviewer administered computer assisted telephone interview (CATI)(**Attachments 25.2 and 26.2, respectively**). The interviews are conducted at a time that is convenient to the subject. Every effort has been made to minimize the length of the questionnaire, and to format it in a manner that optimizes clarity and minimizes the burden on the respondents in all three modes of collection offered.

Some participants receive a contact to request the buccal sample separately from their interview contact. Among the participants targeted for this buccal cell collection contact will be those found to have selected cancers such as prostate cancer and non-Hodgkin lymphoma, in order to learning more about possible links between these cancers and pesticide use. This form of participation, including the contact to request verbal consent (**Attachment 9.1**), completing the consent (**Attachment 9.2 or 9.3**), and collecting the buccal collection kit requires approximately **10** minutes.

Additional contacts remaining in phase IV are the participants in the biomarker component of the study, BEEA. The BEEA participants will continue to complete an in-person interview (**Attachment 19.1**) at their home, and provide blood, urine, **buccal cell** and **household dust** specimens; **it will take approximately 90 minutes in total to complete all of these components of the home visit**. Male pesticide applicators enrolled in the AHS will be contacted by telephone about this study, **and, with this revision, a group of male, geographically- and age-matched, registered voters, the control group, also will be contacted**. **We will also conduct an in-person interview (Attachment 19.2) and collect biospecimens and household dust from the control group**. These respondents are **telephone** screened to ensure they are the correct respondent, to determine eligibility (including eligibility for a blood draw), and to gain verbal informed consent (**Attachment 20.1, 20.2, 20.3 or 20.4**). Additionally, all of the AHS

participants who are contacted by phone (including those who decline to participate in the BEEA Study or are ineligible) will be asked for permission to collect some information about their cancer screening practices. If they verbally consent, three questions are asked regarding their history of cancer screening tests, including digital rectal exams, PSA testing, and colonoscopies and sigmoidoscopies. This initial telephone contact will take approximately 20 minutes to complete. In telephone contacts with controls the cancer screening questions will only be administered to respondents who have consented to the BEEA home visit.

Participants in the home visit component of the BEEA will be scheduled to receive a visit at a time that is convenient to them. They will be administered a structured, computer-assisted in-person interview (CAPI), a format of interview that again minimizes the burden on the respondents.

For the dust collection questionnaire (**Attachment 21**), it is more convenient to have the respondents complete these questionnaires in advance, by paper and pencil, than any other method. During the already scheduled home visit, the study phlebotomist will review the written informed consent form, administer the CAPI, collect the blood and urine samples, and collect the participant's disposable vacuum bag (or empty the dust from vacuums without disposable bags).

Two Privacy Impact Assessments (PIAs) have been promoted and approved by the Department of Health and Human Services in 2012. A PIA is designed to identify and protect employee and public citizens' personally identifiable information (PII) and it ensures that the government has considered necessary safeguards for the PII passing through or being collected, maintained, or disseminated in the AHS's IT systems. The names of the IT systems for this project are titled, "NIH NIEHS Agricultural Health Study (AHS)" and "NIH NCI Agricultural Health Study – Westat (AHSW)" (**Attachment 28**).

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

There is no other source of similar information to that which will be collected in this effort. Most epidemiologic studies of farming and pesticides have been conducted retrospectively and these studies have had many weaknesses. Most relied on rather crude indicators of exposure, such as farming or use of general pesticide classes, while very few have employed comprehensive, quantitative measurements of specific pesticides as we do in the AHS.

Dust is being collected in the Lung Health Study¹, a sub-study of the AHS focused on non-malignant respiratory conditions, being led by the National Institute of Environmental Health Sciences. Since the Lung Health Study and BEEA are drawn from the same cohort population, we will evaluate whether it is appropriate to utilize dust specimens from both sub-studies to increase power to evaluate certain hypotheses.

The smartphone app has been developed to assess physical activity for epidemiologic studies. The app uses procedures similar to those employed by other NCI studies (e.g., OMB #0925-0642), but, to our knowledge, this will be the first study to use smartphone technology to characterize farming activities and agricultural exposures.

Control of confounding by cigarette smoking and other lifestyle factors has been a problem in almost all previous studies. These weaknesses make it difficult to draw reliable conclusions from past studies. Exposure assessment is particularly strengthened by the prospective design of the study and design of the questionnaires.

The investigators for AHS are members of AGRICOH, an international consortium of agricultural cohort studies (<http://agricoh.iarc.fr/>) (**Attachment 3**), whose objectives are to

¹ In 2008, a determination was made by Sherry Mills, Clinical Exemption Committee Chair that the AHS Lung Health Study did not require PRA/OMB clearance or Clinical Exemption since it was a clinical trial that would be conducted by NIH intramural staff as part of their official duties.

characterize ongoing and planned studies, identify areas where pooling would be advantageous, and identify areas for replication of findings.

A.5 Impact on Small Businesses or Other Small Entities

Since this data collection involves farmers it will involve small businesses. Participation of all subjects is entirely voluntary and scheduling of interviews and biospecimen collection is at the convenience of the participants to minimize disruption of personal or work time. In addition, the study has been structured so that interviewing of farmers shall be conducted, to avoid interference with time required for planting, growing and harvesting.

A.6 Consequences of Collecting the Information Less Frequently

The protocol for phase IV questionnaires and collection of buccal cells has involved a one-time collection of data for each respondent over the next three years. The design of the study requires an update on medical history every five years to minimize exposure misclassification and identify the occurrence of non-cancer endpoints which cannot be obtained by any other existing data system.

The BEEA study involves two additional questionnaires (an eligibility screener and an interview questionnaire), and specimen collection (i.e., urine, buccal cell, blood and dust). For most BEEA respondents, including the proposed control group, this is a one-time collection.

For study subjects in the Recently Exposed study group, the questionnaires and specimen collection will involve 3 repetitions of the procedures outlined above, collected at time points before, during and after selected pesticide or other agricultural exposures. Recently Exposed participants who agree to airborne dust monitoring will receive the questionnaires and specimen

collection twice, in association with separate air monitoring sample collection visits (which do not involve any questionnaires).

For the smartphone app, BEEA participants will log their daily work activities for 30 days during a six-month timespan. These days will be randomly selected to provide information on a variety of activities.

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

The BEEA study involves special circumstances requiring a small minority of the study subjects to respond to the CAPI possibly three times within a 3 month-period. The completion of the CAPI and collection of the biological samples must occur initially, and then within a proscribed time following exposure to selected pesticides or other agricultural exposures. This time frame for repeated collection of information and biological samples is necessary in order to evaluate short-term hematologic alterations (complete blood count and lymphocyte subset measurements), which are known to occur following exposure to agents that may influence cancer risk. These procedures will allow us to evaluate the biological plausibility and mechanisms-of-action underlying associations between pesticides and other agricultural exposures and risk of various malignancies.

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

A 60-day Federal Register Notice of this proposed data collection was published in the Federal Register on November 27, 2015, Pages 74115 – 74116. Comments were solicited on the proposed information collection. No public comments were received. .

The investigators for this study consult with a National Advisory Panel (NAP) annually to get their views on the activities being conducted by the study. The last meeting was held

March 1, 2012. The NAP consists of epidemiologists, toxicologists, farmers, and pesticide educators (**Attachment 4**).

Additionally, the investigators for AHS are members of AGRICOH, an international consortium of researchers following agricultural cohorts designed to characterize ongoing and planned studies, identify areas where pooling would be advantageous, and identify areas for replication of findings.

A.9 Explanation of Any Payment or Gift to Respondent

Materials to be utilized in the study are provided to the respondent (e.g., a small bottle of mouthwash to be used in the buccal rinse collection) and return postage for any materials to be returned to the Coordinating Center is provided via the use of pre-stamped Business Return Permits on the return envelopes. Each respondent who returns a buccal cell sample will receive \$5.00 as an incentive for the time spent providing the sample. The \$5 is provided as an incentive to the respondent to accurately read and follow the instructions for the buccal cell collection. Participants in the BEEA component will receive \$100 per home visit as an incentive for the time taken to participate in the interview and biospecimen collection. The home visit incentive was increased by \$25 dollars to account for the increase in the estimated duration of the home visit from 60 to 90 minutes. Additionally, consenting Recently Exposed and some Control subjects are mailed test results (**Attachment 17.11**) – there are participant letters for Normal, Essentially Normal, and Abnormal results, as well as a physician letter for Abnormal results meriting physician contact (if consented).

A.10 Assurance of Confidentiality Provided to Respondents

Procedures have been developed to protect the confidentiality of the subjects. A Certificate of Confidentiality was obtained prior to onset of data collection, and has been renewed through 2019 (**Attachment 5**). Though data collection is not anticipated to extend past September 2019, if this does occur a renewed Certificate of Confidentiality will be applied for through NIH. The data collection is covered by NIH Privacy Act Systems of Record 09-25-0200, “Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH, HHS/NIH/OD” (**Attachment 6**). In addition, all contractor staff sign a pledge agreeing that all information provided by the respondents will be accorded the highest degree of confidentiality allowable (**Attachment 7**). Subjects are informed of the measures taken to protect their confidentiality in the introductory letter for Phase IV. A different version of the introductory letter has been developed for next of kin to be sent to households of known deceased cohort members (**Attachment 24.2**). All letters are sent out on AHS Health Follow Up coordinating center letterhead. Additionally, respondents are informed again of measures taken to protect their confidentiality prior to beginning the phase IV CAWI or telephone interview. For the questionnaires administered by telephone, informed consent will be documented verbally (**Attachments 25.1, 25.2, 26.1 and 26.2**). Completion of the CAWI or return of the paper/pencil questionnaire will document informed consent for those who choose to complete the follow up in either of these modes. An additional verbal consent will be administered for those respondents participating in the buccal cell collection (**Attachment 9.1**). Differing BEEA introductory letters are issued for **participants** depending on whether they are **AHS participants** (**Attachments 17.1 and 17.2**) or **Control Group participants** (**Attachments 17.14 and 17.15**). During the BEEA

telephone eligibility screener interview they are administered a verbal consent (**Attachment 20.1, 20.2, 20.3 or 20.4**). Lastly, at home visits an informed consent form will be administered to AHS participants for one, **two**, or three home visits (**Attachments 18.1 through 18.6**), and to control participants for one visit (**Attachments 18.9, 18.10, or 18.11**). There is a separate consent for the air monitoring sample collection visits (**Attachments 18.7 or 18.8**) and for the smartphone application (**Attachments 22.3 or 22.4**). Note that the smartphone application does not collect any PII from users and does not require PII in order to be installed on the smartphone or to transmit data. Users register using a unique study ID and only this study ID is included in data transmissions.

Buccal cell specimens collected in phase II (1998-2003), phase III (2003-2010), and phase IV (2013-2018) are stored labeled with an ID number only, no name, and in a manner that will permit efficient retrieval and optimum stability for later use. BEEA blood, **buccal cell**, urine, **dust, and air monitoring** specimens are handled in the same manner. The procedure for collecting the buccal cells involves the use of a commercial mouthwash in a manner compatible with normal use of the mouthwash. This procedure causes little or no discomfort and has a minimal possibility of infection. The blood collection procedures for BEEA component using venipuncture has minimal physical risks such as the possibility of swelling or bruising, whereas the urine collection procedures pose no risks. The risks associated with the genetic analysis of these samples are considered to be minimal, as the analyses to be done within the AHS are not of a sensitive nature. Genetic analyses to be performed, address polymorphic normal genetic variants. The risks of disclosure of the genetic information have been minimized through the records handling precautions taken and the removal of personal identifiers from both the interview instrument and the biologic specimens.

Personally identifiable information (PII), such as Social Security Numbers (SSNs) is collected to provide tracing capabilities. Additional procedures to protect security for PII include:

1. All study subjects are assigned an I.D. number at the time of the study enrollment. Personal identifier data are kept separate from the questionnaire data, which are held at the Coordinating Center. The I.D. number, not the participant name, is used to track participant activities throughout all phases of the study. Completion of the CAWI or return of the paper/pen questionnaire will document informed consent for those who choose to complete the follow up in either of these modes. Verbal permission is obtained from the CATI participants. Verbal permission will also be obtained for the BEEA CATI screener (**Attachment 20.1, 20.2, 20.3 or 20.4**), whereas written consent, as indicated by a signed informed consent form, is required at the home visit prior to administration of the CAPI and collection of blood, buccal cell, urine, and dust specimens; and at the farm visit prior to air monitoring sample collection (**Attachments 18.1-18.6, 18.9, 18.10, or 18.11**).
2. BEEA Field laptop security configurations will be in compliance with major standards and industry best practices, including Federal Desktop Core Configuration (FDCC) and Whole Disk Encryption (WDE). Field staff using field laptop computers will have individual Windows accounts with strong passwords which prevent unauthorized access to the laptop in the event it is lost or stolen. Regular changing of the passwords also will be part of this security standard.
3. The computer data files with identifier information will be available to only a limited number of Coordinating Center staff for a limited time. These data will be handled under the Privacy Act System of Record Notice, 09-25-0200, Clinical Research: Environmental Epidemiologic Studies in the Division of Cancer Epidemiology and Genetics, HHS/NIH/NCI (**Attachment 6**).
4. Previously collected hard copies of questionnaires that contain any personal information (primarily the female/family health questionnaires and selected follow-up questionnaires) are stored in locked rooms at the Coordinating Center. All AHS Coordinating Center personnel involved with the project have signed confidentiality agreements (**Attachment 7**). A Certificate of Confidentiality was obtained prior to onset of data collection, and has been renewed through 2019 (**Attachment 5**).
5. After the data are analyzed, personal identifiers will be kept by the AHS Coordinating Center if another phase of the study is undertaken, otherwise the data will be destroyed. At the completion of the study, all personal identifiers will be removed from the data.
6. All collaborators allowed access to PII's for other studies are required to sign a confidentiality agreement (**Attachment 8**) indicating that data and/or PII will not be shared with individuals not covered by the confidentiality agreements.

Extensive safeguards are in place to ensure the confidentiality of each subject is protected. Each subject is assigned a six-digit number; these IDs are used for any references to subjects on an individual basis. Names and other identifying information are kept in separate databases maintained by the AHS Health Follow Up Coordinating Center and the AHS Coordinating Center. These data files are joined only for performing linkages to the mortality, end stage renal disease, and cancer incidence databases. Contact of subjects occurs only through the AHS Health Follow Up Coordinating Center and the AHS Coordinating Center. Several layers of passwords exist to ensure unauthorized access to the electronically stored data is not permitted. Hard copies of questionnaires from phase I that contain any personal information (primarily the female/family health questionnaires and selected follow-up questionnaires) are stored in locked rooms at the AHS Coordinating Center. All personnel involved with the project have signed confidentiality agreements.

Since the last IRB approval no participants have elected to withdraw from the Agricultural Health Study. Such requests are honored without question. There has been no indication of personal harm or injury to any of the participants in the study. Usually the request to discontinue participation is made due to a participant leaving agricultural employment and losing interest in participating in the study.

The original concept for the AHS was approved by the Board of Scientific Counselors of the Division of Cancer Etiology in March 1992. The questions from which the follow-up questionnaires were developed were approved by the NCI Epidemiology and Biostatistics Program for Technical Evaluation of Questionnaires (TEQ) for Phase II and III questionnaires and the NIEHS Epidemiology Branch for Phase IV questionnaires. All comments and

suggestions which came out of the review were incorporated into the questionnaire. The BEEA study was approved by the NCI Senior Advisory Group for scientific merit.

All materials for this proposed information collection for the phase IV follow up (i.e., questionnaire, contact letters, telephone scripts) have been approved as an amendment to an existing approved protocol by the IRBs representing the National Institutes of Health (**Attachment 23.1**); and Social & Scientific Systems, Inc., the AHS Health Follow Up Coordinating Center for the study (**Attachment 23.2**).

Initial approval from the AHS Coordinating Center, Westat, IRB required for processing of death certificates from the cohort was received, and subsequently approved every year. The current Buccal collection and BEEA study were approved by the NCI IRB and Westat's IRB and subsequently approved every year (**Attachments 12 and 13**).

A.11 Justification for Sensitive Questions

Most questions asked during phase IV (2013-2018) and the additional BEEA component are typically not considered sensitive. Questions include those on the handling of pesticides, farm operations, occupations other than farming, and source of drinking water. Information on these factors has been collected in phases I, II, III and is now being updated in phase IV.

Some questions, such as those about alcohol consumption, medical history, and reproductive health may seem sensitive to some respondents. However, these are important factors to evaluate as possible confounders, especially for breast cancer among women, lung cancer and oral cancer among men and women, reproductive difficulties and other chronic diseases. These represent questions that are common to health studies. Completion of the CAWI or return of the paper/pen questionnaire will document informed consent for those who

choose to complete the follow up in either of these modes. Verbal consent is obtained prior to the start of the phase IV telephone interview and will be obtained prior to the BEEA telephone screener; written consent will be obtained before the BEEA home visit CAPI and sample collection. For those in the Recent Exposure Group of the BEEA, a written informed consent form will be administered at the first home visit, and for air monitoring participants, at the first air monitoring visit and home visit. Respondents are informed that their responses will be kept confidential and they have the right to skip any questions even if they consent to the interview as a whole.

Personally identifiable information (PII) was collected in the form of SSN. Participant's SSN were collected in phases I and phase II and since all SSN are now known, it will not be necessary to ask for this information again. Social Security Numbers are used for tracking vital status, cause of death, and cancer incidence in both states and the incidence of birth defects in Iowa utilizing registries. Participants were advised that SSN was requested to enable checking of health records, that disclosure is voluntary, and refusing to give the SSN will in no way affect any rights, privileges, or benefits the respondent or their family may have now or in the future.

Individuals who were enrolled into the study but who are no longer at the address given during enrollment (based on subsequent attempts at follow-up) have been submitted and will continue to be submitted (through NIOSH) in the standard format to the IRS under their Project 057 Taxpayer Address Request Program. Identifying data provided to the IRS include only SSN and the first four letters of the last name of the cohort member. IRS provides in return the most current address in IRS records if a match (SSN + all four letters of the last name) are found. The purpose of this effort is to identify members of the cohort who have moved out of state, to enable

adjustment of person-years for incidence and mortality calculations. Persons who have moved out of state can be followed for vital status and cause of death, but not for cancer incidence.

A.12 Estimates of Annualized Hour and Cost Burden

The estimated annualized burden for the phase IV and BEEA data collection, as well as the new control and smartphone app components, is estimated to be 11,438 hours (see Table A.12-1). This amounts to a total of 34,314 hours over a three-year period.

Based on a median hourly wage rate of \$11.68 for Farming Occupations (http://www.bls.gov/oes/current/oes_nat.htm#45-0000), and, for controls a median hourly wage rate of \$15.77 for All Occupations (averaged for Iowa and North Carolina), the total cost to participants will be approximately \$403,216.98 which corresponds to an annualized average cost of \$134, 405.66 (Table A.12-2).

Table A.12-1 ESTIMATES ANNUALIZED BURDEN HOURS					
Type of Respondent	Form Name	Number of Respondents	Number of Responses per Respondent	Average Time Per Response (in hours)	Total Annual Burden Hours
Private and Commercial Applicators and Spouses	Phase IV Buccal IA/NC Scripts for Verbal Consent for Buccal Kit (Attachment 9.1)	100	1	3/60	5
Private and Commercial Applicators and Spouses	Phase IV Buccal IA/NC Written Consent for Buccal Kit (Attachment 15.1 or 15.2)	100	1	5/60	8
Private and Commercial Applicators and Spouses	Phase IV Buccal Kit Follow-up (used as needed): NC/IA Reminder Script (Attachment 9.2 or 9.3), Missing Consent Script (Attachment 9.4), or Damaged/Missing Sample Script (Attachment 9.5)	30	1	2/60	1

Private Applicators	BEEA CATI Screening Script for RSG Eligibility (Attachment 20.1), REG Eligibility (Attachment 20.2) or AMG Eligibility (Attachment 20.3)	480	1	20/60	160
Private Applicators	BEEA IA/NC Consent for RSG Home Visit (Attachments 18.1 or 18.2) or REG Home Visit (Attachments 18.3 or 18.4) or AMG Home Visit (Attachments 18.5 or 18.6)	196	1	5/60	16
Private Applicators	BEEA RSG/REG/AMG IA/NC Pre-Visit Show Card (Attachment 17.7 or 17.8)	160	1	5/60	13
Private Applicators	BEEA Paper/Pen Dust Questionnaire (Attachment 21)	160	1	10/60	27
Private Applicators	BEEA Pre-Home Visit Script (Attachment 10.1)	160	1	2/60	5
Private Applicators	BEEA RSG Home Visit CAPI, Blood, Buccal cell, Urine & Dust (Attachment 19.1)	160	1	90/60	240
Private Applicators	BEEA RSG/REG/AMG IA/NC Pre-Visit Show Card (Attachment 17.7 or 17.8)	20	3	5/60	5
Private Applicators	BEEA Paper/Pen Dust Questionnaire (Attachment 21)	20	3	10/60	10
Private Applicators	BEEA Pre-Home Visit Script (Attachment 10.1)	20	3	2/60	2
Private Applicators	BEEA REG Home Visit CAPI, Blood, Buccal cell, Urine & Dust (Attachment 19.1)	20	3	90/60	90
Private Applicators	BEEA REG IA/NC Post-Exposure Scheduling Script (Attachment 10.2 or 10.3)	20	1	2/60	1
Private Applicators	BEEA RSG/REG/AMG IA/NC Pre-Visit Show Card (Attachment 17.7 or 17.8)	16	2	5/60	3
Private Applicators	BEEA Paper/Pen Dust Questionnaire (Attachment 21)	16	2	10/60	5
Private Applicators	BEEA Pre-Home Visit Script (Attachment 10.1)	16	2	2/60	1
Private Applicators	BEEA AMG Home Visit	16	2	90/60	48

	CAPI, Blood, Urine, Buccal cell & Dust (Attachment 19.1)				
Private Applicators	IA/NC Consent for AMG Farm Visit (Attachments 18.7 or 18.8)	16	1	5/60	1
Private Applicators	Pre-Farm Visit Script (Attachment 10.4)	16	2	2/60	1
BEEA Controls	Control CATI Eligibility Script (Attachment 20.4)	215	1	20/60	72
BEEA Controls	IA/NC Control Home Visit Consent (Attachments 18.10 or 18.11)	67	1	5/60	6
BEEA Controls	IA/NC Pre-Visit Show Card (Attachment 17.16 or 17.17)	67	1	5/60	6
BEEA Controls	Paper/Pen Dust Questionnaire (Attachment 21)	67	1	10/60	11
BEEA Controls	Pre-Home Visit Script (Attachment 10.1)	67	1	2/60	2
BEEA Controls	Control Home Visit CAPI, Blood, Buccal cell, Urine, & Dust (Attachment 19.2)	67	1	90/60	101
Private Applicators	BEEA 'Life in a Day' Smartphone App Consent and Setup (Attachments 22.3 or 22.4)	78	1	20/60	26
Private Applicators	BEEA 'Life in a Day' Smartphone Application (Attachment 22.2)	78	30	10/60	390
Private Applicators	Phase IV Follow-up CAWI Survey (Attachment 25.1), CATI Script (Attachment 25.2), or Paper/pen (Attachment 25.3)	13,855	1	25/60	5,773
Spouses	Phase IV Follow-up CAWI Survey (Attachment 25.1), CATI Script (Attachment 25.2), or Paper/pen (Attachment 25.3)	10,201	1	25/60	4,250
Proxy	Phase IV Follow-up CAWI Survey (Attachment 26.1), CATI Script (Attachment 26.2), or Paper/pen (Attachment 26.3)	635	1	15/60	159
Total		25,486	29,641		11,438

Note: The burden calculation in Table A.12-1 now includes the time to collect samples at all the home visits.

Table A.12-2 ESTIMATES OF ANNUALIZED BURDEN HOURS

Type of Respondent	Form Name	Total Annual Burden Hours	Hourly Wage Rate	Total Respondent Costs
Private and Commercial Applicators and Spouses	IA/NC Scripts for Verbal Consent for Buccal Kit (Attachment 9.1)	5	11.68	\$58.40
Private and Commercial Applicators and Spouses	IA/NC Written Consent for Buccal Kit (Attachment 15.1 or 15.2)	8	11.68	\$93.44
Private and Commercial Applicators and Spouses	Buccal Kit Follow-up (used as needed): NC/IA Reminder Script (Attachment 9.2 or 9.3), Missing Consent Script (Attachment 9.4), or Damaged/Missing Sample Script (Attachment 9.5)	1	11.68	\$11.68
Private Applicators	BEEA CATI Screening Script for RSG Eligibility (Attachment 20.1), REG Eligibility (Attachment 20.2) or AMG Eligibility (Attachment 20.3)	160	\$11.68	\$1,868.80
Private Applicators	IA/NC BEEA Consent for RSG Home Visit (Attachments 18.1 or 18.2) or REG Home Visit (Attachments 18.3 or 18.4) or AMG Home Visit (Attachments 18.5 or 18.6)	16	\$11.68	\$186.88
Private Applicators	IA/NC BEEA RSG Pre-Visit Show Card (Attachment 17.7 or 17.8)	13	\$11.68	\$151.84
Private Applicators	IA/NC BEEA RSG Paper/Pen Dust Questionnaire (Attachment 21)	27	\$11.68	\$315.36
Private Applicators	BEEA RSG Pre-Home Visit Script (Attachment 10.1)	5	\$11.68	\$58.40
Private Applicators	BEEA RSG Home Visit CAPI, Blood, Buccal cell, Urine & Dust (Attachment 19.1)	240	\$11.68	\$2,803.20
Private Applicators	IA/NC BEEA REG Pre-Visit Show Card (Attachment 17.7 or 17.8)	5	\$11.68	\$58.40
Private Applicators	IA/NC BEEA REG Paper/Pen Dust Questionnaire (Attachment 21)	10	\$11.68	\$116.80

Private Applicators	BEEA REG Pre-Home Visit Script (Attachment 10.1)	2	\$11.68	\$23.36
Private Applicators	BEEA REG Home Visit CAPI, Blood, Buccal cell, Urine & Dust (Attachment 19.1)	90	\$11.68	\$1051.20
Private Applicators	IA/NC BEEA REG Post-Exposure Scheduling Script (Attachment 10.2 or 10.3)	1	\$11.68	\$11.68
Private Applicators	IA/NC BEEA AMG Pre-Visit Show Card (Attachment 17.7 or 17.8)	3	\$11.68	\$35.04
Private Applicators	IA/NC BEEA AMG Paper/Pen Dust Questionnaire (Attachment 21)	5	\$11.68	\$58.40
Private Applicators	BEEA AMG Pre-Home Visit Script (Attachment 10.1)	1	\$11.68	\$11.68
Private Applicators	BEEA AMG Home Visit CAPI, Blood, Buccal Cell, Urine & Dust x 3	48	\$11.68	\$560.64
Private Applicators	IA/NC BEEA Consent for AMG Farm Visit (Attachments 18.7 or 18.8)	1	\$11.68	\$11.68
Private Applicators	BEEA AMG Pre-Farm Visit Script (Attachment 10.4)	1	\$11.68	\$11.68
Controls	BEEA CATI Control Eligibility Script (Attachment 20.4)	72	\$15.77	\$1,135.44
Controls	IA/NC BEEA Control Home Visit Consent (Attachments 18.10 or 18.11)	6	\$15.77	\$94.62
Controls	IA/NC BEEA Pre-Visit Show Card (Attachment 17.16 or 17.17)	6	\$15.77	\$94.62
Controls	IA/NC BEEA Paper/Pen Dust Questionnaire (Attachment 21)	11	\$15.77	\$173.47
Controls	BEEA REG Pre-Visit Script (Attachment 10.1)	2	\$15.77	\$31.54
Controls	BEEA Control Home Visit CAPI, Blood, Buccal cell, Urine, & Dust (Attachment 19.2)	101	\$15.77	\$1,592.77
Private Applicators	'Life in a Day' Smartphone Application Consent and Set-up (Attachment 22.3 or 22.4)	26	\$11.68	\$303.68

Private Applicators	'Life in a Day' Smartphone Application (Attachment 22.2)	390	\$11.68	\$4,555.20
Private Applicators	CAWI Survey (Attachment 25.1), CATI Script (Attachment 25.2), or Paper/pen (Attachment 25.3)	5,773	\$11.68	\$67,428.64
Spouses	CAWI Survey (Attachment 25.1), CATI Script (Attachment 25.2), or Paper/pen (Attachment 25.3)	4,250	\$11.68	\$49,640.00
Proxy	CAWI Survey (Attachment 26.1), CATI Script (Attachment 26.2), or Paper/pen (Attachment 26.3)	159	\$11.68	\$1,857.12
Total		11,438		\$134,405.66

A.13 Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no capital costs, operating costs or maintenance costs to report.

A.14 Annualized Costs to the Federal Government

To complete phase IV, the total projected cost to the Federal Government over the three-year period -- including the new control group and smartphone app components for the Agricultural Health Study -- is \$4,956,426 and the annualized cost is \$1,652,142 (see Table A.14-1). This is a \$400,770 increase from the previously approved revision, and accounts for the costs related to implementation and oversight of the new control group component, buccal cell sample collections, and air monitoring visits. This includes contract costs for the AHS Coordinating Center (Westat, Inc.) prime, the University of Iowa sub-contractor to Westat, the AHS Health Follow Up Coordinating Center (Social & Scientific Systems, Inc.) and various collaborating and contract laboratories. Estimated costs for NCI and NIEHS staff time are also included.

TABLE A.14-1. ANNUALIZED COSTS TO THE FEDERAL GOVERNMENT	
	Total Cost
AHS Coordinating Center (Westat Inc.) Contract Cost	\$871,116
Social & Scientific Systems, Inc. Contract Cost	\$569,340
Oversight by NCI COR, GS15-8 (\$155,705) (5% effort)	\$7,785
Other NCI Scientific Oversight, GS13-5 (\$102,932) (10% effort)	\$10,293
Oversight by NIEHS COR, GS 14-6 (118,580) (5% effort)	\$5,920
Other NIEHS Scientific Oversight, T-42 (146,880) (10% effort)	\$14,688
Publication of Results	\$3,000
Laboratory Costs	\$170,000
TOTAL ANNUAL COST	\$1,652,142

A.15 Explanation for Program Changes and Adjustments

This revision is a program change due to agency discretion and represents an increase of 759 burden hours from the previous submission approved in 2013. The increase in burden for this revision is accounted for by the addition of the control and smartphone app components, and a correction to the burden for recently exposed participants receiving three visits. See Supporting Statement B, Section B.2, for more a more detailed discussion of proposed revisions to procedures. The control component will include a new telephone eligibility script (Attachment 20.4), consent form (Attachment 18.9, 18.10, or 18.11), pre-visit show card (Attachment 17.16 or 17.17), home visit CAPI questionnaire (Attachment 19.2), and sample collection, all modeled on the existing BEEA data collection instruments and procedures. The smartphone app will involve participants completing a consent form (Attachment 22.3 or 22.4) loading an NCI app on compatible smartphones and using the app to make brief log entries regarding farm activities (Attachment 22.2). The app uses procedures similar to those employed by other NCI epidemiologic studies to track physical activity. Finally, the REG participants who

agree to the farm visits will receive a new pre-farm visit script (Attachment 10.4) and complete a new consent form for farm visits (Attachment 18.7 or 18.8)

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

Data obtained from the study are being analyzed using standard procedures for cohort studies. Cox, Poisson and logistic regression will continue to be used to evaluate cancer risks from agriculture and other exposures using the EPICURE, STATA and SAS package of statistical programs. Data will be cross-classified by age, race, and sex, but analyses by race/sex specific groups will also be performed. Adjustments for confounding factors (e.g. smoking, alcohol, diet, etc.) will depend upon the exposures and cancers under consideration.

Analysis will proceed from the simple to the complex. The analyses of phase I involved comparing the mortality from various diseases among farmers with the mortality experience of the entire population of the states of Iowa and North Carolina. The disease incidence of individual farmers, their spouses, and commercial pesticide applicators compare the incidence rates among exposed subjects with rates among unexposed subjects. The objective of these detailed analyses is to evaluate the data with respect to the relationship between cancer risk and level, frequency and duration of exposure to specific chemicals. Currently, the analyses of phase I has been completed and are being replicated with the phase II data. The goal will be to replicate findings from the phase I data collection, when the combined data of phases I, II and III are analyzed. Below is an example of a sequential series of analysis for a selected health outcome (e.g. cancer, other chronic diseases, respiratory or neurological symptoms) and pesticide and other agricultural exposure(s). For analysis of cancer, health outcome information is obtained through linkage to state cancer registries. For analysis of non-cancer outcomes,

health outcome information is obtained via participant self-report, through state mortality registry links or the US End Stage Renal Disease registry (USRDS).

1. Ever exposed to pesticides verses never exposed. This will include separate analyses of farmers (both men and women), spouses of farmers who may receive exposure directly or indirectly, and commercial applicators.
2. For persons directly engaged in pesticide application i.e., farmers (both men and women) and commercial applicators, risks will be assessed by specific pesticides used by year of first use, application method, frequency of use, years of use, amount applied, use of protective equipment, frequency of mixing, time spent mixing and applying, use of tractors with and without cabs, and hygienic habits (washing, changing clothes). Continuous variables (e.g., frequency of exposure, amount applied, etc.) will be analyzed with and without categorization. Categories will be used to provide relative risks by limited number of strata and continuous measures provide excess relative risk per unit to exposure. For spouses of farmers who do not engage in direct application of pesticides, analyses will assess risk from handling pesticide contaminated clothing, pesticide drift from nearby fields, transporting pesticides, and household use of pesticides.
3. In the sample of 2000 study subjects from the AHS who participate in the BEEA component and who are or were directly engaged in pesticide application, the risk of preclinical disease conditions, such as MGUS, will be evaluated in relation to the use of specific pesticides. Estimates of specific pesticide exposure will be quantified by years of use, application method, frequency of use, amount applied, use of protective equipment, frequency of mixing, time spent mixing and applying, use of tractors with and without

cabs, and hygienic habits (washing, changing clothes). Continuous variables will be analyzed with and without categorization.

4. Endotoxin levels will be measured in the dust samples collected within BEEA.

Determinants of exposure levels from previously collected questionnaire data will be evaluated and used to refine previously developed algorithm of exposure developed from published literature.

In addition to internal cohort analysis, the disease experience of the cohort will be compared to state and national data on mortality, cancer incidence, and end stage renal disease. All-cause mortality from specific chronic diseases will be evaluated by calculating expected death rates based on age-, sex-, and race-specific rates in the two states being studied. Similar analyses will be conducted for cancer incidence. Expected numbers of incident End-Stage Renal Disease (ESRD) cases will be obtained using data from the USRDS which covers the entire United States, and expected numbers are based on state-specific incidence rates will be calculated using data from the CMS Funded renal disease networks in North Carolina and Iowa. These databases will also be used to prospectively ascertain cases in the study cohort. Again, the groups under study will range from the entire cohort or subgroups defined as applicators or spouses.

Full-scale data collection, cleaning and analyses will be followed by publication in peer-reviewed, scientific journals. Our project time schedule for the completion of phase IV is given in Table A.16-1.

Component	Time after OMB approval
Data collection	1-36 months after approval
Data editing	2-48 months after approval
Data analysis	24-60 months after approval
Publication	36-60 months after approval

Our project time schedule for the completion of the Phase IV Buccal Cell and BEEA components (including the control and smartphone app components) are given in Table A.16-2.

Component	Time after OMB approval
Data collection	1-36 months after approval
Data editing	2-60 months after approval
Review pilot data and conduct data analyses	2-60 months after approval
Publication	12-60 months after approval

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

There are no reasons to preclude display of the OMB expiration date on the questionnaires.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement.