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 2010.

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The Agricultural Health Study (AHS) program staff is requesting approval of this revision to begin information collection in February, 2013. 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. The stimulus for this prospective investigation comes from the growing evidence that, despite a low mortality overall, farmers experience an excess of several cancers, including lymphatic and hematopoietic system, connective tissue, skin, brain, prostate, stomach and lips. This suggests a common set of exposures which may explain the high rates in farmers and rising rates in the general population. NCI is primarily interested in cancer outcomes and NIEHS is interested in other disease outcomes. For this phase of the data collection, NIEHS will be taking the lead role in collecting information for this phase of the study.

This revision is to initiate and complete the phase IV follow-up interview (2013-2015) as well as to continue and complete the ongoing Study of Biomarkers of Exposures Effects in Agriculture (BEEA) and buccal cell collections. The primary objective of the AHS study remains to be determination of the health effects resulting from occupational and environmental exposures in agriculture. We are using a similar questionnaire to ones that have been employed in previous AHS interviews to obtain information on non-cancer outcomes. New for phase IV, questionnaire data will be collected by using one of three methods of the cohort member's choosing: self-administered computer assisted web survey; self-administered paper-and-pen; or an interviewer administered computer assisted telephone interview. Additionally, because loss to follow up of diseased individuals is a critical issue, we have added proxy interviews for those deceased or too ill to complete themselves will be completed by using one of the three methods.

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 phase IV (2013-2015) can be initiated and concluded. The data will be 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. 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, and buccal cells). 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. The enrollment form gathered information on demographic characteristics, pesticide use, general health and health risk factors, and overall farming characteristics. The applicator was then given additional questionnaires (an applicator questionnaire, a spouse questionnaire, and a female/family health questionnaire) to be completed by the applicator and spouse at home.

These questionnaires focused on additional details on pesticide use, 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). 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. 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. This revision proposes to continue and complete the collection of buccal cells. Buccal cell DNA is now being evaluated for the potential effect of inherited polymorphisms and the interaction of environment and genomic predisposition.

The National Cancer Institute (NCI) has collaborated with a number of different Institutes and Agencies for this study. NCI is primarily interested in cancer outcomes and determinants of exposure and National Institute of Environmental Health Sciences (NIEHS) is interested in other disease outcomes. Additionally, the Environmental Protection Agency (EPA) and the National Institute for Occupational Safety and Health (NIOSH) provide support for a limited exposure assessment effort.

In the past, NCI had taken the lead on administering questionnaires and now NIEHS will be assuming the responsibility for collecting new information on medical history from the full cohort. Currently, passive follow-up of this study is being jointly funded by NCI and NIEHS, with NIEHS funding the phase IV cohort wide interview and NCI funding the Study of Biomarkers and Exposures and Effects in Agriculture (BEEA). Currently, NCI is collecting very little questionnaire information, except to finalize the collection of information for the BEEA and buccal cell collection from a small number of selected cancer cases. BEEA was originally proposed in the 2010 submission and is expected to continue information collection through May

2015. All data collected by the study are being shared jointly between NCI and NIEHS and this relationship will continue. Additionally, the co-investigators from each Institute share the Contracting Officer's Representatives (COR) responsibilities. NCI will continue to play a lead role through membership on the Agricultural Health Study Executive Committee and in actively evaluating the links between occupational and environmental exposures and cancer. NCI and NIEHS have a formal memorandum of understanding regarding their shared roles in the Agricultural Health 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 1,600 study subjects from the Agricultural Health Study over the age of 50 years (BEEA) over five years. Currently, biospecimens have been collected from 647 study subjects. Over the course of five years, 50 study subjects from the 1,600 will be selected because they currently use the insecticide diazinon. Diazinon has been associated with an excess risk of leukemia in the AHS. All known leukemogens show a perturbation in white blood cells shortly after exposure; therefore, the possibility of this perturbation among the diazinon users in the BEEA will be evaluated.
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. This new data collection effort (phase IV) will allow the identification of new cases of adult chronic diseases, not available through disease registries.

To date, there have been over 140 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

During phase IV, a 25-minute questionnaire will be collected by using one of three methods of the cohort member's choosing: self-administered computer assisted web survey (CAWI) (**Attachment 25**); self-administered paper-and-pen (Paper/pen) (**Attachment 25**); or an interviewer administered computer assisted telephone interview (CATI) (**Attachment 25**). Proxy interviews, 15-minutes in length, for those cohort members unable to complete the follow

up will be completed by using one of the three methods as well (**Attachment 26**). Prior to completing the questionnaire, the respondent is screened to ensure that the instrument corresponds to the correct respondent, and to obtain informed consent (**Attachments 25 and 26**). For those who prefer a telephone interview, Computer-Assisted Telephone Interview (CATI) techniques will be employed. 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 (**Attachment 9**). This form of participation, including the contact to request verbal consent, completing the consent, and collecting the buccal collection kit requires approximately 5 minutes.

Additional contacts remaining in phase IV are to participants in the biomarker component of the study, BEEA. From 2010 through 2015, a total of 1600 participants (1072 in Iowa, and 528 in North Carolina) will be enrolled. The BEEA participants will continue to complete an in-person interview (**Attachment 19**) at their home, and provide blood and urine specimens. Approximately 2,880 male pesticide applicators enrolled in the AHS will be contacted by telephone about this study. These respondents are screened to ensure they are the correct respondent, to determine eligibility (including eligibility for a blood draw), and to gain verbal informed consent (**Attachments 20 and 21**). 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 5 minutes to complete.

Participants in the home visit component of the BEEA (N=960) 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. The time required to complete one home visit, including reviewing the written informed consent form, administering the CAPI, and collecting the blood and urine samples, is approximately 95 minutes.

Thirty BEEA participants, identified during the telephone screener according to their reported plans to use diazinon in the coming year, will be asked to complete two additional home visits. These two visits will be typically occur several months after the initial visit, but must occur within proscribed time windows around the actual dates the respondent uses diazinon – specifically, one day after final use and again 21 days from this time.

Two Privacy Impact Assessment's (PIA) 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.

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 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 an additional questionnaire and biospecimen collection (i.e., urine and blood). For 50 of these study subjects in the Recently Exposed study group who have used the insecticide diazinon, the questionnaire and biospecimen collection will involve 3 repetitions of the procedures outlined above. The first sample will be collected prior to the diazinon application, the second sample will be collected within 1-day of the diazinon application and the third sample will be collected 21 days subsequent to the diazinon application.

The design of the BEEA component requires an update on exposures and medical history that occurred in the year prior to the blood and urine collection. This design will minimize exposure misclassification, which cannot be obtained by any other existing data system. For those who applied diazinon, this design will capture short term perturbations in white blood cells counts characteristic of all known leukemogens. Meaningful comparison can only be made by comparing before and after samples from the same person, because there is a good deal of normal white blood count variation between people. The white blood cell perturbations manifest themselves within one day of exposure to a leukemogen and in some cases may last for 21 days. Less frequent collection of blood and urine would not permit the collection of critical biospecimens precisely timed to the diazinon application. These precisely timed samples are necessary to evaluate the possible leukemogenic effects of diazinon.

The request for phase IV is so that the remaining applicators and spouses, or their proxies, can be contacted to complete the BEEA component, involving one additional contact for a selected subset of the cohort and three specially timed contacts for 50 additional study subjects (for a total n=1600). There are approximately 2900 remaining to be contacted for BEEA.

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 the 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 window around the actual dates the respondent uses diazinon – specifically, one day after final use and again 21 days from this time. 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 all known leukemogens. These procedures will allow us to evaluate the hypothesis that diazinon is leukemogenic.

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 12/06/2012 in Vol. 77 and Page No. 72871. Comments were solicited on the proposed information collection. No public comments have been 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 $75 per home visit as an incentive for the time taken to participate in the interview and biospecimen collection. Additionally, if the lab results for the hematologic alteration assays among Recently Exposed subjects are abnormal, a letter will be mailed to the participants with their test results (**Attachment 17.13**).

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 documented verbally (**Attachments 25.1, 25.2, 26.1 and 26.2**). 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. An additional verbal consent will be administered for those respondents participating in the buccal cell collection who reside in Iowa and those who reside in North Carolina (**Attachment 9.1**). Two differing BEEA introductory letters are issued for applicators depending on whether they reside in Iowa (**Attachment 17.1**) or North Carolina (**Attachment 17.2**). During the BEEA telephone eligibility screener interview they are administered a verbal consent (**Attachment 20 and 21**). Lastly, at home visits an informed consent form will be administered either for one home visit or for three home visits (**Attachment 18**).

Buccal cell specimens collected in phase II (1998-2003), phase III (2003-2010), and phase IV (2013-2015) 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 and urine 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 analysis 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 (SSN) are 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 obtained for the BEEA CATI screener (**Attachment 20 or 21**), 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 and urine specimens (**Attachment 18**).

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 Coordinating Center staff for a limited time. These data will be handled 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 confidentially 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 12**); and Social & Scientific Systems, Inc., the AHS Health Follow Up Coordinating Center for the study, (**Attachment 12**).

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

A.11 Justification for Sensitive Questions

Most questions asked during phase IV (2013-2015) 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 blood and urine collection. For those in the Recent Exposure Group of the BEEA, a written informed consent form will be administered at each 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 BEEA component and phase IV data collection of the Agricultural Health Study is estimated to be 10,465 hours (see Table A.12-1). This amounts to a total of 31,396 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), the total cost to participants will be approximately $366,694 which corresponds to an annualized average cost of $122,231 (Table A.12-2).

Table A.12-1 ESTIMATES ANNUALIZED BURDEN HOURS

Type of Respondent	Instrument	Estimated Annual Number of Respondents	Number of Responses per Respondent	Average Time Per Response (in hours)	Total Annual Burden Hours
Private and Commercial Applicators and Spouses	Reminder, Missing, and Damaged Scripts for Buccal Cell (Attachment 9)	100	1	5/60	8
Private Applicators	BEEA CATI Eligibility Script (Attachment 20 or 21)	480	1	20/60	160
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 1 (Attachment 19)	160	1	30/60	80
Private Applicators	BEEA Schedule Home Visit Scripts (Attachment 10)	20	3	5/60	5
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 3 (Attachment 19)	20	3	30/60	30
Private Applicators	Paper/pen, CAWI or CATI (Attachment 25)	13,855	1	25/60	5,773
Spouses	Paper/pen, CAWI or CATI (Attachment 25)	10,201	1	25/60	4,250
Proxy	Paper/pen, CAWI or CATI (Attachment 26)	635	1	15/60	159
Total					10,465

Note: The time to collect the biological samples are included in the burden calculation in Table A.12-1.

Table A.12-2 ESTIMATES OF ANNUALIZED BURDEN HOURS

Type of Respondent	Instrument	Total Annual Burden Hours	Hourly Wage Rate	Total Respondent Costs
Private and Commercial Applicators and Spouses	Reminder, Missing, and Damaged Scripts for Buccal Cell	8	11.68	$93.44
Private Applicators	BEEA CATI Screener	160	$11.68	$1,868.80
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 1	80	$11.68	$934.40
Private Applicators	BEEA Schedule Home Visit Script	5	$11.68	$58.40
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 3	30	$11.68	$350.40
Private Applicators	Paper/pen, CAWI or CATI	5,773	$11.68	$67,428.64
Spouses	Paper/pen, CAWI or CATI	4,250	$11.68	$49,640.00
Proxy	Paper/pen, CAWI or CATI	159	$11.68	$1,857.12
Total		10,465		$122,231.20

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 buccal cell collection and biomarker component (BEEA) for the Agricultural Health Study -- is $3,739,115 and the annualized cost is $1,246,372 (see Table A.14-1). 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

	Labor Hours	Wage Rate	Total Cost
AHS Coordinating Center (Westat Inc.)	2,918	$98.36	$287,014.48
University of Iowa	4,074	$66.81	$272,183.94
Social & Scientific Systems, Inc.	10,346	$55.03	$569,340.38
TOTAL CONTRACTOR COST			
NCI Staff	78	$65	$5,070.00
NIEHS Staff	72	$65	$4,680.00
Other Costs including:			
Publication of Results			$3,000
Laboratory Costs			$105,083
TOTAL ANNUAL COST			$1,246,371.80

A.15 Explanation for Program Changes and Adjustments

This revision is a program change due to agency discretion and represents an increase in burden from the previous submission approved in 2010. The increase in burden for this revision is accounted for by the initiation of the phase IV follow up scheduled from February 2013 through December 2015. The phase IV follow-up interviews will be initiated and completed (2013-2015) as well as to continue and complete the ongoing information collection related to the Study of Biomarkers of Exposures Effects in Agriculture (BEEA) and buccal cells. The primary objective of the AHS study remains to be determination of the health effects resulting from occupational and environmental exposures in agriculture. We are using a similar questionnaire to ones that have been employed in previous AHS interviews to obtain information on non-cancer outcomes.

New for phase IV, questionnaire data will be collected by using one of three methods of the cohort member's choosing: self-administered computer assisted web survey; self-administered paper-and-pen; or an interviewer administered computer assisted telephone interview. Additionally, because loss to follow up of diseased individuals is a critical issue, we have added proxy interviews for those deceased or too ill to complete themselves will be completed by using one of the three methods.

The Agricultural Health Study has been conducted through contractors since its inception. During the current Phase of the study, there is one main contractor for the study, the AHS Coordinating Center (Westat). Westat is responsible for cohort maintenance, conduct of the BEEA study and buccal sample collection, and regular linkage to registries to update vital status and disease. The University of Iowa is a subcontractor to Westat. The phase IV Health Follow Up portion of the AHS is being conducted by Social & Scientific Systems, Inc. (SSS), the support services contractor to the NIEHS Epidemiology Branch. SSS is acting as the AHS Health Follow Up Coordinating Center. In this role, they will be contacting eligible cohort participants for participation in the phase IV interview. All cohort contacts will be coordinated with Westat to ensure that participants are not overburdened with AHS related activities.

As noted in the introduction of this supporting statement, NIEHS will be taking the lead role in collecting updated health information for this phase of the study. For this reason, the OMB clearance number is being transferred from NCI to NIEHS.

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 is 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 1,600 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.

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.

TABLE A.16-1. Project Schedule for Phase IV

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 BEEA and Buccal Cell collection components are given in Table A.16-2.

TABLE A.16-2. Project Schedule for Completion of BEEA and Buccal Cell Collection

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.