Supporting Statement A for:

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

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Submitted by:

Occupational and Environmental Epidemiology Branch
Epidemiology and Biostatistics Program
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Rockville, Maryland 20852

Contact Person: Michael C.R. Alavanja, DrPH
NCI Project Officer
Executive Plaza South, Room 8000

Phone: (301) 435-4720
FAX: (301) 402-1819
e-mail: alavanjm@mail.nih.gov

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A. JUSTIFICATION

A.1 Circumstances Making the Collection of Information Necessary

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 1: 1-6). To address some of these limitations, in 1992 the National Cancer Institute (NCI) initiated a 20-year prospective cohort study of approximately 90,000 registered pesticide applicators and their families in North Carolina and Iowa titled "The Agricultural Health Study (AHS)" (Attachment 1: 4; OMB#: 0925-0406/ exp. 11/2011). 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.

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.

Cohort enrollment began in the two selected study sites, Iowa and North Carolina, in December 1993 and January 1994 respectively (OMB initial approval #0925-0406, exp. 08/1996). 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 or sent 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 1: 7).

During phase II (1998-2003) of the study (OMB approval #0925-0406, exp. 11/2005), we interviewed 60,728 enrolled cohort members (3,241 had died; 5,735 were diagnosed with cancer; 4,872 migrated out of the state of Iowa and North Carolina, no longer applied pesticides, or left farming) resulting in a 80.1% response rate among eligible cohort members (N=75,810). 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.

The focus of phase III (OMB approval #0925-0406, exp. 11/2011) is to continue to follow the cohort to determine disease incidence and mortality. 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. Updated information on pesticide and other agricultural exposures, health status, and residential histories will continue to be collected from cohort members in order to enhance information gathered during enrollment and to obtain information on possible pesticide exposures since the phase II interview.

Additionally, biomarkers of early biological effect can also be 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 currently being assessed. In phase III, buccal cells have been collected from approximately 1,100 additional study subjects, contributing to a total of 35,978 buccal cell collections to date. We are now evaluating buccal cell DNA for the potential effect of inherited polymorphisms and the interaction of environment and genomic predisposition.

With this revision we are also proposing a new biomarker component of the AHS, the Study of Biomarkers of Exposures and Effects in Agriculture (BEEA). This five-year effort has two primary objectives. First, we propose to determine the prevalence and study the etiology of monoclonal gammopathy of undetermined significance (MGUS) in a sample of 1,600 cancer-free, male AHS pesticide applicators over the age of 50, with well-characterized occupational

exposures and lifestyle factors. MGUS has been recently been observed to precede all cases of multiple myeloma in the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial and multiple myeloma has been observed to occur in excess in the AHS cohort. Preliminary observations from the AHS cohort have also shown that MGUS occurs almost twice as frequently as would be expected in a population of the same age and racial distribution in Olmsted County, Minnesota. To achieve this objective we will compare the prevalence of MGUS in the AHS cohort with the prevalence in two general population-based cohorts (i.e., Olmsted County and NHANES III) with well-characterized MGUS prevalence levels. We will also examine the associations between MGUS and specific pesticides within the AHS cohort, and determine whether selected biomarkers are associated with excess MGUS and whether these biomarkers are significantly associated with specific pesticides.

The second objective will establish a resource with the remaining biospecimens collected from the participants for the BEEA study that will be used to evaluate the biological plausibility and the mechanism-of-action of associations between pesticides and cancers observed in earlier AHS studies. Many of these pesticides are non-genotoxic and their mechanism of carcinogenesis has not been determined. The biospecimen resource will include blood and urine samples.

Under Section 411 of the Public Health Service Act (42 USC § 285a), the Division of Cancer Epidemiology and Genetics of the NCI is authorized to collect information to generate and test hypotheses concerning environmental and host determinants of cancer. The 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 III that began in 2003 can be continued and concluded. Specifically, 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.

A.2 Purpose and Use of the Information

The Agricultural Health Study continues to have six major objectives. The fifth major objective below will be enhanced with the proposed new effort, BEEA. The six major objectives remain:

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 being enhanced from the previous OMB submission (2008) by the proposed 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. 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, we will evaluate for the possibility of this perturbation among the diazinon users in the BEEA.

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 (1993-1998; OMB#: 0925-0406/ exp. 8/1996) and phase II telephone interviews (1998-2003; OMB#:0925-0406/ exp.11/2005) administered previously 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.

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 phase I and II are analyzed. Below is an example of a sequential series of analysis for a selected cancer(s) and pesticide exposure(s).

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 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, we will also evaluate the risk of preclinical disease conditions, such as MGUS, 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.

The analytic plan for non-cancer outcomes will be similar to that proposed for cancer with the addition of comparisons focusing on prevalence of symptoms and specific conditions at enrollment of the cohort.

Using national data bases such as the National Health and Nutrition Examination Survey (NHANES; OMB #: 0920-0237/exp. 3/2007), the National Survey of Family Growth (NSFG; OMB#: 0920-0315/ exp. 9/2003), and the National Household Interview Survey (NHIS; OMB#: 0920-0214/ exp.12/2007), and data from Centers for Medicare and Medicaid Services (CMS) and the United States Renal Disease System (USRDS; OMB#: 0938-0447/ exp. 1/2007), the prevalence of childhood and adulthood asthma, infertility, arthritis, hypertension, diabetes, developmental delay, attention deficit disorder, kidney failure, and other conditions can be compared to that in the AHS cohort. The age-, race-, and sex-specific rates for these conditions in the national samples will be compared with the prevalence rates in the entire cohort and in subgroups of the cohort based on exposure to specific pesticides, work practices, and exposure level as defined by constructed exposure scales. In addition, the prevalence rates among "exposed" and "unexposed" subgroups of the cohort can be compared.

Mortality from specific chronic diseases such as kidney and neurologic diseases will be evaluated by calculating expected death rates based on age-, sex-, and race-specific rates in the two states being studied as well as based on rated in the US as a whole. 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 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 farmers) to specific subgroups defined by predetermined exposures scales, exposure to specific exposures, or intensity and duration of exposure.

As with the analysis of cancer outcomes, an attempt will be made to characterize risks by intensity and duration of exposure as well as by ever-exposure to pesticides and other agricultural agents. Data from the questionnaires on known disease risk factors, demographic factors, and information on other occupational demographic factors, and information on other occupational and environmental exposures will be used to adjust risk estimates as warranted. For example, an analysis of risk for chronic kidney disease might take into account history of hypertension and diabetes, family history of kidney disease, use of analgesic medications, and exposure to solvents as well as age, race, and sex.

To date, we have published over 140 papers detailing study methods and exposure assessment methods (Attachment 1: 8-22), high pesticide exposure events (Attachment 1: 23-27), environmental measures (Attachment 1: 28-32), cancer and other health outcomes (Attachment 1: 33-55), and diet (Attachment 1: 56).

A.3 Use of Improved Information Technology and Burden Reduction

During phase III, a 35-minute Computer-Assisted Telephone Interview, CATI v.2, is being administered to all respondents by telephone using interviewers trained for this purpose (Attachment 2). Prior to administering the questionnaire, the respondent is screened to ensure that the interviewer has contacted the correct respondent, and to gain verbal informed consent (Attachment 3A or 3B, depending on whether it is the Iowa or North Carolina Field Station). Computer-Assisted Telephone Interview (CATI) techniques will be employed. The phase III 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. We also have been asking a selected number of participants (N=1,200) to provide buccal cell samples in addition to completing the CATI interview. Finally, some phase III participants receive a contact to request the buccal sample separately from their phase III 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 4A – 4C). This form of participation, including the contact to request verbal consent, completing the consent, and collecting the buccal collection kit requires approximately 5 minutes.

The majority of phase III contacts have been completed; however, some phase III CATI contacts as well as stand-alone buccal requests remain to be completed.

Additional contacts remaining in phase III are to participants in the proposed biomarker component of the study, BEEA, for which we are submitting this revision. Over the five year study period we will enroll 1600 participants (1072 in Iowa, and 528 in North Carolina); however, the numbers referenced here apply to the respondent universe for a three-year period. We are asking the BEEA participants 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 (Attachment 20A or Attachment 20B). 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, we will ask three questions 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.

A Privacy Impact Assessment (PIA) was promoted to the Department of Health and Human Services in 2008. 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 NCI Agricultural Health Study – Iowa (AHSI)", "NIH NCI Agricultural Health Study – North Carolina (AHSNC)," and "NIH NCI Agricultural Health Study – Westat (AHSW)."

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 an International Agriculture Consortium (Attachment 5), whose objectives are to determine interest in, and utility of, a consortium of cohort studies on agricultural populations, 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, we have structured the study 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 III questionnaires and collection of buccal cells has involved a one-time collection of data for each respondent. The design of the study requires an update on exposures and 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 newly proposed component of the phase III investigation (BEEA) 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 investigators for AHS have not contacted the cohort more that once during phase III except in those cases when a separate contact was needed to request a buccal specimen from a new cancer case. The request for this extension of phase III is so that the remaining applicators and spouses that were not yet contacted in the past three years of data collection, can be contacted to complete this phase of the study as well as to conduct the BEEA component, involving one additional contact for a selected subset of the cohort (n=1550), and three specially timed contacts for 50 additional study subjects. There are approximately 450 respondents remaining to contact. Phase IV of the study is currently being finalized and may involve one additional contact with selected subsets of the cohort.

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 proposed data collection was published in the Federal Register on 3/4/2010 in Vol. 75 and Page No. 9903. 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 on February 27, 2009. The NAP consists of epidemiologists, toxicologists, farmers, and pesticide educators (Attachment 6).

Additionally, the investigators for AHS are members of an International Agriculture Consortium (Attachment 5), whose objectives are to determine interest in, and utility of, a consortium of cohort studies on agricultural populations, 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 Field Station or the Coordinating Center is provided via the use of pre-stamped Business Return Permits on the return envelopes. We will provide each respondent who returns a buccal cell sample (N=450) with $5.00 as compensation for the time spent providing the sample. The $5 compensation is provided as an incentive to the respondent to accurately read and follow the instructions for the buccal cell collection. We will provide each participant in the

BEEA component (N=960) with $75 per home visit as compensation 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 27).

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 2011 (Attachment 7). Though data collection is not anticipated to extend past April 2011, 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 8). 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 9). Subjects are informed of the measures taken to protect their confidentiality in the introductory letter. Two phase III introductory letters are issued for applicators depending on whether they reside in Iowa (Attachment 10A) or North Carolina (Attachment 10B). A different version of the introductory letter has been developed for spouses of applicators who live in Iowa (Attachment 10C). All letters are sent out on North Carolina or Iowa Field Station letterhead. Additionally, respondents are informed again of measures taken to protect their confidentiality prior to beginning the phase III telephone interview. Since the questionnaires will be administered by telephone, informed consent will documented verbally (Attachment 3A or 3B). An additional verbal consent will be administered for those respondents

participating in the buccal cell collection who reside in Iowa (Attachment 4A) and those who reside in North Carolina (Attachment 4B). Similarly, two differing BEEA introductory letters are issued for applicators depending on whether they reside in Iowa (Attachment 21A) or North Carolina (Attachment 21B). During the BEEA telephone eligibility screener interview they are administered a verbal consent (Attachment 20A or 20B). Lastly, at home visits an informed consent form will be administered either for one home visit (Attachment 22A or 22B) or for three home visits (Attachment 22C or 22D).

Buccal cell specimens collected in phase II (1998-2003) and phase III (2003-present) are stored without personal identifiers, in a manner that will permit efficient retrieval and optimum stability for later use. BEEA blood and urine specimens will be handled in the same manner. Genetic data resulting from analysis of the buccal cells, blood, and urine will not be provided to the Field Stations. 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 being 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 by the Field Stations 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 most phases of the study. Verbal permissions is obtained from the phase III CATI participants after they have been read a consent form that states, "The information you provide will be kept confidential, and will not be disclosed to anyone but the researchers conducting this study, except as otherwise required by law." (Attachment 3A or 3B) Verbal permission will also obtained for the BEEA CATI screener (Attachment 20A or 20B), 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 (Attachments 22A-22D).

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 8).
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 personnel involved with the project have signed confidentiality agreements (Attachment 9). A Certificate of Confidentiality was obtained prior to onset of data collection, and has been renewed through 2011 (Attachment 7).
5. After the data are analyzed, personal identifiers will be kept by the Iowa and North Carolina Field Stations 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 11) 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 Field Stations. These data files are joined only for performing linkages to the mortality and cancer incidence databases. Contact of subjects occurs only

through the Field Stations. 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 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 questionnaires from which the follow-up questionnaires were developed were approved by the Epidemiology and Biostatistics Program for Technical Evaluation of Questionnaires (TEQ) on January 14, 1992. Phase II questionnaires received TEQ approval on May 14, 1998. Phase III questionnaires received TEQ review at the November, 2004 meeting. All comments and suggestions which came out of the TEQ review were incorporated into the questionnaire. The BEEA study was approved by the Senior Advisory Group on July 20, 2009 for scientific merit.

The protocol for the administration of the phase II questionnaires received initial NCI IRB approval on June 9, 1998. All materials for this proposed information collection (i.e., questionnaire, contact letters, telephone scripts) have been approved by the IRBs representing the National Cancer Institute (Attachment 12A)[1]; Westat, Inc., the Coordinating Center for the study, (Attachment 12B); the University of Iowa; and Battelle Centers for Excellence in Public Health

[1] The 2010 NCI IRB application was submitted in March, 2010.

Research and Evaluation, Inc. Iowa Field Station initial IRB approval was received on March 13, 1998 and subsequent approvals every year through 2010 (Attachment 12C). The North Carolina-Batelle IRB initial approval was received on September 18, 1997 and subsequent approvals every year through 2010 (Attachment 12D). Initial approval from Westat IRB required for processing of death certificates from the cohort was received on December 8, 1997 and subsequent approvals every year through 2010 (Attachment 12B). It is anticipated the BEEA study will be approved by the NCI IRB and Westat's IRB in April, 2010 (Attachments 26A and 26B). The two field stations have received IRB approval for 2010 (Attachments 26C and 26D).

A.11 Justification for Sensitive Questions

Most questions asked during phase III (2005-2008) and the additional BEEA component are typically not considered sensitive. Questions include those on the handling of pesticides, fertilizers, farm operations, occupations other than farming, and source of drinking water since enrollment and medical history. Information on these factors has been collected in phase I and phase II and is now being updated in phase III.

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. Verbal consent is obtained prior to the start of the phase III 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 phase 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 not longer at the address given during enrollment (based on subsequent attempts at followup) 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 Burden Hours and Costs

The estimated annualized burden for the BEEA component and remaining phase III data collection of the Agricultural Health Study is estimated to be 550 hours (see Table A.12-1). This amounts to a total of 1,650 hours over a three-year period. Based on a median hourly wage rate of $26.81, the total cost to participants will be approximately $44,102 which corresponds to an annualized average cost of $14,701 (Table A.12-2).

Table A.12-1 ESTIMATES OF ANNUAL BURDEN HOURS

Type of Respondent	Instrument	Estimated Annual Number of Respondents	Frequency of Response	Average Time Per Response Minutes/ Hour	Annual Burden Hours
Private Applicators, Spouses, Commercial Applicators	Phase III Telephone Interview[2] & Buccal Cell[3] Scripts	150	1	5/60 (0.083)	13
Private Applicators, Spouses, Commercial Applicators	Phase III CATI[4]	150	1	35/60 (0.583)	88
Private Applicators, Spouses, Commercial Applicators	Phase III Buccal Cell Reminder, Missing or Damaged Scripts[5]	150	1	5/60 (0.083)	13
Private Applicators	BEEA CATI Screener[6]	960	1	20/60 (0.33)	320
Private Applicators	BEEA Home Visit CAPI[7], Blood, & Urine x 1	310	1	20/60 (0.33)	103
Private Applicators	BEEA Schedule Home Visit Script[8]	10	3	5/60 (0.33)	3
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 3	10	3	20/60 (0.33)	10
Total		1740			550

[2] The telephone interview scripts are Attachments 3A and 3B.
[3] The buccal cell scripts are Attachments 4A, 4B, and 4C.
[4] The Phase III CATI v.2 survey is Attachment 2.
[5] The buccal cells reminder, missing and damaged scripts are Attachments 16A, 16B, 17A, 17B, 18A, and 18B.
[6] The BEEA CATI eligibility screener script is Attachment 20A and 20B.
[7] The BEEA CAPI is Attachment 19. The pre-visit preparation cards are Attachments 23C and 23D.
[8] The BEEA script for scheduling the first post-Diazinon application visits are Attachments 25C and 25D. The BEEA pre-visit reminder script is Attachment 24C.

Note: Though biological samples are mentioned in Table A.12-1, the collection of them in not calculated into the time per response in the above table.

Table A.12-2 ANNUALIZED COST TO RESPONDENTS

Type of Respondent	Instrument	Estimated Annual Number of Respondents	Annual Burden Hours	Hourly Wage Rate	Respondent Cost
Private Applicators, Spouses, Commercial Applicators	Phase III Telephone Interview & Buccal Cell Scripts	150	13	$26.81	$335.13
Private Applicators, Spouses, Commercial Applicators	Phase III CATI	150	88	$26.81	$2,345.88
Private Applicators, Spouses, Commercial Applicators	Phase III Buccal Cell Reminder, Missing or Damaged Scripts	150	13	$26.81	$335.13
Private Applicators	BEEA CATI Screener	960	320	$26.81	$8,579.20
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 1	310	103	$26.81	$2,770.27
Private Applicators	BEEA Schedule Home Visit Script	10	3	$26.81	$67.03
Private Applicators	BEEA Home Visit CAPI, Blood, & Urine x 3	10	10	$26.81	$268.10
Total		1740			$14,700.74

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

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

A.14 Annualized Costs to the Federal Government

The total projected cost to the Federal Government to complete phase III including the new biomarker component (BEEA) for the Agricultural Health Study is $1,611,123 and the

annualized cost is $537,041 over the three-year period (see Table A.14-1). This includes contract costs for Coordinating Center (Westat, Inc.), the University of Iowa, and to the Battelle Centers for Excellence in Public Health Research, Inc., and various collaborating and contract laboratories. Estimated costs for NCI staff time are also included.

TABLE A.14-1. ANNUALIZED COSTS TO THE FEDERAL GOVERNMENT

	Labor Hours	Wage Rate	Total Cost
Coordinating Center (Westat Inc.)	1,871	$30/hour	56,120
University of Iowa	6,180	$22/hour	135,970
Battelle Centers for Excellence in Public Health Research, Inc.	3,189	$21/hour	66,970
Laboratory costs	5,122	$35/hour	$179,263
TOTAL CONTRACTOR COST			
NCI Staff	1,667	$50/hour	$83,350
Other Costs including: Equipment Costs			$12,702
Publication of Results			$666
Travel of staff to implement/monitor			$2,000
TOTAL ANNUAL COST			$537,041

A.15 Explanation for Program Changes and Adjustments

This revision is a program change due to agency discretion and represents a decrease in burden from the previous submission approved in October, 2008. The substantial decrease in burden for this revision is accounted for by fewer Phase III participants being interviewed. The phase III collection was scheduled from November 2005 through November 2011 and has been impacted by restricted scheduling due to the planting season and budgetary issues, resulting in the need for additional time to complete the questionnaire administration. This request will allow the Agricultural Health Study to complete phase III of its research and to add an important additional component, the study of Biomarkers of Exposures and Effects in Agriculture (BEEA) which will help NCI investigators to identify occupational exposures in the agricultural

environment that increase the risk of monoclonal gammopathy of undetermined significance (MGUS).

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

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 III is given in Table A.16-1.

TABLE A.16-1. PROJECT SCHEDULE FOR PHASE III

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

Our project time schedule for the completion of the BEEA component is given in Table A.16-2.

TABLE A.16-2. PROJECT SCHEDULE FOR COMPLETION OF BEEA

Component	Time after OMB approval of proposed revisions
Data collection	1-60 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.