DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

To: Office of Management and Budget

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From: Michael Alavanja, Agricultural Health Study Project Officer

Date: January 7, 2010

Re: Agricultural Health Study non-substantive change request
OMB #0925-0406

This memorandum summarizes the revisions to the study design plan and questionnaire for a biomarker research effort within the Agricultural Health Study (AHS), in accordance with the stipulations of the current OMB approval (#0925-0406, expiration date 10/31/2011). The questionnaire that will be used for this biomarker component of the AHS asks about exposures over a shorter period of time (i.e., whereas the previous questionnaire asked about exposures in the last five years, this questionnaire collects information about exposures only within the last year) and contains questions already approved by OMB. Therefore, NCI is requesting that these changes be considered under the Non-substantive Change Request procedure.

As discussed in the OMB package submitted for the AHS, this study includes licensed pesticide applicators and their spouses in Iowa and North Carolina. Enrollment in this study began in 1993, and participants have been followed over time with periodic updates of their lifetime pesticide exposure history and other information.

In the proposed biomarker component of the AHS, we will follow up on a previous investigation within the AHS cohort that found an elevated prevalence of monoclonal gammopathy of undetermined significance (MGUS), which is a precursor marker for multiple myeloma that is measured in blood. Blood samples were previously collected from 685 AHS participants and tested for MGUS (Landgren et al. 2009). The proposed study will include an additional 1,600 male AHS participants over 50 years of age. This biomarker research effort has two primary objectives. First, we propose to reevaluate the prevalence and study the etiology of MGUS. The prevalence of MGUS in the AHS cohort will be compared to the prevalence in two population-

based cohorts with well-characterized MGUS prevalence levels: 1) residents of Olmsted County, MN; and 2) participants in the National Health and Nutrition Examination Survey (NHANES III), a CDC program that collected blood samples and information from a nationally representative sample of the U.S. population. We will also examine the associations between MGUS and exposure to 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.

Once this enhanced resource of biospecimens is available, it 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. As an example of one future study involving repository samples, we will investigate monoclonal B-cell lymphocytosis (MBL), a marker which has been shown to precede chronic lymphocytic leukemia in previous studies. Several pesticides in current widespread use in the AHS have been linked to leukemia. We will determine the prevalence of MBL in the AHS cohort and evaluate potential associations with specific pesticides of interest to better explain the relation between pesticide exposures and leukemia risk.

Most of the subjects (N=1,550) who meet the eligibility criteria for this study will be selected at random from the AHS cohort. We will only conduct a single home visit with these 1,550 subjects. However, we will also select a subset of 50 subjects who are current users of diazinon (a particular insecticide that has been associated with leukemia in the AHS cohort) for a pilot study. We will conduct three home visits with these 50 subjects at the following time points: 1) in the off-season (i.e., winter) prior to exposure; 2) on the day after cessation of diazinon use; and 3) 21 days (±3 days) after diazinon use.

In addition to collecting blood and urine samples, all participants in the AHS biomarker study will be asked to complete a brief telephone interview to determine eligibility and ask about cancer screening practices, and an in-person interview at the time of biospecimen collection. As discussed above, the questionnaire for the in-person interview will be a shortened version of OMB-approved instruments used previously in the AHS. Whereas previous AHS questionnaires have asked about exposures over a period of at least several years, this questionnaire focuses on more recent exposures (within the last year) which are potentially important for the interpretation of the biomarker assay results.

A copy of the questionnaire – including items for both the telephone and in-person interviews – is attached. Most questions were adapted from the most recent AHS questionnaire (Phase III instrument), though some questions came from previous AHS submissions (the source of each question is noted in Table 1 below). Please note the following specific changes in this version of the questionnaire:

- Questions about blood clotting disorders and history of cancer screening practices were added to the telephone eligibility/screening interview; this information has not been collected previously. The question about blood clotting disorders is necessary because

this is one of the exclusion criteria to ensure safety of participants. The questions about cancer screening practices are needed to assess comparability of the study sample to the general population in terms of the likelihood of cancer diagnosis.

- Questions about regular use of blood thinning medications and recent x-ray procedures were added to the questionnaire; this information has not been collected previously. This information is needed because blood thinning medications and x-rays could potentially affect the interpretation of assays/tests using blood samples collected in this study.

- Some questions were asked in a different manner in previous AHS questionnaires, but have been revised based on the wording from questionnaires in other studies to better capture the exposure(s) of interest. In particular, the wording of questions related to aspirin and ibuprofen use were adapted from the baseline and supplemental questionnaires of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (OMB #0925-0407).

We anticipate that this personal interview will take approximately 15-25 minutes to complete depending on the number of pesticides that were used in the last year. Pilot testing of the questionnaire is currently under way. We are currently pursuing Institutional Review Board (IRB) approval for the proposed biomarker component of the AHS. Estimates of the total burden hours and respondent costs are provided in Tables 2 and 3 below.

The biomarker component of the AHS is an inter-agency collaborative effort involving investigators from the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), the Environmental Protection Agency (EPA), and the National Institute for Occupational Safety and Health (NIOSH). In addition to funding from NCI, financial support is being provided by the EPA with the expectation that field work will begin in 2010. We would appreciate if you could consider this request for expedited review in order to begin field work for this project with EPA support.

Reference:

Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, Katzmann JA, Rajkumar SV, Alavanja MC. Pesticide exposure and the risk of monoclonal gammopathy of undertermined significance in the Agricultural Health Study. Blood 2009;113(25)6386-6391.

Table 1. Overview of the source of each question in the biomarker questionnaire from previous AHS instruments and a brief explanation of whether/how the question was modified (Note: P1-P3 refer to the version of the previous survey instrument in the AHS, where: P1 = Phase I enrollment and farmer applicator questionnaires; P2 = Phase II questionnaire; and P3 = Phase III questionnaire)

No.	Question	Corresponding AHS question (P1-P3 instrument, question label/number)	Modifications (if any)
	Telephone interview		
1	Birth date	P3, verifynamedob	Minor wording changes
2	Blood clotting disorder	n/a	New question
3	Cancer history	P1 enrollment, #28	Simplified version of this question
4	Digital rectal exam	n/a	New question
5	PSA test	P3, psachecked	Minor wording changes
6	Colonoscopy or sigmoidoscopy	n/a	New question
	Home interview		
1	Height	P3, hgtft, hgtin	Same
2	Weight	P3, weightnow	Same
3	Aspirin use	P1 farmer applicator, #89a	Modified time frame and wording (changes to wording based on PLCO baseline and supplemental questionnaires)
4	Ibuprofen use	P1 farmer applicator, #89b	Modified time frame and wording (changes to wording based on PLCO baseline questionnaire)
5	Blood thinning medications	n/a	New question
6	Prescription medications	P3, sections 12-22	Simplified version of these questions
7	Selected medical conditions	P3, sections 12, 14, and 19	Simplified version of these questions
8	Recent infections	P1 farmer applicator, #88	Simplified version of this question

9	Recent x-ray procedures	n/a	New question
10	Alcohol intake within last week	P3, drink_durwk, drink_wkend	Modified time frame and wording
11	Alcohol intake within last 24 hours	P3, drink_durwk, drink_wkend	Modified time frame and wording
12	Use of tobacco products	P3, smokfreq P1 enrollment, #27	Modified time frame and wording
13	Current farming	P3, acfarm	Modified time frame
14	Crops raised	P3, Q2.3	Modified time frame
15	Animals raised (type/number)	P3, Q2.5, Q2.6	Modified time frame and wording
16	Poultry confinement area	P1 enrollment, #18	Modified time frame and wording
17	Swine confinement area	P1 enrollment, #18	Modified time frame and wording
18	Other farming activities with potential endotoxin exposure	P1 farmer applicator, #4 P3, clngrainbins, nrmoldyhaystrw	Modified time frame and wording
19	Recent welding	P1 farmer applicator, #4e	Modified time frame and wording
20	Recent painting	P1 farmer applicator, #4k	Modified time frame and wording
21	Recent mechanical repairs	P1 farmer applicator, #4f	Modified time frame and wording
22	Non-farm occupations	P3, section 7	Same
	Occupational pesticide use module		
1	mix/load/apply in last 12 months	P3, mixapl	Modified time frame
2	Product name	P3, pesticide_verbatim	Modified time frame

3	Number of days exposed in last 12 months	P3, daysyrlife	Modified time frame
4	Application dates and time spent	n/a	New question
5	Mix/load pesticides	P3, cropmxld	Modified time frame and wording
5a	Mix/load-product formulation	P3, liqgran	Minor wording changes
5b	Mix/load-PPE	P3, glovemx, glovetyp, Q5.35	Minor wording changes
6	Apply pesticides in last 12 months	P3, persappl	Modified time frame and wording
6a	Applied to crops, animals, other	P3, crannc	Minor wording changes
6b	Application-product formulation	P3, liqgran	Minor wording changes
6c	Application method	P3, apply_method	Minor wording changes
6d	Application-PPE	P3, gloveappl, gloveappltyp, Q5.38	Minor wording changes
	Home and garden pesticide use module		
1	Mix/load/apply in last 12 months for home/garden use	P1 enrollment, #9	Minor wording changes
2	Products used in home/garden in last 12 months	P3, pesticide_verbatim	Modified time frame and wording

Table 2. Estimates of total burden hours

Type of respondent	Estimated number of respondents	Frequency of response	Average time per response (minutes/hour)	Annual burden hours
Randomly selected	1,550	1.00	1.5 hours*	2,325.0
Recently exposed	50	3.00	1.5 hours	225.0
Totals	1,600			2,550

* The 1.5 hour average response time is based on time estimates for the following activities: 1) screening questionnaire, 10 minutes; 2) greetings/introduction to study, 10 minutes; 3) answering any questions about the study, 10 minutes; 4) informed consent, 15 minutes; 5) CAPI interview, 20 minutes; 6) blood collection and labeling, 15 minutes; 7) urine specimen retrieval, 5 minutes; 8) salutations, 5 minutes

Table 3. Estimated cost to respondents

Type of respondent	Estimated number of respondents	Frequency of response	Average time per response	Hourly wage rate	Respondent cost
Randomly selected	1,550	1.00	1.5 hours	$26.48	$61,566
Recently exposed	50	3.00	1.5 hours	$26.48	$5,958
Totals	1,600				$67,524