EXHIBIT 4

The Agricultural Health Study

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The Agricultural Health Study, a large prospective cohort study, has been initiated in North Carolina and Iowa. The objectives of this study are to: 1) identify and quantify cancer risks among men, women, whites, and minorities associated with direct exposure to pesticides and other agricultural agents; 2) evaluate noncancer health risks including neurotoxicity, reproductive effects, immunologic effects, nonmalignant respiratory disease, kidney disease, and growth and development among children; 3) evaluate disease risks among spouses and children of farmers that may arise from direct contact with pesticides and agricultural chemicals used in the home, lawns and gardens, and from indirect contact, such as spray drift, laundering work clothes, or contaminated food or water; 4) assess current and past occupational and nonoccupational agricultural exposures using periodic interviews and environmental and biologic monitoring; 5) study the relationship between agricultural exposures, biomarkers of exposure, biologic effect, and genetic susceptibility factors relevant to carcinogenesis; and 6) identify and quantify cancer and other disease risks associated with lifestyle factors such as diet, cooking practices, physical activity, smoking and alcohol consumption, and hair dye use. In the first year of a 3-year enrollment period, 26,235 people have been enrolled in the study, including 19,776 registered pesticide applicators and 6,459 spouses of registered farmer applicators. It is estimated that when the total cohort is assembled in 1997 it will include approximately 75,000 adult study subjects. Farmers, the largest group of registered pesticide applicators, comprise 77% of the target population enrolled in the study. This experience compares favorably with enrollment rates of previous prospective studies. *Key words*: cancers, exposure assessment, farmers, lymphoma, noncancer toxicity, pesticides, prospective cohort. *Environ Health Perspect* 104:362–369 (1996)

Farming is a demanding occupation requiring individuals to carry out a variety of tasks. Farmers, farm workers, and farm family members may operate agricultural machinery, apply pesticides and fertilizers, build and repair equipment, and handle livestock which may put them at risk of injury and disease. Farmers and farm workers have long been recognized as being at high risk of injury, nonmalignant respiratory disease (e.g., farmers' lung), and some types of dermatitis (e.g., cattle ringworm, chemical burns, and irritant dermatitis) (*1*). On the other hand, studies from North America, Europe, Australia, and New Zealand have established that farmers have a lower overall mortality rate, a lower heart disease mortality rate, and lower mortality rates for cancers of the lung, esophagus, bladder, and colon than the general population (*2–5*). Low mortality rates from these cancers and for heart disease have been attributed to lower smoking rates among farmers (*2,6–9*), with possible additional contributions from diet and a physically active lifestyle (*2*).

Despite an excellent overall mortality experience, farmers in many countries appear to have higher rates than the general population for Hodgkin's disease, leukemia, multiple myeloma, non-Hodgkin's lymphoma, and cancers of the lip, stomach, prostate, skin (melanotic, nonmelanotic), brain, and connective tissue (*2–5*). While each cancer is not elevated in every study of agricultural workers, the tendency toward excess is intriguing given the diversity in agricultural practices within and between countries. These cancers do not initially appear to have much in common. They vary in frequency, histology, and prognosis. On more careful reflection, however, two factors of commonality stand out (*2*). First, they are not strongly associated with tobacco use. Second, several of these tumors (e.g., non-Hodgkin's lymphoma, leukemia, soft-tissue sarcoma, and cancers of the skin, stomach, brain, and lip) are excessive among persons with naturally occurring or medically induced immunodeficiencies. This latter connection suggests that agricultural exposures or other factors in the rural environment may contribute to cancer among farmers through immunologic perturbations.

Specific factors that may contribute to cancer incidence excess among farmers include prolonged occupational exposure to sunlight, diet, contaminated drinking water, and occupational exposure to a variety of potentially hazardous chemicals and biological agents (*2,10–14*). Agricultural workers and their families may have exposure to pesticides, animal viruses, mycotoxins, dust, fuels, oils, engine exhaust, and fertilizers. Cancer patterns in related agricultural groups, including flour millers (*15*), agricultural extension agents (*16*), soil and forest conservationists (*17*), commercial pesticide appliers (*18*), slaughterhouse workers (*3*), and veterinarians (*3,5*), also suggest that agricultural exposures deserve attention. To date, however, the strongest links of exposures and malignancies have been with pesticides (*4,19*).

Potential noncancer health outcomes that may be influenced by agents found in the farm environment, particularly pesticides, include deleterious effects on the nervous, renal, respiratory, and reproductive systems of both men and women (*20,21*). Much of the evidence for such effects comes from experimental studies and case reports. Other than studies of potentially increased cancer risk among agricultural workers, few population studies of health outcomes have been conducted. Health effects in children and women living on farms are also of potential concern, yet few studies have focused on health risks to these groups.

Studies evaluating chronic disease risks from agricultural exposures have typically been of a case–control design where recollection of exposures of many years in the

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past may result in misclassification, or cohort studies where few details regarding exposure were available. In case–control studies nondifferential misclassification due to inaccurate recall of exposure history would be expected to underestimate the true risk, while better recall on the part of cases (i.e., case recall bias) could bias estimates in either direction. In cohort studies done to date, such as the studies conducted on farmers in Sweden (*22,23*), Iceland (*24*), and in New York (*25*), little detail on specific agricultural exposures were available. Even in the few studies with some exposure data, such as a large Canadian study, information was available on the use of categories of pesticides in general but not on specific chemicals, and little information was available on potential confounding factors such as smoking and diet (*19,26–29*).

We have initiated a large prospective cohort study in North Carolina and Iowa called the Agricultural Health Study (Fig. 1) in order to: 1) identify and quantify cancer risks among men and women as well as whites and minorities associated with direct exposure to pesticides and to other agricultural agents; 2) evaluate noncancer health risks including neurotoxicity, reproductive effects, immunologic effects, nonmalignant respiratory disease, kidney disease, and growth and development; 3) evaluate disease risks among spouses and children of farmers that may arise from direct contact with pesticides and agricultural chemicals used in the home, lawns and gardens, and from indirect contact, such as spray drift, laundering work clothes, or contaminated food or water; 4) assess current and past occupational and nonoccupational agricultural exposures using periodic interviews and environmental and biologic monitoring; 5) study the relationship between agricultural exposures, the occurrence of biomarkers of exposure, biologic effect, and genetic susceptibility factors relevant to carcinogenesis; and 6) identify and quantify cancer and other disease risks associated with lifestyle factors such as diet, cooking practices, physical activity, smoking and alcohol consumption, and hair dye use.

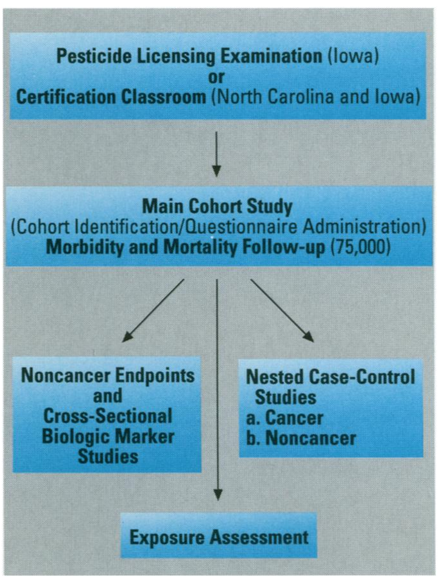

Figure 1. Agricultural health study.

Methods

The Agricultural Health Study is a collaborative effort involving the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (EPA). It is being conducted in Iowa and North Carolina through field stations at the University of Iowa and Battelle/Survey Research Associates. The study has four major components including the main prospective cohort study, noncancer endpoints and cross-sectional biologic marker studies, nested case-control studies, and exposure assessment.

Prospective Cohort Study

A prospective cohort approach offers two distinct advantages over other study designs including the opportunity to evaluate a number of diseases simultaneously, and to perform periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures should improve recall and reduce nondifferential misclassification. Determining exposure prior to onset of disease will eliminate case-recall bias, an issue sometimes raised regarding weaknesses of case-control studies.

Farmers and pesticide applicators are identified when they seek a restricted-use pesticide license from the state Cooperative Extension Services or Departments of Agriculture. All persons in Iowa and North Carolina who wish to apply restricted-use pesticides must obtain a pesticide applicator license by undergoing training or testing in the safe handling of pesticides; the license is valid for three years. There are two licensing categories: "private" applicators (i.e., farmers), are estimated to be 70% of licensed applicators and "commercial" applicators comprise the remaining 30% and include persons employed by pest control companies or by businesses that use pesticides but whose primary function is not pesticide application, such as grain millers and warehouse operators.

At the licensing facility, each pesticide applicator is asked to complete a 21-page, optically scannable enrollment questionnaire. In Iowa, both commercial and farmer applicators attend some of the same sessions and are invited to participate in the study. In North Carolina, farmers and commercial applicators attend separate training sessions; only farmer applicators from North Carolina are enrolled. Since the enrollment questionnaire includes exposure data on 50 pesticides, crops grown and livestock raised, protective clothing/equipment used, smoking and alcohol consumption, fruit and vegetable intake, medical conditions as well as basic demographic data, the enrollment questionnaire will be the basis for a large number of cohort analyses. In addition, the enrollment questionnaire asks applicators to identify their spouse and whether or not they have young children living at home; this provides the opportunity to enroll the spouses of farmers and obtain information about their children.

Farmer applicators completing the enrollment questionnaire are given three take-home questionnaires—the applicator, spouse, and female and family health questionnaires—which are also optically scannable. Commercial applicators receive the applicator questionnaire and, if female, the female and family health questionnaire. They are not given the spouse questionnaire since the work site of commercial applicators is generally not proximate to their home; the possibility of accidental exposure to pesticides by a commercial applicator's spouse is therefore less than for a spouse of a farmer applicator. The take-home questionnaires are designed to supplement information in the enrollment questionnaire (see Appendix A).

Before 1994, all Iowa applicators were tested every three years. In October 1993, an option to acquire a license through three consecutive years of training was initiated. Classes since 1994 consist of a mix of applicators who have already attended one or more sessions (and had multiple opportunities to enroll in the study), as well as persons beginning their application process (who would be new to the study). Thus, the second and third years of the study provide an opportunity to re-interview a sample of the cohort to assess the reliability of information provided in the enrollment questionnaire. Applicators returning for their second training class are asked to fill out a shortened version of the enrollment questionnaire which requests information on pesticide use, work practices, and smoking history. These responses will be compared to the responses obtained in the prior year to obtain estimates of reliability. It is expected that approximately 3000 follow-up questionnaires will be obtained in the second year.

In both states, response rates for the supplemental take-home questionnaires have been about 50% during the first year. The low response rate raises potential questions regarding the quality and generalizability of studies based on the supplemental data. One would like to pursue nonresponders through telephone interviews and structured "refusal conversion" procedures. The large size of the Agricultural Health Study and accompanying cost of such activities, however, precludes such an effort. Alternatively, a series of smaller efforts have been developed to evaluate whether responders and nonresponders differ in any way that might affect the interpretation of study results. In one such effort, farmer applicators enrolled in the Agricultural Health Study who had completed the supplemental take-home questionnaire were compared to those who did not complete the take-home questionnaire. Although a number of differences were found, all the differences were small and etiologically insignificant (Tarone et al., under review), suggesting that any bias resulting from using data from the supplemental questionnaires would be minimal. Additional efforts have been undertaken to obtain information from nonresponders. Three random samples of 1000 persons have been selected: women 30–39 years old, women 40–64 years old, and men 40–64 years old. Nonrespondents in each sample will be contacted for a brief telephone interview covering selected questions from either the farmer applicator or the spouse and family health questionnaires. These samples will provide data to compare responders to initial nonresponders for information that is not covered on the enrollment questionnaire and for which it is important to assess possible bias or lack of generalizability such as the etiology of spontaneous abortion (i.e., women 30–39 years old) and neurologic and immunologic disease for women 40–64 years old and men 40–64 years old.

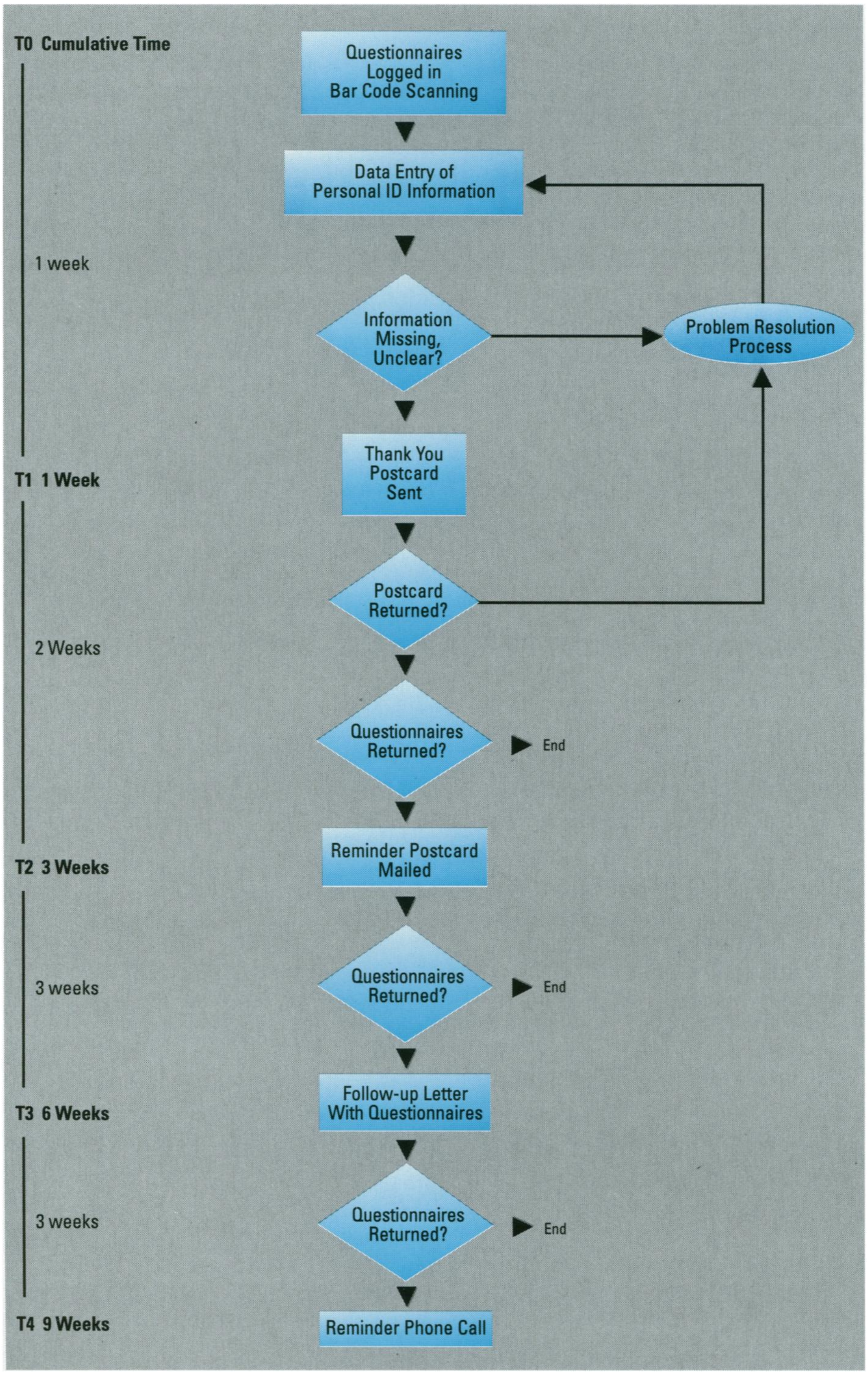

Figure 2. Field station follow-up procedure.

The field stations administer and collect enrollment questionnaires. Follow-up procedures for obtaining subsequent mailed questionnaires include reminder cards, phone calls, and remailing take-home questionnaires (Fig. 2). The cohort will be linked annually with the state cancer registries to obtain information on cancer incidence and periodically to the National Death Index to determine mortality.

Noncancer Endpoints and Cross-Sectional Biologic Marker Studies

Noncancer endpoints will be studied in a variety of ways. For example, the United States Renal Data Survey will be used to periodically update the incidence of end-stage renal disease in the cohort. The health information on selected noncancer outcomes (i.e., renal, neurological, reproductive, developmental, and immunological endpoints) obtained from questionnaires of applicators and their families will be compared with that of a national sample obtained using data from the National Health and Nutrition Examination Survey. In addition, the incidence and prevalence of diseases and symptoms will be contrasted between persons exposed and unexposed to specific pesticides or other factors of interest. The cross-sectional data may also be used to identify groups of particular interest for investigating health endpoints (e.g., childhood development, immunologic or neurologic dysfunction, and asthma) where biologic markers of exposure or early disease would enhance the study.

Nested Case–Control Studies

Over the course of the study, a series of nested case–control studies on a variety of diseases is anticipated. For cancer, rapid ascertainment procedures will be used to identify cases as soon as possible after diagnosis, usually within 1–6 months. Controls will be selected from the nondiseased cohort members. This design is an efficient method to obtain additional information for use in evaluating the risk of specific selected diseases. Cases and controls will be interviewed to obtain more detailed information on known nonfarm, nonpesticide related risk factors than was possible to collect at enrollment. In addition, they will be asked to provide a blood sample, which can be analyzed for genetic susceptibility biomarkers to explore the interaction between exogenous exposures and genetic risk. Tumor tissue will be obtained from all cases for pathologic review. Initial plans call for case–control studies of non-Hodgkin's lymphoma, leukemia, skin melanoma, and cancers of the prostate, brain, ovary, breast, lung, colon, stomach, testis, and pancreas. Pilot efforts regarding breast cancer are underway.

A similar methodology will be used to look at noncancer endpoints; the specific details will be dependent upon the disease endpoint being studied and have not yet been finalized.

Exposure Assessment

Interviews will serve as the primary source of information on agricultural, environmental, and lifestyle exposures. Questionnaire information on pesticide exposures will be supplemented and enhanced with detailed monitoring conducted on a small sample of the cohort and with data on pesticide exposures from the Pesticide Handlers Exposure Database (*30,31*). Pesticide exposure will be directly assessed by environmental and biologic monitoring for approximately 200 families in the cohort. Monitoring will include family members as well as the applicator to evaluate direct and indirect exposure. Food and water samples will also be collected and analyzed.

The questionnaires seek information on the frequency and duration of pesticide use, type of application methods, protective equipment used, and personal hygiene practices. The monitoring effort among the 200 families obtains actual measurements so that pesticide exposures can be related to factors thought to influence exposure. This comparison will provide a quantitative indication of the relative importance of work practices and occupational exposure. With monitoring data on specific pesticides, it will be possible to relate biomarkers of internal dose, target dose and biological effect, application procedures, and protective practices.

The monitoring component of the project, although extremely valuable, will be limited to only a sample of the cohort. These monitoring data and exposure information from the questionnaire will, therefore, be supplemented with information from the Pesticide Handlers Exposure Database. This database, developed by the EPA in conjunction with Health and Welfare Canada and the American Crop Protection Association, includes best-case scenario data from approximately 120 registrant-submitted monitoring studies which can be pooled to estimate pesticide exposure to different parts of the body while engaged in mixing, loading, and applying pesticides and when using various protective practices. The monitoring data in this resource, although not on farmers in our cohort, can be used to provide a relative ranking of exposures from different application patterns reported by our subjects and aid in the development of pesticide exposure scores.

Although the Pesticide Handlers Exposure Database contains more records than any published study, some applicator exposure scenarios encountered in the Agricultural Health Study may not be included. In addition, this database lacks information on specific pesticides and no information on nonoccupational exposures experienced by family members of the

Table 1. Demographic characteristics of agricultural health study cohort: year 1 enrollment[a]

	Number (%)			
	Total applicators (*n* = 20,235)	Farmer applicators (*n* = 16,535)	Commercial applicators (*n* = 3,700)	Spouse of farmer applicators (*n* = 6,459)
Age (years)				
<40	6585 (32.6)	4702 (28.4)	1883 (51.0)	1683 (26.1)
40–60	8384 (41.4)	7054 (42.7)	1330 (35.9)	3269 (50.6)
>60	3188 (15.7)	2971 (18.0)	209 (5.6)	1349 (20.9)
Unknown	2086 (10.3)	1808 (10.9)	278 (7.5)	158 (2.4)
Mean	45.3	46.7	39.2	48.4
Female	594 (2.9)	454 (2.8)	140 (3.8)	5979 (92.6)
Nonwhite	586 (2.9)	573 (3.5)	13 (0.3)	134 (2.1)
Highest grade completed				
<12	1846 (9.1)	1739 (10.5)	107 (2.9)	459 (7.1)
12	8514 (42.1)	7076 (42.8)	1438 (38.9)	2575 (39.8)
>12	8167 (40.4)	6287 (38.0)	1880 (50.8)	3240 (50.2)
Unknown	1708 (8.4)	1433 (8.7)	275 (7.4)	185 (2.9)
Smoking status				
Never	9373 (46.3)	7730 (46.8)	1643 (44.4)	4566 (70.7)
Former	5693 (28.1)	4733 (28.6)	960 (25.9)	1119 (17.3)
Current	3358 (16.6)	2509 (15.2)	849 (22.3)	627 (9.7)
No answer	1811 (8.9)	1563 (9.4)	248 (6.7)	147 (2.3)
Years personally mixed/ applied pesticide				
<1	660 (3.3)	382 (2.3)	278 (7.5)	273 (4.2)
2–5	2600 (12.8)	1761 (10.7)	839 (22.7)	541 (8.4)
6–10	3015 (14.9)	2358 (14.3)	657 (17.7)	401 (6.2)
11–20	5641 (27.9)	4814 (29.1)	827 (22.4)	569 (8.8)
21–30	3437 (17.0)	3097 (18.7)	340 (9.2)	315 (4.9)
>30	1851 (9.1)	1754 (10.6)	97 (2.6)	265 (4.1)
Unknown	3031 (15.0)	2369 (14.3)	662 (17.9)	4095 (63.4)
Median	15.4	16.4	10.8	12.8
Days per year personally mixed or applied pesticide[b]				
<5	2731 (13.5)	2389 (14.4)	342 (9.2)	969 (15.0)
5–9	3472 (17.2)	3139 (19.0)	333 (9.0)	608 (9.4)
10–19	4586 (22.7)	4065 (24.6)	521 (14.1)	475 (7.4)
20–39	3577 (17.7)	2930 (17.7)	647 (17.5)	222 (3.4)
40–59	1167 (5.8)	732 (4.4)	435 (11.8)	48 (0.7)
60–150	1112 (5.5)	533 (3.2)	579 (15.7)	30 (0.5)
>150	273 (1.3)	123 (0.7)	150 (4.1)	14 (0.2)
Unknown	3317 (16.4)	2624 (15.9)	693 (18.7)	4093 (63.4)
Median	23.3	20.4	44.7	11.7

[a]Subject enrollment will take 3 years. These data represent subjects enrolled in year 1.
[b]During years applied.

applicants. These omissions underscore the need for the monitoring project. Thus, the monitoring component and the Pesticide Handlers Exposure Database make important as well as complementary contributions to the exposure assessment effort. Together they can be used to develop a comprehensive assessment of exposure, which exceeds previous exposure assessments of the agricultural environment conducted in the context of an epidemiologic study.

Advisory Groups

An Advisory Panel composed of epidemiologists, biostatisticians, agricultural exposure experts, and farmers has been assembled to provide advice and oversight to the collaborating agencies during the development and conduct of the project. The Advisory Panel meets annually to review study protocols, evaluate study progress, and comment on analyses and reports. In addition, advisory panels were also established in each state by the Field Stations working with the state departments of agriculture and the cooperative extension services. These state panels provide insight into specific state agricultural issues and act as liaisons to state agencies and agricultural associations.

Results and Discussion

Recruitment

Data are currently available from the first year of enrollment, but should reflect the proportionate distribution of the ultimate cohort. During the first year, we enrolled 16,535 farmers, 3,700 commercial applicators, and 6,459 spouses of farmers for a total of 26,694 subjects (Table 1). These data are being analyzed to evaluate the enrollment process and to characterize the anticipated cohort.

Based on enrollment figures for the first year, we estimate the total cohort will include approximately 49,000 farmer applicators (62% of the cohort), 20,000 spouses of farmer applicators (24%), and 7,000 commercial pesticide applicators (14%).

During the first year, 77% of the eligible farmer applicators completed the enrollment questionnaire (74% in Iowa and 82% in North Carolina). This response rate compares very favorably with the response rates achieved by other recent prospective cohort studies which generally have enrollment rates below 70% (Tarone, et al., under review). Response rates for return of the take-home questionnaires were approximately 50% (i.e., 50% of those completing the enrollment questionnaire completed the take-home questionnaires).

Currently about 3% of the applicators enrolling are women and 3% are minorities. In addition to the female applicators, 93% of the spouses are females. With the current enrollment rate of spouses (i.e., a spouse questionnaire is completed) at approximately 50% and with a married rate of about 80%, we expect to enroll over 19,000 females by the end of the study. Approximately 15,000 additional female spouses will be registered through information provided by the applicator on the enrollment questionnaire. Although a completed spouse questionnaire is not available for these individuals, they are considered eligible for inclusion in the nested case–control studies. When enrollment is complete this study will be the largest cohort available to study the effect of agricultural exposures on women's health.

A supplemental minority recruitment effort conducted through African-American churches has been implemented through the North Carolina Field Station because of the small number of African-Americans eligible to enter into the study through the normal enrollment process. Over the past several decades the number of minorities farming in North Carolina as well as the rest of the United States declined even more precipitously than for white farmers (*32*). This supplemental recruitment cohort will differ from the main cohort in that it will include nonlicensed farmers, retired farmers, and their spouses in addition to currently licensed applicators. The special recruitment effort will draw respondents from several eastern North Carolina counties, the historic locus of African-American farming in North Carolina. Approximately 1,800 minority subjects will be enrolled through the normal recruitment process and 1,400 more will result from the supplemental minority recruitment effort in North Carolina for a total of 3,200.

Demographics

The mean ages of the farmer applicator and his/her spouse are 46.7 and 48.4 years of age, respectively, while commercial applicators are significantly younger, with a mean age of 39.2 (Table 1). (Preliminary analysis of responders versus nonresponders to the take-home questionnaires indicates older applicants are more likely to return these questionnaires; this accounts for the slightly higher mean age of the spouses). Although the mean age of minorities enrolled through standard procedures is 45.9 years old, pilot data suggest the mean age will be substantially older for those enrolled through the special recruitment effort. We therefore expect minorities will make a disproportionate contribution to the total number of chronic disease cases coming from the cohort because of their more advanced age.

The cohort is overwhelmingly white (97%), reflecting the general proportions of racial groups seeking licenses in the study areas. Nearly all of the nonwhite applicators (82%) are African-American and most (98%) live in North Carolina.

About 90% of the applicators and 93% of the farmers' spouses have graduated from high school and approximately 40% have completed some college. A larger proportion of commercial applicators and farmers' spouses have attended college than farmer applicators. Because we used self-completion questionnaires, there was some concern about illiteracy. This has not been a significant problem for enrollment. In the small number of cases where the applicator was illiterate, anecdotal evidence from the field indicates a literate spouse usually assisted with the completion of the enrollment questionnaire. However, literacy may be a barrier with the take-home questionnaires and may account for some of the nonresponse. Special supplemental surveys designed to evaluate nonresponse will be informative in this regard as these interviews will be conducted by telephone.

Overall, 17% of the applicators and 10% of the spouses of farmer applicators are current smokers (Table 1). These rates are lower than the rate for the United States as a whole (28% for males and 23% for females) (*33*). More commercial applicators (22%) are current smokers than are farmers (15%), and more North Carolina farmers smoke (20%) than do Iowa farmers (10%).

Commercial pesticide applicators in the study are a diverse group; 45% of the commercial applicators applied herbicides to crops, 37% applied pesticides to lawns and gardens, 25% applied insecticides to crops, 13% applied pesticides to homes, and 4% were engaged in forestry applications. Although they are younger and had somewhat fewer years of experience applying pesticides, commercial applicators tend to mix or apply pesticides more frequently than the farmer applicators (Table 1). This younger group of heavier users may therefore be particularly useful for studying noncancer endpoints with relatively short latency periods such as certain reproductive and neurological disorders.

Farm Characteristics

Agriculture in Iowa and North Carolina differs considerably. Consequently, agricultural exposures experienced by this cohort will be more diverse than in many previous studies. In Iowa, the major crops are corn, soybeans, oats, hay, and alfalfa. North Carolina agriculture is more varied (Fig. 3). Corn, soybeans, and hay are major crops, but North Carolina farmers also grow tobacco, peanuts, cotton, sweet corn, and cucumbers.

Farms in North Carolina are generally smaller than Iowa farms (Fig. 4). More than half of the farms in North Carolina are under 200 acres; only 19% of the Iowa farms are 200 acres or less. At the other end of the scale, 17% of Iowa respondents report farm sizes of over 1,000 acres; only 9% of North Carolina farmers reported farms of that magnitude.

In Iowa, 47% of the farmers report that they raise hogs and 44% raise beef, while only about 5% report sheep or dairy operations. In North Carolina, raising beef is reported by about 23% of farmers while raising sheep is reported by less than 1%. Hogs are raised by 9%, and dairy cattle and poultry are reported by 3–5% of the North Carolina farmers. Raising poultry is more prevalent in North Carolina than in Iowa.

Pesticide Use

The average farmer applicator in this cohort has mixed or applied pesticides for 16 years while the average commercial applicator has mixed or applied pesticides for approximately 11 years (Table 2). Although commercial pesticide applicators tended to mix or apply pesticides for fewer years than the farmer applicators, they mixed or applied pesticides more days per year (a median of 45 days per year for commercial versus 20 days per year for farmer applicators). Approximately one-third of the spouses of farmers also apply pesticides. The average spouse has applied pesticides for approximately 13 years at a median frequency of 12 days per year.

The contribution of women to farm operations is often overlooked, yet a survey of farm women found 47% ran farm errands, 37% took care of animals, 22% harvested crops, and 5% applied fertilizers and pesticides (*34*). Our own early data confirm these observations.

Agricultural Activities and Exposures

The questionnaires provided information on a variety of activities and exposures. A substantial percentage of farmer applicators weld (60%), grind metal (63%), and repair engines (39%). Less than 4% of the spouses perform any of these particular activities. Grinding animal feed at least monthly is performed by 36% of the farmers and 6% of the spouses, while butchering animals or providing veterinary services to livestock on a monthly or more frequent basis is performed by 33% of the farmers and 11% of the spouses.

For farmer applicators who have held nonfarm jobs, the most prevalent exposures reported on these jobs were engine exhaust (20%), solvents (16%), welding fumes (15%), and gasoline (15%). Commercial applicators report an even wider variety of other significant exposures on nonfarm jobs, including exposure to gasoline (42%), engine exhaust (40%), grain dust (31%), welding fumes (31%), and solvents (28%). Spouses report fewer exposures to additional agents than either farmer or commercial groups, with exposure most frequently occurring to solvents (7%), X-ray radiation (5%), and engine exhaust (4%).

Studies of the chronic disease rates among women who do not engage in mixing or application but who, nonetheless, may be exposed because they live on a farm will be important in their own right. Their exposures are likely to exceed those experienced by most of the general population. Data being collected on household activities, including laundry, vacuuming, and pesticide storage, and location of the house or well in relation to areas where pesticides are mixed or applied, will aid in this evaluation of household exposure (*35*).

Exposure Assessment

Although environmental and biological monitoring among pesticide-exposed workers have been conducted to characterize exposure, pesticide exposure monitoring is virtually nonexistent in previous epidemiologic studies of cancer and other chronic diseases (*19*,*36*). Improving exposure assessment in the context of a prospective epidemiologic study is a key objective of the Agricultural Health Study. When finalized the exposure monitoring component will be designed to provide information

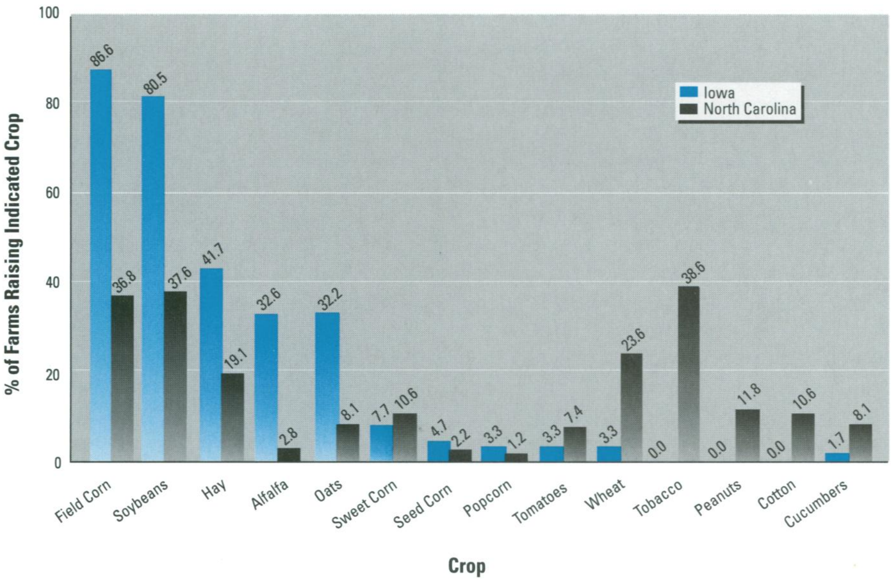

Figure 3. Top crops in Iowa and North Carolina.

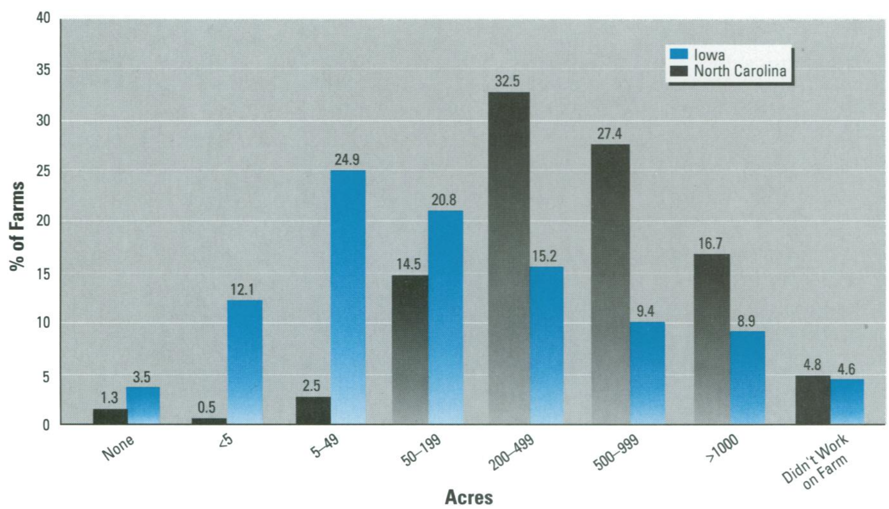

Figure 4. Distribution of farm size in Iowa and North Carolina.

Table 2. Types of pesticide applications performed by private and commercial applicators in the Agricultural Health Study

Type of pesticide application	% Applicators with indicated exposure	
	Private applicator (n = 16,535)	Commercial applicator (n = 3,700)
Termite control	3.1	2.0
Rodent control	21.9	11.1
Lawn and garden	27.7	37.1
Greenhouse	4.0	2.9
Stored grain	13.4	10.1
Highway weed control	6.4	9.1
Forestry	1.6	3.5
Aerial spraying	0.9	0.9
Herbicide, crop	70.1	45.1
Herbicide, other	0.5	2.4
Insecticide, farm crop	54.7	24.6
Insecticide, farm animal	24.2	7.6
Insecticide, pets	13.1	7.8
Insecticide, home	11.7	13.2
Insecticide, commercial buildings	1.8	4.6
Fungicide	14.1	7.0
Fumigant	9.3	4.1

regarding the total exposure to pesticides from all routes (i.e., food and water ingestion, air inhalation, and skin exposure) and from environmental and occupational sources. It will also provide monitoring data that can be used to complement information obtained by interview and create relative exposure rankings for all individuals in the cohort.

The epidemiologic analyses in this study will be based primarily on exposure information obtained from the questionnaires because this information is obtained on all participants. The proposed monitoring effort will provide additional data to develop a more reliable exposure classification. No existing database contains information combining use of specific pesticides by application methods, formulation types, and work practices, yet these factors are all important exposure determinants. For example, monitoring studies have indicated that most dermal exposure to pesticides occurs from hand contact (*37*). A logical analysis would be to compare disease rates among persons who reported use of protective gloves with rates of those who did not, while controlling for pesticide formulation type, application method, and other work practices. Such a comparison, however, would be deceptive if there was no actual difference in exposure between the two groups. Monitoring will improve our confidence in exposure groupings based on interview data. Integrating environmental monitoring with questionnaire data on exposure determinants will enhance the validity of exposure assessment in the etiologic analysis.

Because of practical limitations and costs, however, it will not be possible to monitor all possible factors that influence exposure. The Pesticide Handlers Exposure Database will be used to fill some of these gaps, particularly regarding application techniques and types of protection. This well-validated database will provide an extremely valuable source of occupational exposure information. On the other hand, the Pesticide Handlers Exposure Database does not include nonoccupational pesticide exposures. This may represent an especially important source of exposure for dependents. The EPA (*38,39*) found that nonoccupational exposures to many pesticides occur at detectable levels in residential air and Starr et al. (*40*) found that house dust in 28 homes of farmers and pesticide formulators in Colorado contained organochlorine pesticides in all environmental media (air, water, food, and house dust/soil). By linking questionnaire data on nonoccupational opportunities for pesticide exposure through household storage or handling of soiled clothes and biomonitoring data, the Agricultural Health Study has an opportunity to make a substantial contribution to our understanding of sources and effects of household exposure to pesticides.

Collaborative Agreements

The sponsoring agencies recognize that the full value of this cohort can be maximized only if it is seen as a national resource available to the scientific community through collaborative agreements with federal investigators. Proposals for such collaborative arrangements to answer specific etiologic and methodologic questions are welcome and will be encouraged for the duration of the study. While the opportunities for collaborative research are many and varied, some examples of potential collaborative research include: chemical analysis and biomarker analysis of blood, DNA, and urine from nested case–control studies, development of economical exposure measures on specific subgroups, intervention studies of good work practices, birth defect surveillance, developmental testing of children, and assessment of nonpesticide exposures on farms (e.g., aflatoxins, dusts, solvents, viruses, and allergies).

Appendix A. Content of Cohort Questionnaires

Enrollment Questionnaire

a. Demographic data
b. Pesticides used (50 pesticides), other pesticide-related questions
c. Lifestyle (i.e., smoking, alcohol, vegetable, and fruit consumption)
d. Brief medical history
e. Family history of cancer, kidney failure, diabetes, and heart disease
f. Farm exposures other than pesticides (not in commercial pesticide applicator version)
g. Personal identifiers, spouse identifiers, children identifiers

Farmer Applicator Questionnaire/ Commercial Applicator Questionnaire

a. Farm exposures (comprehensive)
b. Pesticide use information (i.e., methods of application, additional pesticides used)
c. Work practices used currently versus those used 10 years ago
d. Other occupational exposures
e. Leisure and work physical activity, physical attributes (e.g., height, weight, eye color, skin pigmentation category)
f. Dietary and cooking practices
g. Medical history (comprehensive)
f. Personal identifiers

Spouse Questionnaire

a. Demographic data
b. Pesticide use
c. Agricultural/other occupational exposures
d. Alcohol and smoking history
e. Physical activity, hair dye use
f. Medical history (comprehensive)
g. Personal identifier

Female and Family Health Questionnaire

a. Reproductive history
b. Pregnancy history
c. Information about children
d. Personal identifiers

Appendix B. Additional Data Gathered

Spontaneous Abortions

a. Basic demographic information
b. Smoking history
c. Pesticide exposures
d. Residential history/water consumption history
e. Pesticide treatment of gardens,

homes, and pets
f. Ionizing radiation exposure
g. Occupational exposures
h. Menstrual/pregnancy/reproductive history
i. Personal identifiers

Neurologic and Immunologic Disease

a. Basic demographic information
b. Agricultural/other occupational exposures
c. Pesticide exposure
d. Pesticide application work practices
e. Other occupational exposures
f. Medical history
g. Neurologic/immunologic symptoms
h. Personal identifier

References

1. Hunter's diseases of occupations, 8th ed (Raffle PAB, Adams PH, PJ Baxter, WR Lee, eds). Boston:Little, Brown Co., 1994;490,554.
2. Blair A, Zahm SH, Pearce N, Heineman E, Fraumeni JF. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health 18:209–215 (1992).
3. Pearce N, Reif JS. Epidemiologic studies of cancer in agricultural workers. Am J Ind Med 18:133–148 (1990).
4. Blair A, Zahm SH. Cancer among farmers. Occup Med State Art Rev 6:335–354 (1991).
5. Blair A, Malker H, Cantor KP, Burmeister L, Wiklund K. Cancer among farmers: a review. Scand J Work Environ Health 11:397–407 (1985).
6. Walrath J, Rogot E, Murray J, Blair A. Mortality patterns among United States veterans by occupation and smoking status. NIH publication no. 85-2756. Washington, DC:National Institutes of Health, 1985.
7. McMichael AJ, Hartshorne JM. Mortality risks in Australian men by occupation groups, 1968–1978. Med J Aust 1:253–256 (1982).
8. Cassel J, Heyden S, Bartel AG, Kaplan BH, Tyroler HA, Cornoni JC, Hames CG. Occupational and physical activity and coronary heart disease. Arch Intern Med 128:920–928 (1971).
9. Surgeon General. Smoking and health: a report of the Surgeon General. Washington, DC:Office of the Surgeon General, 1971.
10. Milham S Jr. Occupational mortality in Washington state, 1950–1979. NIOSH publication no 83-116. Cincinnati, OH:National Institute of Occupational Safety and Health, 1983.
11. Davis DL, Hoel D, Fox J, Lopez A. International trends in cancer mortality in France, West Germany, Italy, Japan, England and Wales, and the USA. Lancet 336:478–781 (1990).
12. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 66:1191–1308 (1981).
13. Donham KJ, VanDerMaaten MJ, Miller JM, Kruse BC, Rubino MJ. Seroepidemiologic studies on the possible relationships of human and bovine leukemia: brief communication. J Natl Cancer Inst 59:851–853 (1977).
14. Sordillo PP, Markovich RP, Hardy WD. Search for evidence of feline leukemia virus infection in humans with leukemia, lymphomas, or soft-tissue sarcomas. J Natl Cancer Inst 69:333–337 (1982).
15. Alavanja MCR, Blair A, Masters MN. Cancer mortality in the United States flour industry. J Natl Cancer Inst 82:840–818 (1990).
16. Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B. Mortality among agricultural extension agents. Am J Ind Med 14:167–176 (1988).
17. Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B, Reed B. Mortality among forest and soil conservationists. Arch Environ Health 44:94–101 (1989).
18. Pesatori AC, Sontag JM, Lubin J, Consonni D, Blair A. Cohort mortality and nested case–control study of lung cancer among structural pest control workers in Florida (United States). Cancer Causes Control 5:310–318 (1994).
19. Morrison HI, Wilkins K, Semenciw R, Mao Y, Wigle D. Herbicides and cancer. J Natl Cancer Inst 84:1866–1874 (1992).
20. Greaves IA. Agricultural health: exposure to toxic substances. Health Environ Digest 6(4):1–4 (1992).
21. Baker SR, Wilkeson CF, eds. Advances in modern environmental toxicology, vol XVIII. The effects of pesticides on human health: exposure to pesticides. Princeton, NJ:Princeton Scientific Publishing Co., 1990;35–130.
22. Wiklund K, Dich J, Holm LE, Eklund G. Risk of cancer in pesticide applicators in Swedish agriculture. Br J Ind Med 46:809–814 (1989).
23. Wiklund K, Dich J. Cancer risks among male farmers in Sweden. Eur J Cancer Prev 4:81–90 (1995).
24. Rafnsson V, Gunnarsdottir H. Mortality among farmers in Iceland. Int J Epidemiol 18:146–151 (1989).
25. Stark AD, Chang H-G, Fitzgerald EF, Riccardi K, Stone RR. A retrospective study of mortality among New York state farm bureau members. Arch Environ Health 42:204–212 (1987).
26. Semenciw RM, Morrison HI, Reidel D, Wilkins K, Ritter L, Mao Y. Multiple myeloma mortality and agricultural practices in the prairie provinces of Canada. J Occup Med 35:557–561 (1993).
27. Wigle DT, Semenciw RM, Wilkins K. Mortality study of Canadian farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. J Natl Cancer Inst 82:575–582 (1990).
28. Morrison HI, Semenciw RM, Morison D, Magwood S, Mao Y. Brain cancer and farming in Western Canada. Neuroepidemiology 11:267–276 (1992).
29. Morrison HI, Savitz D, Semenciw R, Hulka B, Mao Y, Morison D, Wigle D. Farming and prostate cancer mortality. Am J Epidemiol 137:270–280 (1993).
30. Van Hemmen JJ. Agricultural pesticide exposure data bases for risk assessment. Rev Environ Contam Toxicol 126:1–85 (1992).
31. Leighton TM, Neilsen AP. The United States Environmental Protection Agency, Health Canada, and National Agricultural Chemicals Association Pesticide Handlers Exposure Database. Appl Occup Environ Hyg 10(4): 270–273 (1995).
32. Wimberley RC, Morris LV, Bachtel DG. New developments in the black belt: dependency and life conditions. In: New directions in local and rural development (Baharanyl N, Zabawa R, Hill W, eds). Tuskegee, AL:Tuskegee University, 1992.
33. CDC. Smoking and health: United States national health interview surveys selected years 1965–1991. Atlanta, GA:Centers for Disease Control, 1995.
34. Sachs CE. American farm women. In: Work and women: an annual review, vol 2 (Stronbery AH, Lawood L, Gutek BA, eds). Newbury Park, CA:Sage Publication, 1987;233–248.
35. Alavanja MCR, Akland MS, Baird D, Blair A, Dosemeci M, Kamel F, Lewis R, Lubin J, Lynch C, McMaster SB, Moore M, Pennybacker M, Ritz L, Rothman N, Rowland A, Sandler D, Sinha R, Swanson C, Tarone R, Weinberg C, Zahm SH. Cancer and noncancer risk to women in agriculture and pest control: the agricultural health study. J Occup Med 36:1247–1250 (1994).
36. Blair A, Zahm SH, Cantor KP, Stewart PA. Estimating exposure to pesticides in epidemiological studies of cancer. In: Biologic monitoring for pesticide exposure ACS symposium series 382 (Wang RGM, Franklin CA, Hoalgeutt RC, Reinert JC, eds). Washington DC:American Chemical Society, 1984;38–46.
37. Honeycutt RC, Zweig G, Ragsdale NN, eds. Dermal exposure related to pesticide use. ACS symposium series 273, Washington, DC:American Chemical Society, 1985.
38. Whitmore RW, Immerman FW, Camann DE, Bond AE, Lewis RG, Schaum JL. Non-occupational exposures to pesticides for residents of two United States cities. Arch Environ Contam Toxicol 26:47–59 (1994).
39. Lewis RG, Bond AE, Johnson DE, Hsu JP. Measurement of atmospheric concentrations of common household pesticides: a pilot study. Environ Monit Assess 10:59–73 (1988).
40. Starr HG Jr, Aldrich FD, MacDougall WD III, Mounce LM. Contribution of household dust to the human exposure to pesticides. Pestic Monit J 8:209–212 (1974).