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The Agricultural Health Study: Strengths and Limitations

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The federal government has recently enrolled over 90,000 farmers, farm family members, and commercial pesticide applicators in a massive health study. The objective is to examine factors that may affect the health of farmers and their families, with a special focus on whether specific pesticide products used on farms are linked to a variety of adverse health effects including cancers, developmental and reproductive effects, and damage to the body's immune system. Called "The Agricultural Health Study (AHS)" and funded by federal research dollars, the AHS is an integrated program of multiple studies directed by a group of scientists at the National Cancer Institute, the National Institute of Environmental Health Sciences, and other federal agencies.

Farmers are known to be healthier, have fewer cancers, and live longer than the general population. However, some previous epidemiologic investigations have found increased rates of several tumors in farmers. The AHS is designed to re-examine these issues while avoiding the many limitations that plagued earlier studies of farmers.

In 1996, the Harvard Center for Risk Analysis was commissioned by the American Crop Protection Association (ACPA) to review and critique the design of the AHS and to suggest to ACPA steps that can be taken by government and industry to strengthen the scientific foundation of the AHS. ACPA is a trade association of corporations with commercial interests in pesticide products that are used on farms throughout the world.

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HCRA recently prepared a detailed review of the AHS in collaboration with an independent advisory committee of scientists chaired by Professor Bernard Goldstein, M.D. of the Robert Wood Johnson Medical School. (The full list of members of HCRA's Advisory Committee of Agriculture and Human Health are listed on page four as peer reviewers.) Copies of the review are available from the Center. The purpose of this issue of **RISK IN PERSPECTIVE** is to summarize the major findings of HCRA's review of the AHS.

Design of the AHS

In the states of Iowa and North Carolina, more than 90,000 subjects have been enrolled in the AHS during required applicator training sessions and through take-home questionnaires. Most of the data in the study are being obtained from farmer-applicators and family members through self-administered questionnaires and telephone interviews. Numerous questions have already been asked of each enrollee regarding their experiences as a farmer, their patterns of chemical use, their lifestyles, and their current health status. For some diseases, such as cancer, information about disease-incidence of enrollees in the future will be obtained from disease registries maintained by the states of Iowa and North Carolina.

In the main prospective cohort study, the 90,000 enrollees will be followed for many years or until death in order to

determine whether use of particular pesticide products or other aspects of farm living are associated with adverse health outcomes. An important design feature of this main cohort study is that information on chemical use is obtained from farmers via survey methods *prior to the diagnosis of disease*.

In addition, more timely yet less conclusive cross-sectional studies are being undertaken to determine whether self-reported health problems are more likely to occur among farmers and members of farm families that report extensive use of pesticide products. The three initial cross-sectional studies are investigating (1) history of spontaneous abortion, menstrual function, and fertility in young women, (2) menopausal status, reproductive history, and selected chronic diseases in older women, and (3) neurologic symptoms and visual impairment among farmer-applicators.

Strengths of the AHS

The design and implementation of any research program as large and complex as the AHS requires many tradeoffs and compromises. It can be expected that responsible scientists will have differing opinions about how a study of this magnitude should be undertaken. Overall, we commend the AHS investigators for making a variety of sound choices in the face of limited resources and a complex challenge.

The single most important strength of this study is the experience, skill, and commitment of the senior investigators, coupled with the energetic field teams in Iowa and North Carolina. The investigators also have received technical advice from a distinguished group of external advisors chaired by Dr. James Felton of the Lawrence Livermore National Laboratory.

From a research design perspective, a principal strength of the AHS is the prospective nature of the cohort study of cancer outcomes: pesticide use patterns are documented before anyone knows who will contract cancer. This study design responds directly to criticisms of previous studies that collected information on pesticide use from farmers or next of kin only after cancers were already diagnosed. A feature of the prospective study that is critical to success is periodic re-interviewing of enrollees to determine how their pattern of chemical use changes over their lifetime and how other aspects of their farm and lifestyle change in the years ahead. More difficult is determining patterns of pesticide use ten or twenty years in the past, the exposures that might be presumed to be associated with any early findings of disease. Because of the long time for cancer to become evident, this information is the primary index of exposure that might be associated with current findings of disease.

For a study of this scale, we have also been impressed with the diligent efforts to enhance response rates to the main enrollment questionnaire. This is the survey instrument that provides the critical identifiers that permit linkage of each enrollee to state-wide disease registries. The instrument also provides self-reported information on each enrollee's historical use of chemicals. Response rates to the main questionnaire are running in the 80 - 85% range, although response rates to a variety of supplemental questionnaires have been less impressive. The higher the response rate, the less likely it will be that selection biases will occur in the study population. For example, if non-responders are disproportionately non-diseased subjects who have made extensive use of chemicals, there is significant opportunity for bias in reported associations. The investigators are aware of this potential problem and have made some efforts to examine the potential ramifications of the non-response issue.

Limitations of the AHS

There are three areas of weakness in the AHS: the lack of a credible plan to understand the extent of chemical exposure, reliability and validity problems with self-reported data on health conditions and chemical use, and the lack of a detailed plan of data analysis for the study. These weaknesses are important to note because even though the study is well underway, it is not too late for the investigators to take steps to reduce or minimize these problems.

First, although 90,000 individuals have been enrolled in the AHS, little effort is being made to measure the nature and extent of enrollee exposure to the chemicals that are used in the farm environment. A significant biomonitoring program, based on urine and/or blood samples taken from

selected farmers and/or farm family members soon after application, has not been fully integrated into the AHS. Early in the study, some small pilot exposure studies were conducted. A variety of plans to provide biomonitoring were proposed and discussed with scientists at the U.S. Environmental Protection Agency. There are also recent discussions that the National Institute of Occupational Safety and Health may play a significant role in exposure assessment but a strong program has yet to be established.

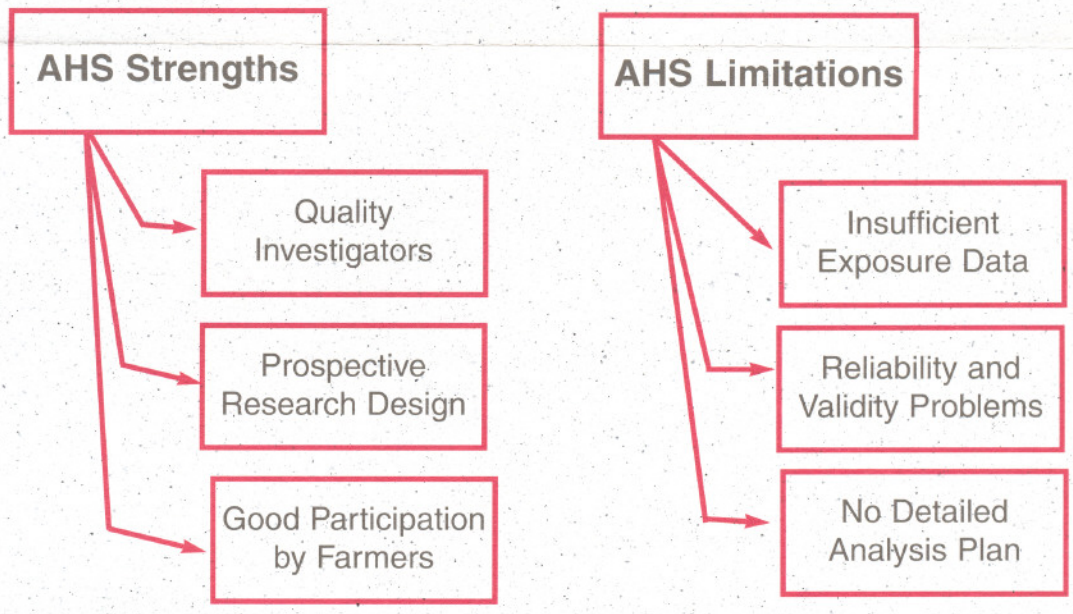
It will be difficult for the AHS investigators to establish whether there is a cause-and-effect relationship between specific diseases and specific chemical agents without good understanding of the relationship between patterns of chemical use (e.g., frequency of use, application method, clothing, protective equipment, crop type, and farm equipment) and actual exposure. Current questionnaires don't ask about the number of acres treated with pesticide. In the absence of valid information on chemical exposure, the investigators will be forced to rely on surrogates of exposure obtained from questionnaire data. Yet previous studies that have used such surrogates have been criticized because few of the surrogates of exposure were validated. Even when validation studies are carried out, they rarely begin with a pre-defined criterion of what constitutes adequate validity and even more rarely are used to disqualify data.

Second, the quality of the self-reported information collected in the AHS is unknown. At least two types of self-reported data need to be scrutinized: the self-reporting of health status by farmers and family members (particularly the non-cancer outcomes) and the self-reporting of chemical use.

Self-reports of health status are prone to error and both positive reports of illness and reports of the absence of illness need to be validated. Where it is infeasible to perform clinical validation studies of some outcomes (e.g., headaches), rigorous reliability studies need to be performed (e.g., to determine whether self-reports are stable in repeated survey administration and whether self-reports are sensitive to the order and wording of questions posed to enrollees).

Of equal concern is the lack of information about the validity and reliability of farmer reports of chemical use. The main enrollment questionnaire asks detailed historical questions about 22 named compounds, including frequency of use per year since the enrollee began farming.

For an additional 28 compounds, there is a question as to whether the compound had ever been used. There are also numerous questions about the farmer's work habits: whether the farmer mixes chemicals, how the farmer applies the chemicals, what type of clothing is worn, whether protective equipment is used, and how clothes are washed after chemical use. These questions are clearly relevant to



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FURTHER READING:

Alavanja, M.C.R., Sandler, D.P., McMaster, S.B., Zahm, S.H., Mcdonnell, C.J., Lynch, C.F., Pennybacker, M., Rothman, N., Dosemeci, M., Bond, A.E., and Blair, A. (1996) *The Agricultural Health Study*. Environmental Health Perspectives 104:362-369.

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exposure but there are numerous sources of potential error in response: reluctance to acknowledge unsafe practices, faulty memory about historical use patterns, confusion about the names of specific compounds, and weariness in filling out the lengthy questionnaire. Unless the self-reported chemical use data are validated, questions will remain about the quality of this critical information.

Finally, the AHS investigators have not published a detailed plan of data analysis that includes a priori hypotheses about specific compounds, specific exposure surrogates, and specific diseases. In a study of 58 compounds, many other factors like dust, diesel exhaust, diet, sunlight and smoking, and dozens of health outcomes, some positive associations will occur by chance. Without any a priori hypotheses, the investigators leave themselves vulnerable to the charge that, once the data were collected, they engaged in a "fishing expedition" to find some associations. The investigators should be encouraged to perform exhaustive analyses of the data, but a distinction should be drawn between hypotheses that were postulated prior to data analysis and then confirmed or refuted, and new hypotheses that were generated based on unexpected associations in the data. It is encouraging that the investigators plan to make these data publicly available for re-analysis by other investigators, but that does not substitute for a well-formulated a priori analysis plan.

Recommendations

The AHS is collecting a large amount of useful information about farmers and farm families. The prospective study of cancer outcomes is particularly well designed in light of the criticisms about potential sources of bias that have been raised about previous studies of pesticides and cancer. Yet there are important weaknesses in the AHS that need to be corrected. Solutions to these problems will require significant resources and additions to the AHS workplan.

We recommend that government and industry commission the additional studies that are required to buttress the scientific foundation of the AHS. These studies should include biological monitoring of the exposures experienced by farmers and farm families, clinical validity studies of positive and negative self-reports of disease status, and validity and reliability studies of self-reporting of chemical use. We also recommend the AHS investigators prepare a detailed plan of data analysis, including a priori hypotheses, that is similar to what a principal investigator would be expected to provide in a major external research proposal to the National Institutes of Health. If these steps are not taken the large amount of data that are being collected will be difficult to interpret. With these refinements, the AHS will be of substantially greater value to the scientific and farming communities.

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In the November 1998 issue of Risk in Perspective (Volume 6, Issue 8) Figure One was omitted. This figure and the entire Risk In Perspective can be found at: www.hsph.harvard.edu/organizations/hcra/novrip.html