July 22, 1997

To the Communications Subcommittee:

At your last meeting, I was asked to provide some background thoughts on Epidemiology and the Agricultural Health Study (AHS) that you could use to build positive messages. Please find some preliminary thoughts attached.

I have put your request for background information on the agenda for the next Epidemiology Work Group meeting (August 7th). This will give you the benefit of input from a broader sphere of scientists. The Epi Work Group will be glad to entertain other requests and looks forward to assisting you in your work on the AHS.

Regards,

John Acquavella

DRAFT

Background Thoughts for the Communications Subcommittee

Farmers' health profile

Farmers are not an occupational population in obvious need of etiologic research. Their total mortality rate is 24% less than the general population rate. Their cancer mortality rate (for all cancers combined) is 16% less than the general population rate. Recent analyses show that the only cancer clearly elevated among farmers is lip cancer - believed attributable to sun exposure.

The AHS rationale

The rationale for the AHS derives from results of a number of poor studies which found associations between farming or pesticide exposure (vaguely defined) and various diseases. The AHS is intended to advance the science in this area by creating a human living laboratory for decades of research. Thus, the time horizon for definitive research is long. In the short term, the AHS investigators will work to confirm some existing theories (e.g. 2,4-D and lymphoma). But, the viability and eventual impact of the AHS will depend on the investigators' ability to generate a new class of scientific leads, most of which will be invalid. This has the potential to be disruptive for the agricultural chemical industry as new leads potentially take on a life of their own. Perhaps the best way to position the AHS is as part of a learning process. The learning process will take years to be resolved and will need to incorporate information from other research (e.g. studies of manufacturing workers) before any conclusions can be established as valid.

A definition of epidemiology

A scientific discipline that conducts studies of people to identify factors that increase or decrease human rates of disease.

The ideal study

The limitations of the AHS can be illustrated by comparison with the hypothetical ideal study. The ideal study would have the following characteristics:

experienced investigators
well reasoned hypotheses defined before the study
well defined study population
comparable exposed and comparison groups
accurate exposure assessment
accurate disease classification

comprehensive data analysis
no systematic bias and no confounding
good documentation
accurate/fair write-up

How the AHS compares to the ideal study:

Investigators. The key NCI investigators are experienced in agricultural research and highly regarded in the epidemiologic community. The key NIEHS investigator (Dr. Sandler) is highly regarded by epidemiologists, but she and the entire NIEHS team are inexperienced in agricultural epidemiology.

Hypotheses. Most of the diseases to be studied in the AHS have scant reasoning to link them putatively to pesticide exposure. Thus, much of the research can be termed "exploratory." That's not unusual in epidemiology, but it is unusual on this big a scale.

The downside for industry and agriculture in this approach is that exploratory research tends to yield uncertain findings. Uncertain findings, at the least, cast doubt on the safety of products. This energizes pesticide opponents, may cause the public to dictate a market change, and typically makes the manufacturer adopt a defensive stance. It would have been preferable if the AHS had a limited scope and focused more detail on a few worthy questions.

Study population. The AHS has a well defined study population. The problem with the study population, from the researchers' perspective, is that they have limited contact with pesticides (farmers report about 12 days/year of use for all pesticides). A researcher would prefer to study people with constant or daily exposure.

Comparability. Comparability is a complicated issue. The fundamental goal in epidemiologic studies is to compare the disease rate for an exposed population to the rate they would have had without exposure. This can never be done in practice. In studies like the AHS, investigators make a questionable assumption that the comparison population has the same disease rate that the exposed population would have - had they not been exposed. Because of this and because of the possibility of bias (discussed later), epidemiologists usually are reluctant to reach conclusions unless there is a fairly big difference in disease rates between the exposed and unexposed groups - say 50% or more. There is a strong sentiment in the epidemiologic community to dispense with this caution. We'll see how the AHS investigators treat small differences in this study.

Exposure assessment. The exposure assessment in the AHS will be inaccurate. Exposure assessment will be based on historical usage as reported by the farmer or applicator on the study questionnaire(s). There are two problems with this approach: 1. usage does not necessarily mean exposure (work practices/equipment/environmental conditions determine exposure to a large degree); 2. recall can be faulty or biased, especially when historical usage information is collected. Attempts at verification over a 3 year period have found less than 70% agreement between purchasing records and reported usage.

Inaccurate exposure classification can produce spurious results. The conventional thinking in epidemiology is that exposure misclassification will most often obscure exposure disease relationships. More recent thinking has begun to recognize that it can also create spurious exposure disease associations. In a study of this size, there will be some, perhaps many, spurious exposure-disease findings due to exposure misclassification.

Accurate disease classification. The AHS will have accurate disease classification for their cancer studies. In these studies, diagnoses will be determined from population based cancer registries in both states. The registries used medical records as a basis for their diagnostic information and have quality control programs in place to insure accurate diagnoses.

The non-cancer research will have less accurate disease classification. This is especially true for the initial studies where disease information is self-reported with no medical verification. Here, disease itself is not being studied, rather reports of disease are being studied.

Data analysis. NCI and NIEHS have a group of very able statisticians. We can expect a complicated analysis for most of their studies.

One important statistical issue for the AHS is the multiple comparison problem - large studies with many statistical analyses will have a number of "statistically significant" findings by chance alone. The researchers have been very vague about how they will handle the multiple comparison problem.

We also have to keep in mind that even the most sophisticated statistical analysis can't correct for other aspects of the study that are less than optimum (e.g. exposure misclassification).

Bias. Bias (really research errors or extraneous factors that favor an incorrect outcome - not prejudicial judgment)

is a concern in every epidemiologic study. Bias can come from a number of sources. Of primary concern is confounding bias. A confounding factor is a factor that causes a disease and is correlated with an exposure you are studying. To the extent that you don't know about or cannot measure such a confounder, results may be biased. The AHS investigators are collecting information about smoking and a few other personal habits that can be confounders, but they have given less thought to assessing potential confounding factors in the farming environment. Farmers work with pesticides approximately 12 days a year, but they work with their farming environment 300+ days per year.

A second issue is recall bias. Specifically, do peoples' health experiences (or correlates of health experience) affect disease or pesticide reporting on the various study questionnaires? There are other areas of bias to consider as well.

Documentation. NCI studies have, in general, high standards for data collection and data management. The AHS is using NCI's prime contractor - Westat - to handle this for them, so I expect they will do a good job in this area.

There is, however, a major gap in the AHS documentation: they are lacking study protocols for their specific sub-studies. There is an overall AHS protocol which lays out, in general, the rationale and methods for the study. But, there are no protocols for the initial sub-studies. A number of these sub-studies are almost completed including: the pesticide related medical visits evaluation, the menstrual effects study, the reproductive outcomes study, and the neurological effects study. The AHS investigators are conducting these studies "on the fly." In the past, they have promised us protocols for these studies, but they have never materialized. This circumvents some of the scrutiny they might get and gives them flexibility in their research since they won't have to worry about deviating from the protocol.

Accurate write-up. Time will tell whether the AHS investigators take an activist or conservative posture in their write-ups.