Published in final edited form as:
Rev Environ Health. 2009 ; 24(4): 311–318.

Evaluation of Agricultural Exposures: The Agricultural Health Study and the Agricultural Cohort Consortium

Laura Beane Freeman, Ph.D.
Occupational and Environmental Epidemiology Branch Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services Bethesda, MD

Farmers experience a complex pattern of mortality and disease, which is not surprising given their complex exposures. Compared to the general population, they display deficits of several cancers, such as those of the lung, bladder, and colon. Conversely, farmers experience excesses of some cancers, including cancer of the lip, skin, brain, lymphatic and hematopoietic system and soft-tissue sarcoma [1-3]. Relatively low rates of tobacco use and alcohol consumption, as well as high levels of physical activity may account for some of the disease deficits. Potentially hazardous exposures, such as pesticides, solvents, engine exhausts, dusts, and zoonotic microbes may contribute to some of the excesses.

As is the case with many occupations and industries, early epidemiologic studies of cancer among farmers used the occupational designation of “farmer” as the exposure determinant. While these studies provided interesting leads into the cancer experience of farmers and clues into potential causes, they lack the detail necessary to identify etiologic agents. During the past few decades, several epidemiologic studies to evaluate cancer and other diseases in agricultural populations have been conducted and others are being initiated. More recently, some have focused on type of farm commodity produced, or specific exposures, such as pesticides.

A major challenge in studying agricultural exposures is adequate exposure assessment. Accurate estimates of exposure in epidemiologic studies are crucial in developing reliable measures of risk. These challenges are not unique to the study of agricultural populations. Importantly, results of studies of agricultural exposures have implications beyond rural settings as exposure to agents traditionally thought of as agricultural extends into urban and suburban environments.

One study that has attempted to study agricultural exposures, specifically pesticides, on a large scale is the Agricultural Health Study, a study initiated by the National Cancer Institute, in partnership with the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health and the Environmental Protection Agency. This study serves as an example of a multi-faceted approach to studying agricultural exposures and cancer.

The Agricultural Health Study

Study Design

The Agricultural Health Study (AHS) is a prospective cohort study of 57,310 licensed pesticide applicators and 32,347 spouses in Iowa and North Carolina [4]. In addition to farmers, the study in Iowa also includes 4,916 commercial pesticide applicators. Since pesticide applicators must obtain licenses to apply restricted use pesticides, this represents an opportunity not only to enumerate a group of individuals with agricultural exposures but to also increase the reliability of the pesticide exposure assessment by enrolling a group of pesticide applicators who are knowledgeable about the pesticides that they are using. The cohort is followed for cancer incidence using population-based cancer registries in Iowa and North Carolina and mortality using the National Death Index. Since 1993, when enrollment began, over 6,000 incident cancers have been diagnosed in the cohort, with over 2,000 deaths due to cancer.

Exposure Assessmen

The AHS relies on self-reported use of specific pesticides and other agricultural exposures. The initial questionnaire administered at enrollment from 1993-1997 focused on fifty commonly used pesticides and asked information about the frequency and duration of their application for use in exposure-response analyses. Pesticide applicators have been shown to reliably report their usage of specific pesticides [5]. In addition to evaluating lifetime days of exposure, an algorithm was developed by industrial hygienists with extensive expertise to account for individual differences that might impact the intensity of the exposure, including the use of personal protective equipment, whether or not the applicator personally mixed the pesticides and different application methods [6]. The incorporation of this exposure algorithm allows for the usage days to be weighted by exposure intensity. A critical element of the pesticide exposure assessment is the validation of the exposure estimates. Several efforts have been undertaken within the AHS to validate and further characterize exposure. A number of important findings from these efforts have emerged. First, the exposure intensity algorithm correlates with exposures measured using biological monitoring data [7], indicating that using questionnaire data from this study is a good approach for rank-ordering exposures. Second, comparing scores from the exposure intensity algorithm and individual determinants of exposure such as kilograms of active ingredient, number of acres treated or duration of the exposure showed that the exposure algorithm was more highly correlated with urinary concentrations of pesticide metabolites than were more simplistic determinants often used in epidemiologic studies, such as days of use and acres treated. Therefore, using the intensity-weighting scores should reduce exposure misclassification. This is an important improvement because misclassification of exposure can be a major problem in epidemiologic studies. Some exposure misclassification undoubtedly remains in the AHS; however, in prospective studies such as this, the exposure assessment is done prior to cancer diagnosis and the resulting misclassification is almost certainly not different among persons who eventually develop cancer than among those who remain cancer free. Such random misclassification of exposure has been shown to bias relative risk estimates toward the null. That is, the observed risk would likely be attenuated estimates of the true risk, to the extent that exposure estimates are misclassified. Finally, these studies show that family members of pesticide applicators may have important exposures to pesticides. [8-10]

Following enrollment, there have been two efforts to update exposure information and non-cancer disease status by computer-aided telephone interviewing. Pesticide usage patterns change over time as new products are introduced and older chemicals are phased out. These updates represent a major advance since new exposures can be identified and the participants are asked to provide exposure information for more recent time period, which should improve the quality of the information. In addition, the spouses of pesticide applicators were also asked about their own use of pesticides in the follow-up phases.

Results

Overall, the farmers and spouses in the AHS have an almost 15% reduction in cancer incidence compared to the general population in the states where the study is conducted [11]. However, for some cancer sites, there are significant excesses observed in farmers and their spouses, including cancers of the prostate and ovary among farmers, and melanoma in the spouses. A major strength of the AHS is the ability to compare risks of cancer among farmers with and without exposure to specific pesticides. To date, the AHS has evaluated over twenty individual pesticides for associations with cancer. Two types of analytic approaches have been used to evaluate these associations. The first is the case-control study, which looks at many exposures and one cancer site. Case-control studies have been conducted for cancers of the breast, colon and rectum, lung and prostate. The second approach is the chemical-specific study, which examines the association between one chemical (or group of chemicals) and multiple cancer sites. Based on these approaches, many positive associations between the use of individual pesticides and specific cancer sites have been observed, many for the first time. Leukemia, non-Hodgkin lymphoma, multiple myeloma, melanoma and cancers of the lung, bladder, rectum, colon, and prostate have all been associated with individual pesticides, many with a positive exposure-response relationship. The following table shows results from analyses of specific chemicals and cancer sites [12-36]. (Table 1).

Although findings to date do not provide conclusive evidence that any pesticide causes a specific cancer, they do suggest that a number of cancer sites might be associated with pesticide exposure and underscore the need for further evaluation. The findings suggest some tentative conclusions about the association between cancer and pesticides overall. First, no individual pesticide appears to be associated with cancers at many sites. Second, most observed associations do not seem to cluster by chemical classification or other grouping of pesticides. A possible exception is that a number of organophosphate insecticides are associated with prostate cancer, especially among participants with a family history of prostate cancer. Third, associations between specific pesticides and some cancers occur in sites that are not elevated overall, (e.g., cancers of the bladder, colon, lung, pancreas and rectum). These observed associations are unlikely to be due to confounding because of the ability to adjust for established and suspected risk factors. Finally, although exposure misclassification might result in an under-estimate of the relative risk in a prospective study, it is unlikely to lead to a false positive association.

It should be noted that, for many chemicals, this study represents the first evaluation of cancer risk in humans, and for most pesticides, these analyses represent the largest study to date. Analyses are currently underway to follow these promising leads by incorporating updated exposure information and additional cancer cases to evaluate whether these associations persist. In the future, mechanistic studies may be undertaken to help in our understanding of these associations.

Future Activities

Based on these results, several future lines of investigation are planned. Nested case-control studies of cancers associated with some pesticides will be developed. The first nested case-control study is being conducted for prostate cancer. This study is designed to evaluate both genetic susceptibilities and potential gene-environment interactions with specific pesticides, (e.g., the organophosphate insecticides).

Other work will take advantage of emerging technologies to understand potential mechanisms of action. Cancer investigations within the AHS have so far focused on exposure to individual pesticides. In the future, it will be important to evaluate combinations of pesticides because they are sometimes applied as mixtures or simultaneously. Mechanistic studies also indicate that agricultural factors other than pesticides may pose a cancer hazard. Engine exhausts, fuels and solvents, welding fumes, organic and inorganic dusts and endotoxins have genotoxic and/or immunotoxic properties that could be involved in cancer etiology [1]. Future and ongoing work will evaluate these and other agricultural exposures, including validation of exposure estimates, when possible. Most evaluations of cancer in the study have focused on the pesticide applicators themselves. Spouses within the study experience exposures more similar to non-farmers or non-applicators than to farmers so results from these evaluations will be more generalizable to the population at large. The AHS has collected residential history information that can be used as part of geographic information systems (GIS) and merged with environmental data to evaluate a number of factors related to agriculture, such as nitrate and other contaminants in drinking water and proximity to commercial animal feeding operations.

The Agricultural Cohort Consortium

The Agricultural Health Study is a large, prospective study that is useful for evaluating associations between agricultural exposures and cancer. However, for some substances, the number of exposed individuals is too small for rigorous analysis, particularly for rarer cancers. A number of other studies around the world have also assembled cohorts of farmers to evaluate diseases associated with agricultural exposures. A Consortium of Agricultural Cohorts has been formed to facilitate research on the health of agricultural populations through pooling of data and collaborative activities. The thirteen cohorts that participated in an initial organizing meeting, hosted by the National Cancer Institute in September 2006 represent 1.3 million individuals with agricultural exposures. These cohorts include populations from the United States, Canada, Norway, France, Korea and New Zealand. Since 2006, other cohorts from around the world have been identified and may participate in selected consortial activities. Study sizes range from a few hundred to several hundred thousand. The amount and detail of information available on exposures and disease vary by study. Pooling of data from these studies may be useful for evaluating risk for rare cancer sites, especially those with the potential for agricultural associations. For example, ovarian cancer has an elevated SIR in the Agricultural Health Study, but it is unlikely that enough cases will accumulate within this study to provide sufficient statistical power to evaluate individual exposures. In such instances, pooling of data across cohorts can be useful. In other situations, the replication of interesting findings from one study may enhance our understanding of observed associations. Finally, the creation of an organizational structure to develop and guide plans for future activities can serve to facilitate collaborative research in the area of agricultural cancer.

Early efforts for cancer research within the Agricultural Cohort Consortium are focusing on pooling data to study rare cancers, such as thyroid cancer. There are, of course, challenges to pooling data from multiple studies. Exposures are almost always assessed differently across studies so decisions about how to harmonize both exposure and disease classifications can be complex. However, such efforts are needed to study rare cancers.

Conclusions

Rigorous evaluation of associations between agricultural exposures and cancer is necessary to inform reasoned policy about reducing exposure to carcinogenic compounds. To provide the most useful information, such evaluations should include detailed exposure assessment and not simply rely upon the designation of “agriculture” or “farmer”. There are many intriguing leads between individual pesticides and specific cancers. These associations should be followed with further evaluation using multiple methods, including classical epidemiological techniques and emerging technologies to explore potential mechanisms of action. Finally, although there is need to expand research in the area of agricultural exposures, there are also many opportunities to capitalize on existing studies. The Agricultural Cohort Consortium represents one such opportunity. The results of such rigorous evaluations will be important, not just for populations traditionally considered "agricultural", but also have larger public health implications for those in the general population with pesticide and other agricultural exposures.

References

1. Cordes, D.; Rea, E., editors. Occupational Medicine: State of the Art Reviews. Vol. Vol. 6. Hanley and Belfus, Inc.; Philadelphia: 1991. Health hazards of farming.
2. Kirkhorn S, Schenker M. Current health effects of agricultural work: respiratory disease, cancer, reproductive effects, musculoskeletal injuries and pesticide-related illness. J Agric Safety Health. 2002; 8:199–214.
3. Blair A, et al. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health. 1992; 8:209–215. [PubMed: 1411362]
4. Alavanja M, et al. The Agricultural Health Study. Environ Health Perspect. 1996; 104:362–369. [PubMed: 8732939]
5. Blair A, et al. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology. 2002; 13:94–99. [PubMed: 11805592]
6. Dosemeci M, et al. A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg. 2002; 46:245–260. [PubMed: 12074034]
7. Coble J, et al. The validation of a pesticide exposure algorithm using biological monitoring results. J Occup Environ Hygiene. 2005; 2:194–201.
8. Curwin B, et al. Pesticide dose estimates for children of Iowa farmers and non-farmers. Environ Res. 2007; 105:307–315. [PubMed: 17659274]
9. Curwin B, et al. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann Occup Hyg. 2007; 51:53–65. [PubMed: 16984946]
10. Bakke B, et al. Exposure to atrazine and selected non-persistent pesticides among corn farmers during a growing season. J Exposure Anal Environ Epidemiol. 2008 In press.
11. Alavanja M, et al. Cancer incidence in the Agricultural Health Study. Scand J Work Environ Health. 2005; 31:39–45. [PubMed: 16190148]
12. Van Bemmel D, et al. S-ethyl-N,N-dipropylthiocarbamate (EPTC) Exposure and Cancer Incidence among Male Pesticide Applicators in the Agricultural Health Study, a Prospective Cohort. Environ Health Perspect. 2008 E-pub ahead of print.
13. Alavanja M, et al. Pesticides and lung cancer risk in the Agricultural Health Study. Am J Epidemiol. 2004; 160:876–885. [PubMed: 15496540]
14. Alavanja M, et al. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study. Am J Epidemiol. 2003; 157:800–814. [PubMed: 12727674]
15. Freeman, L. Beane, et al. Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. Am J Epidemiol. 2005; 162:1070–9. [PubMed: 16236997]
16. Bonner M, et al. Malathion exposure and the incidence of cancer in the Agricultural Health Study. Am J Epidemiol. 2007; 166:1023–34. [PubMed: 17720683]
17. Bonner M, et al. Occupational exposure to carbofuran and the incidence of cancer in the Agricultural Health Study. Environ Health Perspect. 2005; 113:285–289. [PubMed: 15743716]
18. De Roos A, et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect. 2005; 113:49–54. [PubMed: 15626647]
19. Engel L, et al. Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. Am J Epidemiol. 2005; 161:121–135. [PubMed: 15632262]
20. Greenburg D, et al. Cancer incidence among pesticide applicators exposed to captan in the Agricultural Health Study. Cancer Causes and Control. 2008 E-pub ahead of print.
21. Hou L, et al. Pendimethalin exposure and cancer incidence among pesticide applicators. Epidemiology. 2006; 17:1–6. [PubMed: 16357585]
22. Kang D, et al. Cancer incidence among pesticide applicators exposed to trifluralin in the Agricultural Health Study. Environ Res. 2008 E-pub ahead of print.

23. Koutros S, et al. Dichlorvos exposure and human cancer risk: results from the Agricultural Health Study. Cancer Causes and Control. 2007; 19:59–65. [PubMed: 17943454]
24. Lee W, et al. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J National Cancer Institute. 2004; 96:1781–9.
25. Lee W, et al. cancer incidence among pesticide applicators exposed to alachlor in the Agricultural Health Study. Am J Epidemiol. 2004; 159:373–380. [PubMed: 14769641]
26. Lee W, et al. Pesticide use and colorectal cancer risk in the Agricultural Health Study. Int J Cancer. 2007; 121:339–346. [PubMed: 17390374]
27. Lynch S, et al. Cancer incidence among pesticide applicators exposed to cyanazine in the Agricultural Health Study. Environ Health Perspect. 2006; 114:1248–1252. [PubMed: 16882534]
28. Mahajan R, et al. Carbaryl exposure and incidence cancer in the Agricultural Health Study. Int J Cancer. 2007; 121:1799–805. [PubMed: 17534892]
29. Mahajan R, et al. Fonofos exposure and cancer incidence in the Agricultural Health Study. Environ Health Perspect. 2006; 114:1838–1842. [PubMed: 17185272]
30. Mahajan R, et al. Phorate exposure and incidence of cancer in the Agricultural Health Study. Environ Health Perspect. 2006; 114:1205–1209. [PubMed: 16882526]
31. Mozzachio A, et al. Chlorothalonil exposure and cancer incidence among pesticide applicator participants in the Agricultural Health Study. Environ Res. 2008 E-pub ahead of print.
32. Rusiecki J, et al. Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J National Cancer Institute. 2004; 96:1375–1382.
33. Rusiecki J, et al. Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study. Int J Cancer. 2006; 15:3118–23. [PubMed: 16425265]
34. Samanic C, et al. Cancer incidence among applicators exposed to dicamba in the Agricultural Health Study. Environ Health Perspect. 2006; 114:1521–1526. [PubMed: 17035136]
35. Purdue M, et al. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer. 2007; 120:642–9. [PubMed: 17096337]
36. Koutros S, et al. Aromatic amine pesticide use and human cancer risk: Results from the U.S. agricultural health study. Int J Cancer. 2008 E-pub ahead of print.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Pesticides evaluated for associations with cancer in the Agricultural Health Study

Active Ingredient	Cancer Sites Associated (# Exposed Cases)	Reference(s)	Type of Analysis
2,2-dichloroethenyl dimethyl phosphate	Prostate (16)[†]	Alavanja, 2003	Case-control
2,4,5-TP	Breast (19)	Engel, 2005 [††]	Case-control
Alachlor	Lymphohematopoietic (54)	Lee, 2004	Chemical-specific
	Leukemia (20)		
Aldicarb	None observed	Purdue, 2007	Chemical-specific
	Colon (15)	Lee, 2007	Case-control
Aldrin	Colon[**] (23)	Purdue, 2007	Chemical-specific
	Breast (52)	Engel, 2005 [††]	Case-control
Atrazine	None observed	Rusiecki, 2004	Chemical-specific
Butylate	Prostate (44) [†]	Alavanja, 2003	Case-control
Captan	None observed	Greenburg. 2008	Chemical-specific
	Breast (23)	Engel, 2005 [††]	Case-control
Carbaryl	Melanoma (37)	Mahajan, 2007	Chemical-specific
	Lung (15)	Bonner, 2005	Chemical-specific
Chlordane	Rectum (9)	Purdue, 2007	Chemical-specific
	Breast (52)	Engel, 2005 [††]	Case-control
Chlorothalonil	None observed	Mozzachio 2008	Chemical-specific
Chlorpyrifos	Lung (70)	Alavanja, 2004	Case-control
	Lung (73)	Lee, 2004	Chemical-specific
	Brain (14)		
	Rectal (24)		
	Lymphohematopoietic (64)		
	Rectal (41)	Lee, 2007	Case-control
Coumaphos	Prostate (16)[†]	Alavanja, 2003	Case-control
Cyanazine	None observed	Lynch. 2006	Chemical-specific
Diazinon	Lung (28)	Alavanja, 2004	Case-control
	Lung (27)	Beane Freeman, 2005	Chemical-specific
	Leukemia (11)		
Dicamba	Colon (59)	Samanic, 2006	Chemical-specific

Active Ingredient	Cancer Sites Associated (# Exposed Cases)	Reference(s)	Type of Analysis
	Lung (52)		
Dichlorvos	None observed	Koutros, 2008	Chemical-specific
Dieldrin	Lung (10) Breast (16)	Purdue, 2007 Engel, 2005 ††	Chemical-specific Case-control
EPTC	Colon (39) Leukemia (18)	Van Bemmel, 2008	Chemical-specific
Fonofos	Prostate (30) † Prostate (167) † Leukemia (16)	Alavanja, 2003 Mahajan, 2006	Case-control Chemical-specific
Glyphosate	None observed	De Roos, 2005	Chemical-specific
Heptachlor	Leukemia (18) Breast (35)	Purdue, 2007 Engel, 2005	Chemical-specific Case-control
Imazethapyr	Bladder (41) Colon (79)	Koutros, 2008	Chemical-specific
Lindane	Non-Hodgkin lymphoma (13) Breast (29)	Purdue, 2007 Engel, 2005 ††	Chemical-specific Case-control
Malathion	No associations observed Breast (101)	Bonner, 2007 Engel, 2005 ††	Chemical-specific Case-control
Methyl bromide	Prostate (45)	Alavanja, 2003	Case-control
Metolachlor	Lung (54) Lung (46) Prostate** (299)	Alavanja, 2004 Rusiecki 2006	Case-control Chemical-specific
Pendimethalin	Lung (32) Lung (34) Rectal (19)	Alavanja, 2004 Hou, 2006	Case-control Chemical-specific
Permethrin	Prostate (16) †	Alavanja, 2003	Case-control
Phorate	Prostate (43)† None observed	Alavanja, 2003 Mahajan, 2006	Case-control Chemical-specific
Toxaphene	Melanoma (8)	Purdue, 2007	Chemical-specific
Trifluralin	Colon (85)	Kang, 2008	Chemical-specific

* Association defined as significant association in highest exposure category or significant dose-response trend

** Inverse association

† Among those with family history of prostate cancer

†† Association based on husband's ever use of specific pesticide