

## Commentary

## Investing in Prospective Cohorts for Etiologic Study of Occupational Exposures

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*Prospective cohorts have played a major role in understanding the contribution of diet, physical activity, medical conditions, and genes to the development of many diseases, but have not been widely used for occupational exposures. Studies in agriculture are an exception. We draw upon our experience using this design to study agricultural workers to identify conditions that might foster use of prospective cohorts to study other occupational settings.*

*Prospective cohort studies are perceived by many as the strongest epidemiologic design. It allows updating of information on exposure and other factors, collection of biologic samples before disease diagnosis for biomarker studies, assessment of effect modification by genes, lifestyle, and other occupational exposures, and evaluation of a wide range of health outcomes. Increased use of prospective cohorts would be beneficial in identifying hazardous exposures in the workplace. Occupational epidemiologists should seek opportunities to initiate prospective cohorts to investigate high priority, occupational exposures.* Am. J. Ind. Med. 58:113–122, 2015. © 2015 Wiley Periodicals, Inc.

**KEY WORDS:** *prospective cohorts; agricultural exposures; occupational epidemiology*

### INTRODUCTION

For centuries, studies of occupational exposures have provided important information to enhance our understanding of the etiology of many diseases. In the 16th century, Agricola described diseases in miners [Weber, 2002] and in the 18th century, Ramazzini [1713] compiled a review of occupationally-related diseases. Investigations of occupational exposures have continued to modern times and have identified many agents in the workplace that have adverse effects on human health [Baxter et al., 2010]. Among exposures evaluated as possible human carcinogens by the International Agency for Research on Cancer (IARC), Siemiatycki et al., [2004] found that 31% classified as carcinogenic, 42% classified as probably carcinogenic, and 43% classified as possibly carcinogenic were identified largely from studies of exposures in the workplace. Many of

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Accepted 10 October 2014

DOI 10.1002/ajim.22403. Published online in Wiley Online Library  
(wileyonlinelibrary.com).

these exposures also occur in non-occupational settings and have adverse impacts beyond the workplace. Occupational exposures have also been linked with the development of non-malignant diseases of the respiratory, nervous, immune, and cardiovascular systems, as well as adverse reproductive and developmental outcomes [Baxter et al., 2010]. Despite the many established links between occupational exposures and human disease, much remains unknown. For example, the occupational exposures classified as possible or probable human carcinogens have limited information from studies in human populations, underscoring the need for additional investigations [Ward et al., 2010; Blair et al., 2011; Straif, 2012]. Populations at risk for occupational disease have special characteristics that increase the priority for conducting research in the workplace. Exposures among workers are typically at higher levels than those experienced by the general population and workers may be uniquely exposed to some agents. Doll and Peto [1981] noted that occupational cancer (and this presumably applies to other occupational diseases) occurs in relatively small numbers of individuals, but results in relatively large disease risks for working populations, which could be greatly reduced or eliminated with exposure control. Thus, they concluded that “detection of occupational hazards should therefore have a higher priority in any program of cancer prevention than their proportional importance might suggest.” Additionally, in many situations, occupational exposures are not under the control of the worker and thus could be considered involuntary, making them a high priority for investigation and subsequent control.

Although various designs have been used in epidemiologic studies of occupational exposures, the workhorse has been the historical cohort. In this design, work history records are typically obtained from companies, unions, or other organizations to establish a cohort of workers, to obtain information on work tasks, and to characterize occupational exposures. Investigators sometimes attempt to obtain contemporaneous exposure-related measurement data, but such data are typically lacking for much of the time period covered by historical investigations. Disease status (incidence or mortality) is ascertained from time of employment or enrollment in the cohort [Merletti et al., 2005] through company medical records or record linkage (e.g., to cancer and other disease registries or mortality records). Although this design has been extremely fruitful, it has limitations. Identification of a target population of workers with suitable historical records for a study is sometimes not possible. The historical cohort is especially problematic for investigating the incidence of non-cancer diseases and for emerging hazards. It is difficult to obtain biologic samples for genetic and mechanistic analyses, which are major components of modern epidemiologic investigations [Rothman et al., 2012]. Finally, because of the reliance on work history records to establish and characterize the cohort, information is typically

lacking on non-occupational risk factors such as smoking history, alcohol use, diet, and environmental exposures to control for potential confounding and to evaluate effect modification [Miller et al., 2005]. Non-occupational information on the cohort can sometimes be obtained from existing records, but it is often incomplete and sometimes non-randomly missing. Such information can be obtained by interviewing cohort participants or their surrogates [Blair et al., 1998; Silverman et al., 2012], but this can be challenging for a historical cohort due to difficulties in locating living cohort members or appropriate surrogates for those deceased. Moreover, information from surrogates can be limited, e.g., co-workers may know about work practices, but may be less informed about other activities, while spouses or relatives may have limited knowledge of the work environment.

## Prospective Cohorts in Etiologic Research

Prospective cohort studies that obtain information directly from individuals and follow them over time are now widely used in epidemiologic research and offer some advantages over the historical cohort and other epidemiologic designs. Many perceive the prospective cohort as the strongest design in observational epidemiology. Early prospective cohorts were used to study tobacco-related diseases [Dorn, 1959; Doll et al., 2004]; and coronary heart disease, e.g., Dawber and Kannel [1966]; Hames et al. [1971]. Since the 1970s, a number of prospective cohorts have been established to investigate cancer and other chronic diseases, e.g., the Nurses’ Health Study [Belanger et al., 1978], Cooper Center Longitudinal Study [Blair et al., 1989], NIH-AARP Diet and Health Study [Schatzkin et al., 2001], European Prospective Investigation into Cancer and Nutrition Study (EPIC) [Riboli et al., 2002], and the Sister Study ([sisterstudy.nihhs.nih.gov](http://sisterstudy.nihhs.nih.gov); [Weinberg et al., 2007]). Although these prospective studies may have collected some information on jobs and associated occupational exposures and some were defined by specific occupations (e.g., doctors, nurses, or teachers), the investigation of occupational exposures was generally a minor focus [MacDonald et al., 2009]. There are a few exceptions. For example, the Nurses’ Health Study has made important contributions to understanding the potential carcinogenic and other health effects of shift work [Schernhammer et al., 2001; Whelan et al., 2007; Lawson et al., 2012] and the Shanghai Women’s Health Study [Ji et al., 2008; Pronk et al., 2009], EPIC study [Neasham et al., 2011], and Sister Study [Ekenga et al., 2014] have evaluated cancer and occupational exposures.

An early prospective cohort developed to focus specifically on occupational exposures was the study of construction workers in Sweden initiated in the 1960s

[Järvholt and Silverman, 2003; Bergdahl et al., 2004] and a few prospective cohorts have focused on agricultural exposures [Alavanja et al., 1996; Merchant et al., 2002; Lebailly et al., 2006; Stoecklin-Marois et al., 2011; Pahwa et al., 2012]. Recently, prospective cohorts have been established to study health outcomes associated with occupational exposures among disaster and emergency response workers, e.g., World Trade Center Rescue and Recovery Workers [Jordan et al., 2011; Wisnivesky et al., 2011] and the GuLF Study (Gulf Long-term Follow-up Study) (<https://gulfstudy.nih.gov/>).

Because the historical cohort design has been so widely used for the study of occupational diseases [Ward et al., 2003; Straif, 2008; Ward et al., 2010] and because of its similarity to the prospective design, a more widespread use of the prospective cohort might have been expected in etiologic studies of occupational exposures. Prospective studies offer several advantages over the historical design, including the opportunity to collect information on job changes and non-occupational factors periodically and to collect biologic samples. Periodic collection of information on work histories and occupational exposures would enhance the quality of occupational exposure assessment, which would help characterize risk and to disentangle mixed exposures [Cordier and Stewart, 2005]. Updating of non-occupational factors that change over time improves assessment of confounding and interaction. Periodic contact also provides a mechanism for communicating study results directly to affected individuals and facilitates participatory research [Ward et al., 2003].

The relatively infrequent use of prospective cohorts in occupational research is striking because of the widespread use of a similar design, e.g., the historical cohort design in studies of the workplace. It is worrisome because of the tendency for recent reviews of the epidemiologic literature to only include findings from prospective cohort designs. Our computer search of the epidemiologic literature from January to March, 2013 on the terms “review” and “meta-analysis” found 34 papers in peer-reviewed journals on a variety of health outcomes that only included findings from prospective cohort studies. The message from this search seems clear. Reviews and meta-analyses that entirely ignore historical cohort, case-control, and cross-sectional studies are able to pass peer-review and enter the scientific literature. Although none of the reviews uncovered in this search focused on occupational issues, it is not obvious that occupational studies would be less affected by this trend, since findings from prospective cohorts appear to be more readily accepted by the scientific community. Continued reliance upon other designs in occupational investigations could have serious consequences for building a case for preventive actions regarding occupational hazards if these designs are judged unworthy of consideration in hazard or risk assessment. We do not believe that results from well-

executed case-control or historical cohort studies should be discounted, but worry that this could happen and we advocate expanded use of the prospective design in the occupational arena.

## **Factors Influencing the Launch of Prospective Studies on Occupational Exposures**

Because prospective cohort studies require a sizable and long-term commitment of resources and investigator effort, a strong rationale is needed. The number of active prospective cohort studies on a variety of health issues indicates that the scientific community is convinced that studies with this design are worth these commitments. Because occupational prospective studies have been successfully initiated among agricultural workers, a review of the background and rationale for launching one of these studies, the Agricultural Health Study (AHS), provides insight into the conditions that favored such studies and the problems that must be overcome to use this design for other occupational exposures.

## **Background in Agricultural Exposures and Health**

Agriculture-related exposures and health risks have long been of interest to the scientific community and to the general public. In the late 1970s and early 1980s, this interest was further stimulated by a number of scientific conferences (the International Symposium on Health and Safety in Agriculture Saskatoon, SK, Canada in 1985 [Dosman and Cockcroft, 1989]; the US Surgeon General’s Conference on Agricultural Safety and Health in 1991 [NIOSH, 1992]; and a conference on migrant worker health in the 1990s [Zahm and Blair, 1993]). In the 1990s, the US National Institute for Occupational Safety and Health (NIOSH) established agricultural safety and health research centers to further stimulate research in the agricultural arena (<http://www.cdc.gov/niosh/agctrhom.html>). This focus and effort in agriculture has continued through research at many institutions and by the development of a consortium of historical and prospective agricultural cohorts (AGRICOH) to provide a mechanism for data pooling to further evaluate hazards in agriculture [Leon et al., 2011]. Although the potential for a variety of adverse health effects from agricultural exposures is clearly recognized, the evidence is conclusive for relatively few exposures. Clarification of possible disease risks from these exposures is important for the health of farm populations and also for non-farm populations who may also have contact with agricultural exposures, such as pesticides, that occur in non-agricultural settings.

## Suitability of Farmers for Prospective Studies

Farmers have several characteristics that make them an excellent group for an occupational prospective study. Although farming operations differ, they share many common exposures and potential hazards, e.g., pesticides, diesel and gasoline engine exhausts, dusts, fuels and oils, noise, biologic exposures and zoonotic agents. Therefore, farmers with different types of farms can be combined to study common exposures. Farmers typically function as both management and labor for farm operation [Blair et al., 1991, 1992; Blair and Zahm, 1991]. Because of these dual responsibilities, they tend to be very knowledgeable about the materials, chemicals, and equipment used on the farm. This circumstance may not occur for all occupations, but would be relevant for small businesses based on skilled trades (e.g., auto repair, plumbing, home building or remodeling, and lawn and garden maintenance). Because farmers serve as management and labor, they can provide detailed information on exposures. Agricultural exposures also have relevance to non-farm populations that may be exposed to pesticides, diesel and gasoline engine exhausts, and various other chemicals. Many farms are family operations with spouses and children engaged in farm work who can provide information regarding farm operations and exposures [Brown et al., 1991]. Family members who are not actively engaged in farm activities may represent a relatively highly exposed bystander population because they, in a sense, "live at the factory."

A key condition in establishing a cohort for a prospective study is an efficient and effective enrollment procedure. The AHS identified farmers in conjunction with pesticide licensing and education activities at county agricultural extension service offices. A critical initial challenge for future prospective studies will be to identify efficient ways to enroll workers with occupational exposures of interest.

## Institutional Support for the AHS

The AHS was initiated and designed by investigators from the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the Environmental Protection Agency (EPA). NIOSH joined the effort soon after the start-up phase. The University of Iowa, a contractor to NIH for the conduct of the AHS, also contributed to the design and development of the study from its earliest stages. These five institutions brought significant research expertise and resources to the study of agricultural exposures and health.

For example, NCI had pursued a two-decade long stepwise effort on agricultural exposures and cancer, including ecologic studies of the geographic patterns of cancer mortality in relation

to information from agricultural censuses [Blair and Fraumeni, 1978; Cantor and Fraumeni, 1980], death certificate-based case-control studies [Blair et al., 1979, 1980, 1981, 1985, 1989; Cantor, 1982; Cantor and Blair, 1984; Dosemeci et al., 1994] and case-control studies of incident lymphatic and hematopoietic cancers [Hoar et al., 1985, 1986; Blair et al., 1987; Zahm et al., 1988, 1989, 1990; Brown et al., 1990, 1993; Cantor et al., 1992; Zahm and Blair, 1992, 1993A, 1993B]. NIEHS brought significant research expertise in the epidemiology of non-cancer outcomes (e.g., reproductive, neurologic) to the AHS. The U.S. EPA, which has regulatory responsibility for agricultural and non-agricultural pesticide use in the United States, contributed expertise in pesticide toxicology and exposure assessment, while NIOSH brought expertise in conducting occupational exposure field studies in agriculture. EPA's knowledge and use of the Pesticide Handlers Exposure Database [PHED, 1995] was a valuable resource for developing pesticide exposure assessment methodology. The University of Iowa brought to the effort a long-standing research program on agricultural issues, including studies of cancer and other outcomes among farm populations [Burmeister, 1981, 1990; Burmeister et al., 1982A, 1983; Burmeister and Morgan, 1982; Donham, 1985; Donham et al., 1987, 1995]. The prior work from these institutions provided the impetus and a foundation for a prospective study on agricultural exposures.

## Influential Support

Although there was substantial experience in the study of agricultural exposures among investigators from the institutions involved in the design and initiation of the AHS, the launch of a long-term, resource-intensive investigation sometimes requires a specific spark. For the AHS, this came as a recommendation from the NCI Board of Scientific Counselors who suggested that the occupational program consider prospective investigations on important issues in occupational cancer. NCI identified several possible candidate occupational groups/exposures and selected agriculture as the most promising for a prospective cohort. A special working group of occupational cancer experts was assembled to provide further advice regarding the review/selection process and agreed that agriculture was a good candidate for a prospective study. Support from these two external groups was critical to launching the AHS.

## Prospective Studies: Impediments and Advantages

Prospective designs have cost and time factors that weigh heavily on their initiation. To have adequate power, cohort studies, whether historical or prospective, must be large compared to the largest case-control studies for even relatively common outcomes. Start-up costs for a prospective

cohort to interview a large number of participants, to assemble records, and to collect biologic specimens are sizable and for most chronic diseases, a follow-up of many years is required before sufficient disease events accrue to provide adequate power for useful analyses. Thus, the payoff for prospective studies is often slow compared to other designs; however, in the long run, prospective studies are cost-effective and collect information on important risk factors for many health outcomes prior to disease onset, advantages that reduce potential case bias effects and offer the opportunity to evaluate hypotheses on important new public health issues often with little additional cost.

The AHS has demonstrated the usefulness of a prospective cohort design for etiologic investigations on occupational exposures through many new findings on agricultural exposures and various chronic diseases and health effects. Because of the absence of non-cancer disease registries in the United States, many of the health outcomes for which adverse effects have been linked to agricultural exposures could not have been studied using another design. For example, pesticides have been associated with retinal degeneration [Kamel et al., 2000], non-malignant respiratory disease [Hoppin et al., 2006; Hoppin et al., 2014], thyroid disease [Goldner et al., 2010], depression [Beseler et al., 2006], diabetes [Montgomery et al., 2008; Starling et al., 2014], Parkinson's disease [Tanner et al., 2011; Goldman et al., 2012], and amyotrophic lateral sclerosis [Kamel et al., 2012]. Exposure to solvents was also studied in relation to fertility [Sallmén et al., 2006]. Findings for pesticides and other agricultural exposures and cancer include several aspects of prostate cancer (family history, aggressive prostate cancer, genetic polymorphisms) [Alavanja et al., 2003; Koutros et al., 2011, 2013], contact with farm animals [Beane et al., 2012], monoclonal gammopathy of undetermined significance [Landgren et al., 2009], telomere length [Hou et al., 2013], and childhood cancer among children of pesticide applicators [Flower et al., 2004]. Many individual pesticides have been evaluated for cancer risk in human studies, some for the first time in the AHS, including atrazine [Beane et al., 2011], glyphosate [De Roos et al., 2005], diazinon [Beane et al., 2005], pendimethalin [Hou et al., 2006], metolachlor [Rusiecki et al., 2006], dicamba [Samanic et al., 2006], fonofos [Mahajan et al., 2006], organochlorine pesticides [Purdue et al., 2007], malathion [Bonner et al., 2007], dichlorvos [Koutros et al., 2008], permethrin [Rusiecki et al., 2009], metribuzin [Delancey et al., 2009], coumaphos [Christensen et al., 2010], and terbufos [Bonner et al., 2010].

## Candidates for Future Prospective Studies in Occupational Health

As with the AHS, future prospective studies on occupational exposures will require a literature sufficient

to indicate the potential for important occupational hazards and convincing evidence that these questions are unlikely to be efficiently addressed by other, less expensive designs. There certainly is no shortage of such occupational issues [Ward et al., 2010]. Practical issues, such as availability of an efficient enrollment approach, likelihood of continued participation, availability for long-term tracking and follow-up, and opportunities for future data collection need to be addressed in establishing a prospective cohort. Relevance of occupational exposures to the general population, although not required, would strengthen the rationale for committing the needed resources. A number of exposures or occupations might meet these conditions. Recent reviews of human carcinogens [Baan et al., 2009; Straif et al., 2009; Ward et al., 2010; Cogliano et al., 2011] list a number of occupational exposures and occupations that are possible candidates for prospective studies. No doubt a similar list could be prepared for non-malignant outcomes. Organic solvents, engineered nanomaterials, diesel exhausts from new technology engines, and paints are examples of exposures where prospective investigations may be needed in the future.

## Organic Solvents

Exposure to different types of organic solvents is widespread among workers and the general public and use patterns have changed over time. With changing patterns of use and frequent substitutions of one solvent for another, prospective studies with periodic data collection offer an advantage over the exposure reconstruction required for historical cohorts. Several adverse health outcomes have been clearly linked with some organic solvents, e.g., cancer with benzene and trichloroethylene. Other solvents are suspected of having links with cancer, as well as neurologic conditions and adverse reproductive outcomes. Widespread use of organic solvents in the chemical, metal, plastics, service, and electronic industries may offer settings for establishing a prospective cohort.

## Engineered Nanomaterials

Development and use of engineered nanomaterials is a rapidly growing industry. Many engineered nanomaterials are composed of chemicals with known health effects, while others are relatively novel materials. Because of their extremely small size and distinctive morphology they may act differently within the body than larger particles and may result in unique exposure pathways and disease consequences. Moreover, the potential for exposure to engineered nanomaterials will likely grow in the general population as uses for these materials increases in consumer products and medical devices. Because nanotechnology is an emerging

industry, a historical cohort would probably not be possible for decades. Now is the time to assemble a registry of exposure individuals that could be used for a prospective cohort study that could be used to evaluate of any potential emerging hazards from these materials instead of waiting to establish a historical cohort and wishing we had acted sooner [Schulte et al., 2011; Riediker et al., 2012].

## Exhaust from New Technology Diesel Engines

Recent studies [Attfield et al., 2012; Silverman et al., 2012] that provided critical new evidence for the classification of diesel exhaust as a human carcinogen [Benbrahim-Tallaa et al., 2012] evaluated exposures from an older engine technology. Although many of these older engines will remain in use for decades, they will eventually be replaced with newer, cleaner-burning engines designed to reduce exhaust exposures. There is a need to characterize the potential health consequences from the switch to new diesel engines among occupational and non-occupational populations. A prospective cohort design would seem a reasonable choice when feasible.

## Painters

Studies of painters have noted excesses of lung cancer [Guha et al., 2010] and IARC has classified occupational exposure as a painter as a human carcinogen [IARC, 2010]. These studies, however, have largely involved exposure to older paint formulations. The composition of paints and other coatings have changed over time and to date there have been no detailed evaluations of risks for the various compositions. New investigations should evaluate risks from paints with lower-toxicity solvents, neutralizing agents (e.g., amines), and biocides, and from other coatings including polyurethanes and epoxies. In addition, cancers other than lung (e.g., bladder) deserve further evaluation.

## CONCLUSIONS

The prospective cohort study has become the design of choice in observational epidemiology, yet it is not as widely applied in occupational epidemiology. Prospective cohort investigations in agriculture have clearly demonstrated the value of this design in the occupational arena. Given the strengths and long-term benefits of the prospective cohort design, we urge occupational epidemiologists and funding institutions to give due consideration to the prospective cohort, which over time may represent an efficient approach to answer critical health questions regarding occupational exposures.

## ACKNOWLEDGMENTS

Authors were supported by funding from the Intramural Research Program of the NIH (National Cancer Institute and National Institute of Environmental Health Sciences), the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, and the U.S. Environmental Protection Agency through its Office of Research and Development.

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Conflict of Interest: The authors report no conflict of interest.

Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health. The United States Environmental Protection Agency through its Office of Research and Development collaborated in the research described here. It has been subjected to Agency review and approved for publication. Disclosure Statement: The authors report no conflicts of interests.