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APPLICATIONS OF OCCUPATIONAL EPIDEMIOLOGY

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Occupational epidemiology is the study of the distribution and determinants of work-related disease and injuries in the workplace. Occupational epidemiologic studies have become an important and integral part of occupational health. Occupational epidemiology has grown rapidly since the late 1970s. Recent developments in occupational epidemiology include the integration of epidemiologic courses into occupational health training, methodologic development, and access to computers and statistical software packages. A primary goal of occupational epidemiology is to determine what kinds of exposures in the workplace are associated with certain diseases or injuries in order to present the best disease-prevention strategy.

Employment in the United States is projected to increase from 121.1 million in 1992 to 147.5 million in 2005, according to a projection by the Bureau of Labor Statistics.[31] In 1993, 6.7 million injuries and illnesses were reported in private industry workplaces, resulting in a rate of 8.5 cases for every 100 full-time workers.[38] Costs of occupational injuries and illnesses in 1992 were estimated to be $173.9 billion, or 3% of the gross domestic product.[19] These changes in occupational workforces and health statistics have recently led to increased attention to occupational health in the United States.

The occupational epidemiologic approach to a particular disease is intended to identify high-risk subgroups within the population and determine the effectiveness of subsequent preventive measures. In principle, the epidemiologic study of work-related disease does not differ from other aspects of epidemiologic research. This chapter reviews the general application of occupational epidemiology and illustrates some studies reported in the literature. It is intended to assist in the practical application of the epidemiologic approach.

USE OF EPIDEMIOLOGY IN OCCUPATIONAL HEALTH

It was the science of epidemiology that demonstrated the serious health risks associated with asbestos, radiation, coal dusts, and other occupational exposures. The rapid growth in the use of potentially hazardous materials has been accompanied by numerous observations of serious health effects in humans as a result of occupational exposures. An example of early occupational epidemiology came from the observations in 1879 of an increased occurrence of lung cancer among miners in Schneeberg.[11] Some decades later an excess of bladder cancer among German aniline workers was reported.[26] An example of modern epidemiologic study is workers at plastic manufacturing plants who handled the gas vinyl chlorine and were discovered in 1974 to be developing hepatic angiosarcoma, an unusual cancer.[39] At about the same time, infertility and an extreme decrease in spermatogenesis were discovered in workers at a California plant producing dibromochloropropane.[41] Some advances have occurred in improving the work environment and avoiding dangerously uncontrolled industrial plant emissions. However, there are still many reported occupational diseases and injuries that could be prevented in the workplace.

Epidemiologic principles can be readily applied to occupational studies. Occupational studies are designed according to the study objectives. In general, there are three major types of epidemiologic studies: descriptive, analytic, and experimental.[28] Most studies in occupational epidemiology are analytic rather than descriptive.

Descriptive studies are used to characterize person, place, and time. What are the age, sex, race, occupation, industry, socioeconomic status, and other personal characteristics of people who get a particular disease? Where does the disease occur? When does the disease occur? Does temporal variation or seasonal fluctuation exist?

Analytic studies determine the etiologic factors associated with a disease by calculating estimates of risk. What exposures do people with the disease have in common? What is the degree of the increased risk by exposure? Analytic methods are available to control for known confounders, but unknown ones are free to distort risk estimates.

Experimental studies involve a search for strategies to alter the natural history of disease. Examples are intervention trials to reduce risk factors, screening studies aimed at identifying the early stages of disease, and clinical trials of different treatment modalities to improve prognosis. Experimental studies have the advantage of randomization, a procedure that distributes both known and unknown confounders equally between the test and control groups.[23]

Occupational epidemiologic studies include observational studies and experimental studies. Observational studies are the most common. The major types of observational studies in epidemiology are the cohort, case-control, and cross-sectional designs. Other types of study designs are ecologic studies, meta-analysis, occupational surveillance, and the recently developed molecular epidemiologic studies.

Occupational epidemiology has been used for testing specific hypotheses. The specific hypothesis means in principle that "a causes b" can be tested through either a follow-up or a case-control study.[13] If the disease is rare, a case-control study is appropriate. If the exposure is rare, a follow-up study is more efficient. If both the exposure and the disease are common, both designs are feasible, and the decision depends on the availability of data, possibility of tracing records, financial resources, length of study periods, and other factors. Methods of study design and measure are described in the next two chapters.

For establishing causal relationships, several criteria have been proposed to evaluate whether a positive association in epidemiologic studies indicates causality. The most important criteria are strength, consistency, biologic gradient, biologic plausibility, and temporality.[10] The strength of an association is the magnitude of the relative risk in the exposed group compared to that of the control group. Consistency of an association is the extent to which it is reported from multiple studies conducted. The biologic gradient of an association is its dose-response validity. The biologic plausibility of the study is based on the assessment that it makes sense in light of what is known about the mechanism of production of the adverse effect. Temporality of the study is a test on the conclusion or observation that the cause preceded the effect in time. Fulfillment of some of the criteria may occur when the association is due to chance or bias. If most of the criteria are met, the likelihood of an association being causal rather than due to chance is high.

TYPES OF STUDIES AND EXAMPLES

Various types of occupational epidemiologic studies are described below with examples.

Cohort Studies

A cohort study is the follow-up (prospective) study in which a group or groups of individuals are defined on the basis or absence of exposure to a suspected risk factor for a disease over time. The disease rate among those exposed to a particular factor is compared with the rate among the nonexposed in the cohort to assess if an association exists between the study factor and disease.

Cohort studies are useful and effective in occupational epidemiology. Occupational cohort studies can be carried out from different approaches, including (1) prospective cohort morbidity and mortality studies and (2) retrospective cohort morbidity and mortality studies. For the prospective cohort study design, rates of disease can be calculated in both the exposed and unexposed groups for a direct measure of the absolute and relative risk. For the retrospective cohort study design, a long time is not required to complete the study because all events (both the exposure and the disease) have already taken place. Occupational cohort studies are usually mortality studies, because records of cause of death are generally more accessible and less biased than the cause of disease records. The central and unique element in occupational cohort studies is the individual work history with detailed exposure information. However, the cohort study design has some limitations: (1) it is inefficient in the evaluation of rare diseases, unless the attributable-risk percent is high; (2) it is expensive and time-consuming (long follow-up of subjects); (3) large numbers of subjects required; (4) the possibility exists of changes in criteria and methods over time; (5) subjects can be lost over time; and (6) administrative problems such as loss of staff and loss of funding occur.

Example 1. Prospective Cohort Mortality Study. Mortality from lung cancer was studied among a large industrial cohort of 26,501 workers who were exposed to formaldehyde.[4] The workers were first employed in 10 plants before January 1, 1966, and were traced to January 1, 1980, to determine vital status. The plant produced a variety of products, including formaldehyde, formaldehyde resins and molding compounds, molded plastic products, decorative laminates, and plywood. Historical exposures to formaldehyde by job, work area, plant, and calendar time were estimated using available monitoring data, and current walk-through surveys were conducted for exposure estimation. The relative risk for lung cancer 20 or more years after first exposure did not rise with increasing exposure to formaldehyde. The lack of a clear exposure-response relationship between lung cancer and formaldehyde exposure in this study is consistent with other reports.[5,33] Mortality from lung cancer was more strongly associated with exposure to other substances, including phenol, melamine, urea, and wood dust than with exposure to formaldehyde. Workers exposed to formaldehyde but not the other substances did not experience an excess mortality from lung cancer. The authors suggested that exposure to phenol, melamine, urea, wood dust, or other exposures may play a more primary role in the development of lung cancer and this association should be further studied in workers involved with resin and molding compound operations.

Example 2. Prospective Cohort Morbidity Study. A four-year longitudinal study conducted in 1972–1976 was designed to evaluate respiratory effects associated with exposure to toluene diisocyanate.[40] The study began with 111 shift workers who were exposed at a polyurethane foam manufacturing plant; 48 of the subjects were still working at the plant on the first Monday of November 1976. Pulmonary function tests including the first second of expiration (FEV_1) were administered to all workers. The workers were divided into three exposure groups; low (< 0.002 ppm), medium (0.002–0.0034 ppm), and high (> 0.0035 ppm). The cumulative exposure of each worker was calculated from the sum of the products of the time spent at the usual job. The cumulative exposure was then divided by the sum of the months spent in the usual job to establish a usual exposure level (in ppm) for each worker during the study period. The decline in FEV_1 (60 ml/year) observed in the high-exposure group exceeded the annual decrement observed in longitudinal studies of normal populations that have demonstrated expected annual declines of 32–47 ml FEV_1. This finding indicates that chronic exposure to levels of toluene diisocyanate greater than 0.0035 ppm results in greater pulmonary function loss than expected.

Case-Control Studies

Case-control studies, also known as retrospective studies, follow a paradigm that proceeds from effect to cause.[30] In a case-control study, individuals with disease (the cases) are selected for comparisons with individuals without the disease (the controls). Cases and controls are compared with respect to exposures associated with the disease under study.

Case-control studies may be preferred if either of the following scenarios exists: (1) the disease of interest is relatively rare and would require a large cohort for follow-up or (2) several occupations or substances may be associated with the disease of interest.

Case-control studies require the exposure to be reasonably common for the study design to be effective. However, some case-control studies might involve few exposed individuals and would not otherwise provide informative data on the epidemiologic problem. Specific individual exposures can be relatively rare from the viewpoint of the general population, but this problem can be overcome by optimizing the particular population for the study.

The application of the case-control approach to studying occupational factors associated with disease is limited primarily by the difficulty in determining the precise nature and extent of past exposures on the basis of an interview. This tends to lead to the use of broadly defined job or industry categories (e.g., usual employment in the leather industry), which dilutes the true risk by including individuals with widely disparate histories of occupational exposures to specific chemicals. Other limitations of case-control study include (1) inefficiency in evaluating rare exposures unless the study is very large or the exposure is common among those with the disease, (2) inability to directly compute incidence rates of disease in exposed and nonexposed individuals, (3) difficulty in establishing the temporal relationship between exposure and disease, and (4) selection and recall bias.

The various sources of systematic error in case-control studies can be referred to as the validity issues. Axelson[3] discussed the various aspects of validity with reference to (1) the possible role of exposure status in the selection of cases and controls, (2) difficulties in obtaining adequate information on exposure among cases and controls, (3) the possible relation of the control entities to one-another (when using persons with diagnoses other than the disease in question) to the exposure, and (4) the effects of confounding factors.

Example 1. A bladder cancer study was conducted to estimate the risk of bladder cancer associated with occupational exposures in Boston.[8] All new cases of bladder cancer were identified in the defined geographic area during an 18-month period. Control groups were selected from local residents ages 20 to 89. Interviews were conducted to obtain information on occupational history and other factors. For each job held longer than 6 months, demographic variables, nature of the employer's industry, job title, time interval on the job, and specific duties performed were obtained. Relative risks were computed and controlled for age and smoking. The relative risk of bladder cancer among men employed in the leather product industry was 2.25 (95% CI = 1.46–3.46). Among men, excess risk of lower urinary tract cancer also was found in several occupational categories where they had been suspected as a priori: rubber-foreman, leather-foreman, painter, and dyestuffs-laborer.

Example 2. A study on the association between pancreatic cancer and occupational exposures was conducted in Finland to identify occupational risk factors.[16] Pancreatic cancer is a highly fatal malignancy without a known cause. The Finnish Cancer Register was used to identify 1,419 patients with primary exocrinic pancreatic cancer diagnosed between 1984–1987, at the age of 40–74, and who died by April 1, 1990. The primary controls were 2,510 deceased subjects who were not known to have significant occupational risk factors. For the final study groups, the occupational exposure histories for 595 incident cases of primary exocrinic cancer of the pancreas and 1,622 controls were constructed. The study found elevated odds ratios for ionizing radiation exposure (OR = 4.3, 95% CI = 1.6–11.4) and inorganic dust containing crystalline silica exposure (OR = 2.0, 95% CI = 1.2–3.5).

Example 3. A case-control study of cancer of the larynx was conducted within a cohort of automobile workers exposed to metal working fluids.[9] Study subjects consisted of 108 cases of laryngeal cancer and 538 controls. Cases were defined as all cohort members with laryngeal cancer detected prior to January 1, 1990, in the metropolitan Detroit and Michigan state cancer registries. Controls were selected from the cohort by incidence density sampling. A risk set was defined for each case and consisted of all subjects at risk of laryngeal cancer at the age of the death (or diagnosis) of the case. Within each risk set, five controls were randomly selected and matched by year of birth, plant, race, and gender. Based on a retrospective exposure assessment, lifetime exposures to straight and soluble metal working fluids, grinding particulate, biocides, selected metals, sulfur, and chlorine were examined. Results suggest that straight mineral oils are associated with almost a twofold excess in laryngeal cancer risk. This finding is consistent with several previous reports in the literature. When categorized exposure variables were examined, the odds ratio increased with increasing exposure, showing evidence of a dose-response relationship: in the highest category of straight metal fluid exposure, > 0.5 mg/m^3 years, the odds ratio was 2.23 (95% CI = 1.25–3.98).

Cross-Sectional Studies

Cross-sectional studies examine the relationships between disease and other variables of interest as they exist in a defined population at one particular point in time.[18] This study design is often called a survey or prevalence study. The cross-sectional designs are usually descriptive prevalence studies, using random or probability sampling procedures to select subjects. Cross-sectional studies are especially suited for inquiring into subtle, perhaps even subclinical health effects for which records are unlikely to exist. Cross-sectional studies are essentially prevalence studies, and the relationship between the health effects and time cannot be readily explored. The prevalence of the health effect is compared among subgroups with various occupational exposures, ages, smoking or other medical histories.

Cross-sectional studies are useful for hypothesis generation and health services planning if done by random sampling. If the information was not collected by a random sampling, the estimates of the prevalence of a disease or of an association between a factor and a disease are of little value, since they are not representative of a study base or source population and are subject to many biases. Prevalence studies are considerably less expensive than cohort studies, because it is possible to evaluate the disease prevalence at only one point in time rather than continually searching for incident cases over an extended period. However, in a prevalence survey, it is difficult to ascertain at what age disease first occurred, and it is therefore difficult to determine which exposures preceded the development of disease.

Although cross-sectional designs can sometimes provide etiologic information, the prevalence rate is not ideal for measuring morbidity because of the composite nature of the prevalence.[13] An etiologic cross-sectional study is meaningful only if a close time-relation exists between exposure and morbidity. Diseases of short duration are not good candidates for cross-sectional designs because they, on average, are likely to be missed; conversely, long-duration diseases are usually overrepresented in cross-sectional studies. In occupational settings, cross-sectional studies are likely to include information only on currently employed individuals, thereby missing retired employees and persons who quit due to illness that may be related to an exposure under study.[7]

Example 1. The National Health Interview Survey, a major data collection program administered by the National Center for Health Statistics, was mandated by the National Health Survey Act of 1956 to provide for a continuing survey to collect information on illness and disability in the United States. In 1988, the survey contained a special section called the Occupational Health Supplement,[37] whose goal was to obtain detailed information on respondent work-related health problems, workplace injuries, and smoking status. Of 42,487 respondents, 1,785 white men indicated that they had work experience in the construction industry. The prevalence rate of asthma per 1,000 construction workers was 19.6.[34]

Example 2. A cross-sectional survey of farmers found evidence of significant associations between self-reported asthma and the use of carbamate insecticides, according to a respiratory health survey on 1,939 male farmers in 17 municipalities in

Saskatchewan, Canada.[29] Farmers were defined as including every male farmland taxpayer or farm worker in each of the 17 rural municipalities studied. Of 2,375 farmers visited, 1,939 participated in the study, and 83 of the participants (4.3%) were reported to be asthmatics. Interestingly, a significant association with asthma was observed in the use of carbamate insecticides. Of the 83 asthmatics, 32 (38.6%) reported having used carbamate insecticides versus 464 (25.1%) of the 1,856 nonasthmatics. The prevalence odds ratio was 1.9 (95% CI = 1.2–3.0). These findings raised the possibility that exposure to agriculture chemicals could be related to lung dysfunction in exposed farmers.

Ecologic Studies

Ecologic studies provide a crude way of exploring associations between occupation or environment and disease. These studies are considered to be hypothesis-generating rather than hypothesis-testing. Disease rates in various groups defined by specific geographic areas are compared. Several major reservations exist regarding the use of ecologic studies in occupational epidemiology. In some instances, they may provide a reasonable and inexpensive way of generating hypotheses. Alternatively, ecologic studies are limited by the use of proxy data for exposure and disease and by the unavailability of data necessary to control confounding factors.[27] The general problem of inappropriate inferences from ecologic data has been referred to as the ecologic fallacy.[24] Other problems with ecologic studies are related to difficulty in selecting groups of proper size. Groups that are too small will have few cases and unstable rates for the disease in question, or they will be affected by migration.

Example. The National Institute for Occupational Safety and Health published the Work-Related Lung Disease Surveillance Report in 1994.[36] One section of the report presented maps showing the mortality rate for asbestos in the United States for 1989–1990. The maps showed the highest mortality rates for asbestosis in the Northeast, Southeast, and West coasts, locations where the shipbuilding industry was located. A case-control study of lung cancer in coastal Georgia[6] revealed a logical and confirmed association between shipbuilding and lung cancer, possibly as a result of asbestos exposure.

Meta-Analysis

Meta-analysis, an analytic method that has been developed recently, is the process of pooling data from multiple studies that can be used to draw conclusions about therapeutic effectiveness or to plan new studies.[17] The final product has both quantitative and qualitative elements; it takes into account the numerical results and sample sizes of individual studies as well as quality of the data, extent of bias, and strength of the study design. Meta-analysis is a systematic review strategy for addressing research questions that are especially useful when results from several studies disagree with regard to the magnitude or direction of effect. Meta-analysis can be applied to occupational studies with divergent findings.

Example. Meta-analysis of studies on lung cancer among silicotics is reported.[32] In the literature, the association between silicosis and lung cancer has been controversial. The studies among silicotics tend to demonstrate an excess risk of lung cancer, but these studies have been criticized because of possible selection and confounding biases. Data from 29 studies were abstracted. Several of the studies suffered from biases due to competing risks of different cause of death. After adjusting for competing risks, all 29 studies demonstrated lung cancer relative risk estimates to be greater than one. The polled relative risk for the studies combined was 2.2 (95% CI = 2.1–2.4). The results of this meta-analysis demonstrate that increased risks of lung cancer exist for persons diagnosed with silicosis. The authors conclude that the association between silicosis and lung cancer is causal, either due to silicosis itself or due to a direct effect of the underlying exposure to silica.

Epidemiologic Surveillance for Occupational Disease

Occupational surveillance is the collection of relevant data, analysis, and dissemination for the purpose of preventing disease and injury in the workplace. Occupational surveillance data are critical for guiding public policy, planning program objectives, and setting research priorities. Surveillance data also can contribute to more efficient targeting of prevention programs for specific populations and subsequent evaluation of program effectiveness. Dissemination of surveillance data can increase public health awareness among occupational health professionals.

Surveillance for occupational disease should be conducted routinely through the linkage of large data systems containing occupational history and health outcomes. Epidemiologic evaluation of employee health status is becoming an increasingly important component of occupational health objectives, such as estimating baseline rates of morbidity and mortality, providing assistance in the design and interpretation of special studies, and affording prompt response to health-related injuries and participation in health-related programs.[21] NIOSH has undertaken new major initiatives in occupational health surveillance and has developed various epidemiologic occupational surveillance programs. State and local health departments have expanded their capacity to perform surveillance activity and have demonstrated the utility of new surveillance methods. The most universal database for the purpose of occupational surveillance is death certificates that contain the decedent's usual occupation and allow the calculation of proportionate mortality ratios for specific occupational or industrial groups.

Example 1. The National Center for Health Statistics has coded all conditions listed on death certificates since 1968, and the usual occupation and industry of each decedent is available for 25 states since 1985. NIOSH's 1994 Work-Related Lung Disease Surveillance Report,[36] based on mortality data from the National Center for Health Statistics and morbidity data from various sources, showed that the proportionate mortality ratio for coal workers' pneumoconiosis was 100:9 for mining machine operators during 1985–1990. For work-related injury surveillance, NIOSH collected and automated death certificates from 52 vital statistics reporting units in the 50 states, New York City, and the District of Columbia for workers at least 16 years old who died as a result of a work-related injury. This surveillance system is called the National Traumatic Occupational Fatalities surveillance.[35] From 1980–1989, 63,589 workers died from injuries sustained while working. The average annual fatality rate per 100,000 civilian workers decreased from 8.9 in 1980 to 5.6 in 1989.

Example 2. Database in the United Kingdom and Canada. In the United Kingdom, decennial reports and periodic supplements have examined mortality in various occupational groupings.[25] The use of census data on occupation allows estimation of a population at risk and therefore calculation of standardized mortality ratios (SMR). A disadvantage of this approach is that a person who is included in the numerator as a death may not appear in the denominator, since death and census records are not truly linked for individuals. In Canada, a monitoring system has been established by linking a 10% random sample of the workforce to the national mortality register.[14] The occupation of each member of this cohort was reported annually to the Unemployment Insurance Commission as a part of a large study. The value of this monitoring system increases through time, as the cohort matures and latency periods before the onset of disease elapse. The system provides a powerful tool for both generating and testing hypotheses, and this power will increase as further mortality experience is accumulated by the cohort. SMRs were calculated based on this data. The SMRs for the lung cancer in plumbers and pipe fitters were found to be significantly elevated (SMR = 1.68, $p < 0.05$).

Other data bases, such as cancer registries, hospital records, workers' compensation records, and physicians' reports also may be used for surveillance. The major limitations to these sources of data are lack of comparability in occupational data, lack of coding, and underreporting.

Molecular Epidemiologic Studies

The term molecular epidemiology has been used in the literature since 1979.[20] The rapid developments in molecular biology are an integral component of occupational epidemiology because biomarkers of exposure have provided useful information to identify susceptible persons and specify disease entities.[2] Interest has been particularly devoted to the identification of chemical adducts to deoxyribonucleic acid in various working groups. The adducts to DNA can be thought of as markers of exposure or as markers of early adverse health effects.[1] Major advances in molecular epidemiology have helped to identify genes and enzymes that play an important role in many diseases.[12] Thus, molecular epidemiology will probably play an increasing role in occupational epidemiology.

Example. Specific mutations in the p53 gene in liver tumors have been studied.[15] Human hepatocellular carcinoma from patients in Qidong, China, in which both hepatitis B virus and aflatoxin B1 are risk factors, were analyzed for mutations in the p53, a putative tumor-suppressor gene. Eight of 16 patients had a point mutation at the third base position of codon 249. The authors suggest that the mutant p53 may be responsible for a selective clonal expansion of hepatocytes during carcinogenesis. In addition, a comparison of p53 mutations in hepatocellular carcinoma from North America, Europe, Africa, and Asia will be of interest to link etiologic agents with genetic changes occurring during human hepatocellular carcinogenesis.

CONCLUSION

The development of occupational epidemiology has been steadily accelerating, both with regard to methodology and the numbers of various studies being conducted. What future developments are to be expected in occupational epidemiology? Exposure assessments in the work environment will be developed. The traditional types of descriptive and analytic occupational epidemiology also will continue. Psychosocial risk factors in the workplace and their health implications is another field that has been attracting interest.[1] Accidents and injuries in the workplace may gain more attention and will be investigated to determine their association with ergonomic factors. The associations of different occupations with risk factors and lifestyles that cause adverse effects on health deserve much additional epidemiologic research. Another development will be the extensive use of computer technology in epidemiologic studies. The explosion of epidemiologic studies since 1950 is directly related to the development of the computer. Yesterday's epidemiologists usually were directly involved in the design of the studies and collection of data. Today's epidemiologists may have access to the data collected by others that are stored on a computer and ready for analysis. For this reason, today's occupational surveillance records and data are very important for epidemiologists, and they should be maintained for the future. In addition, statistical software for data analysis will be developed. However, the need for careful data analysis and cautious data interpretation is necessary.

The ultimate goals in occupational epidemiology remain the identification or confirmation of new occupational disease and the study of dose-response characteristics in order to prevent occupational diseases and injuries.[22] If occupational epidemiologic studies are well designed and conducted, and if the data are properly analyzed and interpreted, they can provide strong and reliable information on which to base policy and ultimately decision-making affecting the health of workers. There is a growing need for epidemiologic follow-up on the preventive efforts of work-related risks that have been discovered over the years. In the future, many causes of occupational diseases may be practically eliminated or decreased by appropriate technology and control. Continual improvement in occupational health and hazard surveillance will be an essential component of future efforts to prevent and control occupational diseases and injuries in the workplace.

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Occupational Medicine

Occupational Epidemiology

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National Institute for Occupational Safety and Health
Morgantown, West Virginia

Volume 11/Number 3 July–September 1996
HANLEY & BELFUS, INC. Philadelphia

STATE OF THE ART REVIEWS

Occupational Medicine: State of the Art Reviews
Vol. 11, No. 3, July–September 1996

OCCUPATIONAL EPIDEMIOLOGY
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