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# Research Methods in Occupational Epidemiology

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## Introduction

Work is central to human existence. Not only is it the motive force for all economies, but it also provides structure and meaning to individuals and societies. Nevertheless, some conditions in the workplace can pose threats to human health. Occupational epidemiology is the study of the distributions and causes of illness and injury that result from these hazards.

All epidemiologic research can be subdivided along two axes. Along one lies the study of various diseases, such as cardiovascular or infectious diseases, that focuses on particular health outcomes. Along the other are the epidemiologic subdisciplines that emphasize classes (or routes) of exposure: environmental epidemiology, nutritional epidemiology, and pharmacoepidemiology are examples, and occupational epidemiology is in this category of exposure-oriented subdisciplines. But there is considerable overlap among categories on both axes with regard to their substantive concerns and research methods. For example, when studying the etiology of a particular disease, such as ischemic heart disease, one would logically begin with an assessment of its occurrence with respect to person, place, and time. An occupational epidemiologist investigating possible hazards of work would begin with descriptive accounts of the distributions of exposures and various health outcomes in worker populations, or, more broadly, in the population at large. Moreover, the study designs and analytic methods used in occupational epidemiology are essentially the same as those applied in studies of diseases with non-occupational causes. For example, an epidemiologist studying acute-onset neurologic symptoms that occurred after an accidental exposure of workers to a toxic chemical adopts investigative techniques familiar to an epidemiologist studying a food-borne epidemic of enteric illness. In both situations, the epidemiologist would determine the size and demographic features of the exposed population, identify the temporal sequence of case occurrence, and ultimately investigate formal hypotheses about potentially causative agents. Similar parallels can be drawn between occupational

epidemiology and other epidemiologic subdisciplines in which the delayed effects of chronic exposures are studied.

There are some important features of occupational epidemiology that distinguish it from other areas of epidemiology, however. For example, some diseases are primarily occupational in origin, such as the pneumoconioses resulting from silica, asbestos, and coal dust; the musculoskeletal trauma caused by vibrating hand tools; and laser-induced eye damage. Moreover, many diseases and injuries are not confined to the workplace. Thus, the disentanglement of occupational and non-occupational risk factors poses a central challenge to epidemiologists.

Another distinctive feature of occupational epidemiology is that the population of interest, or study base, is defined either explicitly or implicitly as a group of workers. Several important implications derive from the fact that occupational epidemiologists study populations defined by their relationship to work. First, working populations are often highly selected populations. We will see that workers tend to be healthier than the general population for several reasons, and this "healthy worker effect" sometimes poses serious challenges to the accurate identification of occupational health risks. Second, the hazards of work occur, for the most part, as unintended consequences of productive activity. The generation of workplace exposures is seldom random but, rather, can be predicted from an understanding of the production processes from which exposures arise. At a minimum, one can often distinguish heavily from less heavily exposed jobs or tasks within a workplace. A preferred strategy is to conduct quantitative monitoring of workers' exposures. Data generated by such monitoring are used for exposure-response analyses and eventually for establishing health-based exposure limits. As we emphasize throughout this book, qualitative and quantitative exposure assessment, typically undertaken by occupational hygienists, is central to the validity and informativeness of epidemiologic research.

## HISTORICAL BACKGROUND

### Recognition of Occupational Diseases

Occupational hazards were known to Hippocrates, who admonished physicians to explore patients' environmental, lifestyle, and vocational backgrounds when diagnosing and treating diseases (Rom, 1992). The Italian physician Bernardino Ramazzini, often acknowledged as the father of occupational medicine, described numerous occupationally related diseases and their causes in his book *De Morbis Artificum*, published in 1700 (Wright, 1964).

Included in his presentations are descriptions of respiratory impairment (silicosis) among stonemasons, ocular disorders among glassblowers, and neurologic toxicity among tradesmen exposed to mercury.

The recognition of many of the well-known occupational hazards can be traced to astute physicians or to workers themselves who associated illness or premature mortality with a particular exposure. Several historical examples, out of literally hundreds, illustrate the process of occupational hazard recognition and subsequent epidemiologic investigation.

Pneumoconiosis among miners of gold and silver in Joachimsthal and Schneeberg, towns in the Erz Mountains on the border of Germany and the former Czechoslovakia, is a vivid illustration. As early as the sixteenth century, Agricola reported premature mortality among these miners. The prevailing view at the time was that the miners' disease was a form of consumptive lung disease; subsequently, it was established that silicosis and silicotuberculosis were predominant contributors to excessive mortality (Corn, 1980). In 1879, Hessing and Hartung recognized that underground metal miners were experiencing seemingly excessive rates of respiratory cancers (Hunter, 1978). In the 1930s, mortality surveys revealed that nearly 50 percent of miners' deaths were due to lung cancer, and roughly 25 percent were due to nonmalignant respiratory diseases (Pirchan and Siki, 1932; Peller, 1939). Numerous epidemiologic studies of uranium and other underground metal miners throughout the world have since provided very convincing evidence for an association between radon exposure and lung cancer (National Research Council, 1999).

Percival Pott, who in 1775 identified soot as the cause of scrotal cancer in London chimney sweeps, is credited with providing the first clear-cut evidence of chemical carcinogenesis from an occupational exposure. Pott's detailed descriptions of the abysmal working conditions suffered by chimney sweeps, who were often required to climb narrow, sharply angled chimneys that were still hot, stimulated social concerns. However, overriding fears of fires in uncleaned chimneys delayed until 1840 passage of legislation prohibiting young boys from working at this occupation (Waldron, 1983). The carcinogenic potential of coal tar products was noted by the end of the nineteenth century, and an experimental model of soot carcinogenesis was first demonstrated in the 1920s (Decoufle, 1982). Inhaled coal tar pitch products, especially polycyclic aromatic hydrocarbons, are now established as risk factors for lung and bladder cancers among coke oven workers, aluminum smelter workers, roofers, metal foundry workers, and twentieth-century adult chimney sweeps (Boffetta et al., 1997).

The recognition of the asbestos-associated diseases occupies an important place in the history of occupational epidemiology. Asbestos had been used for various artistic and ritualistic purposes for centuries before it was

exploited on a broad industrial scale. Pottery containing asbestos dating from 2500 B.C. found in Finland attests to the long history of asbestos use (Lee and Selikoff, 1979). Major industrial use of asbestos began after large deposits were discovered in Canada, South Africa, and Italy during the last half of the nineteenth century. In 1907, Murray described a case of pulmonary fibrosis, detected at autopsy, in a British asbestos textile worker. The term *asbestosis* was first used by Cooke et al. in 1927. Intensive investigations of the magnitude of asbestosis prevalence among exposed workers followed in the 1930s in the United Kingdom (Merewether and Price, 1930) and the United States (Dreesen et al., 1938). Fatal and nonfatal forms of asbestosis were subsequently identified in many exposed populations (Becklake, 1991), and excessive lung cancer risks among asbestotics suggested a potential carcinogenic effect of asbestos fibers (Lee and Selikoff, 1979). The suspicions regarding the carcinogenicity of asbestos have been confirmed repeatedly in epidemiologic studies of occupationally exposed persons since the 1950s (Steenland and Stayner, 1997).

Alice Hamilton's 1925 book *Industrial Poisons in the United States* depicted a variety of occupational diseases, ranging from solvent-induced narcosis to "phossy-jaw" among matchmakers exposed to phosphorus. Hamilton's work stimulated other physicians' concerns about health hazards in uncontrolled workplaces. The following excerpt from Adelaide Ross Smith's 1928 account of the work conditions encountered by women workers exposed to benzene (termed "benzol") in a small sanitary tin can factory in New York State is a vivid example:

There was no direct ventilation of coated can covers. They emerged from the machine immediately after coating without having been heated and smelling directly of benzol. . . . The eight coating machines consumed 45 to 50 gallons daily of a compound containing 75 percent of benzol. Adjoining the coating room and connected with it by a wide-open doorway was another room where paper gaskets were made. . . . [A twenty-six-year-old woman] was employed for some months in the room adjoining the coating machines. She had always been well and was not bothered by the work until she became pregnant. Then she suffered from severe nausea and vomiting. . . . Severe and prolonged nosebleeds were followed by bleeding from the gums and rectum and into the skin. She stopped work and improved. . . . A premature child was born at seven months and three hours after delivery the mother died following severe uterine hemorrhage.

Hazardous exposures in small factories remain a serious problem to this day, particularly in developing countries. Regrettably, significant health hazards are still often only detected after episodes of profound poisoning have occurred. Moreover, the health of women workers worldwide has become an increasingly prominent focus in occupational epidemiology, as women have assumed a larger fraction of the labor force. Increasingly, as

the major occupational health problems are being identified and regulated in Western countries, the burden of occupational disease is shifting to developing countries, through both the movement of hazardous industry and the development of new manufacturing industries in these countries (Pearce et al., 1994). Thus, it is important to take a global approach to studying and controlling occupational hazards.

### Development of Systematic Epidemiologic Methods

Many occupational health risks were initially identified by case-series reports of apparent disease excesses, or clusters, either by clinicians providing medical care for workers or by the workers themselves. The discovery, in 1895 by the German surgeon Ludwig Rehn, of three cases of bladder cancer in workers exposed to aromatic amines in a fuschin dye factory and, more recently, the identification of a rare tumor of the blood vessels in the liver, angiosarcoma, among workers exposed to vinyl chloride (Creech and Johnson, 1974) are clear-cut examples of the utility of case-series reporting for identification of workplace hazards. Suspicions about infertility resulting from exposure to the nematocide dibromochloropropane (DBCP) first arose when male production workers in California noted seemingly low numbers of pregnancies in their partners. This observation prompted an investigation demonstrating abnormally low sperm counts and infertility in some workers (Whorton et al., 1977). Similar toxic effects have been seen subsequently in workers who applied DBCP on fruit plantations in Asia, Africa, and Central America (Slutsky et al., 1999).

The case-series approach serves as a valuable indicator of occupational hazards, primarily in situations where the health outcome is rare and has dramatic manifestations (e.g., liver angiosarcoma) and there is a characteristic exposure that can be identified as the probable cause. However, case-series reports are inadequate to assess a wide spectrum of relatively common health outcomes that may not be closely related to specific workplace exposures. Instead, more fundamentally complete epidemiologic study designs that include comparison groups and exposure assessments are required.

The development of the retrospective, or historical, cohort design illustrates some methodological contributions of occupational epidemiology. Landmark studies conducted during the 1950s in the United Kingdom of cancer risks in the gas works (Doll, 1952), dyestuff (Case et al., 1954), and asbestos (Doll, 1955) industries made dual contributions of identifying specific occupational carcinogens and advancing the historical cohort design that is now a standard technique in occupational epidemiology (Checkoway and Eisen, 1998). Historical cohort studies of workers exposed to aromatic amines (Case et al., 1954; Veys, 1969) and vinyl chloride (Waxweiler et al., 1976;

Mundt et al., 2000) ultimately confirmed earlier observations from the aforementioned cancer cluster reports (Rehn, 1895; Creech and Johnson, 1974).

The desire to improve study cost efficiency for in-depth assessments of relations between exposure and disease motivated refinements in the design of case-control studies. In addition to the widely used population-based and hospital-based case-control studies, occupational epidemiologists rely heavily on case-control studies that are nested within occupational cohorts (Checkoway and Demers, 1994). Cross-sectional studies and longitudinal repeated measure designs are other methods that are especially well suited for investigations of disease symptoms and impairments in physiological function. Investigations of chronic and acute occupational respiratory diseases, for example, have relied extensively on cross-sectional and repeated measures studies (Eisen et al., 1991; Pearce et al., 1998). Each of these epidemiologic designs will be described in considerable detail throughout this book.

The emergence of occupational epidemiology has followed the same course as that of other epidemiology subdisciplines: clinical observations of rare diseases among small groups have motivated methodological advances to accommodate studies of both rare and more common health effects in large populations. As a result of these advances, investigations of occupational cohorts composed of thousands to tens of thousands of workers, and population-based case-control studies of hundreds of cases and controls, even for studies of relatively rare diseases, have become commonplace.

## THE SCOPE OF OCCUPATIONAL EPIDEMIOLOGY

### Defining Research Questions

Occupational epidemiology, like all other branches of the discipline, is fundamentally concerned with the prevention of disease. The principal method of working toward this goal consists of identifying and then investigating hypotheses about causal links between particular hazards and diseases. There are various studies in which hypotheses are developed, and it may be useful to describe briefly the most common of these.

As mentioned, the occurrence of disease clusters has prompted research throughout the history of occupational epidemiology. After becoming aware of an apparent disease cluster, the management of a company or the workers may choose to commission a formal epidemiologic study. Government agencies are sometimes requested to undertake a study. A study may take the form of a focused investigation of the potential work-related causes of a particular

illness or injury, or it may be a broader assessment of various occupational health risks. Inevitably, the scope of any investigation is heavily influenced by available resources and by assumptions about whether the cluster revealed a specific closely circumscribed hazard or was possibly indicative of more widespread risks. For example, the occurrence of several aplastic anemia cases in a workforce exposed to solvents might trigger a detailed investigation of exposures and hematological dysfunction, or the study could be enlarged to include investigations of other solvent-related sequelae, including neurotoxicity, adverse reproductive outcomes, and cancer.

A desire to examine the health profile of a working population—even without any particular prior suspicions or hypotheses regarding adverse exposure-related effects—may motivate development of injury and illness surveillance programs within industries. Population-based examination of routinely available data on disease occurrence and occupation, such as that contained in vital statistics records in some countries, is another form of occupational health surveillance. For example, the now classic studies of Kennaway and Kennaway (1936), linking recorded occupational classifications with mortality data in the United Kingdom in the 1920s and 1930s, led to the identification of an association between mineral oil mists and laryngeal cancer. Both industry-based and population-wide approaches to occupational health surveillance can provide valuable information about relative disease burdens and may suggest leads for more focused etiologic research.

Findings from other disciplines can also provide direction to research in occupational epidemiology. A typical situation arises when the toxic properties of a substance are demonstrated experimentally in animals or cell-culture systems. The next logical question is whether that substance exerts similar effects in humans. Worker cohorts exposed to the substance in question then become valuable target populations for study because workplace exposures are generally, although not always, greater than those in the ambient environment. (High background levels to contaminants in water or soil and intense localized industrial effluent discharges of toxic chemicals are important exceptions to this generalization.) Moreover, estimates of occupational exposures at the personal level are usually more feasibly made and are more valid than those obtained for exposures from ambient, dietary, and other sources of the same agents. Epidemiologic research that follows directly from experimental findings will tend to have a sharp focus on a particular health outcome or category of related outcomes (e.g., adverse reproductive effects). When exposure data are adequate, estimation of the quantitative relations between exposure and risk (dose-response models) is a logical next research goal. Government agencies often rely on this type of information to set workplace or environmental exposure limits.

There are some diseases with poorly understood etiologies for which occupational exposures are suspected of having some pathogenic role. Population-based case-control studies of occupational exposures can be especially effective strategies for exploring prior hypotheses and generating new causal leads. Examples can be found in the epidemiologic literature on the neurodegenerative disorders, Alzheimer's disease and Parkinson's disease. Population-based case-control studies provide evidence supporting associations of (1) industrial solvents with Alzheimer's disease (Kukull et al., 1995) and (2) various metals and pesticides with Parkinson's disease (Seidler et al., 1996; Gorell et al., 1997; Liou et al., 1997).

Many occupational epidemiology studies are explicitly designed to test previously specified hypotheses and, where possible, to quantify relations between exposure and disease risks. A research hypothesis may be suggested by numerous avenues, including prior epidemiologic findings for the agent(s) of interest, toxicological research, and physical or chemical similarities to those of agents known to be hazardous. For example, man-made mineral fibers bear structural similarities to asbestos and have largely replaced the latter as an insulating material. Large research programs in the United States and the European Union have been mounted to investigate the potential health effects of the substitute fibers; these programs rely extensively on occupational epidemiology (Boffetta et al., 1999; Marsh et al., 2001).

Epidemiologic studies are sometimes identified as being either "hypothesis-generating" or "hypothesis-testing." According to this view, more weight should be given to a finding that results from a study explicitly designed to investigate a given hypothesis (a hypothesis-testing study) than to a finding that was not anticipated or not explicitly sought from the start. These latter findings are regarded as more provisional because they may be more likely to have arisen by chance and so are said to be useful only in generating hypotheses that a future study may test. There are several flaws with this logic. First, occupational epidemiology studies are nearly always observational rather than experimental. This means that the investigator is not able to manipulate the exposures and population selection the way an experimentalist can. Randomization is relied on in the laboratory to minimize the risk that experimental conclusions are biased by factors not under the direct control of the investigator. Because of this limitation in all observational studies, epidemiologic research should be seen as providing evidence for or against a particular association, rather than as formal tests of hypotheses. As we will see, even the most well designed and conducted epidemiologic study is limited by potential bias and uncontrolled confounding. As a result, a ranking of hypothesis-testing versus hypothesis-generating studies seems unnecessarily rigid. The question of whether the hypothesis tested was identified a priori or arose from the results themselves is but one of many important issues that a reviewer

must evaluate in weighing the evidence from a particular study. There are many equally important criteria of study quality that are described in detail in the chapters that follow.

### Hazard Identification and Quantification

The list of environmental hazards identified wholly or in large measure through occupational epidemiologic studies is long and includes many of the well-known threats to human health. Lead, mercury, silica, asbestos, vinyl chloride, the dioxins, isocyanates, benzene, carbon disulfide, and other organic solvents are some notable examples. The recognition of each of these as a human health hazard can be traced back through a long history of investigations, often beginning with the detection of a disease cluster, or an astute clinical observation. Such an initial clue was often followed by rather crude field studies, which provided preliminary information, and the motivation to proceed to more refined (and more expensive) studies. In general, the process of hazard recognition can be divided into two phases: one first asks "Does the hazard exist?" and then, if this is answered affirmatively, "How big is the hazard, or how much exposure causes how much risk?" We will see that studies at the first phase, when it is not yet established whether an agent is hazardous, are often characterized by simple, qualitative exposure assessments. However, once a hazard is determined to exist, one needs to refine exposure estimation, in order to quantify the exposure-risk relation. In Chapter 2 we describe in some detail the range of different approaches to exposure assessment and how exposure data of various types are applied in research.

Often the epidemiologist is confronted with the problem of detecting small risks. Suppose that a workplace agent causes or contributes to elevated disease risk, but the effect is rather weak. In this case, it may not be possible even to determine that the agent is hazardous, without conducting a study of a very large population with highly refined exposure measurements. We will see that crude exposure measurements are likely to introduce a bias that results in underestimation of the magnitude of associations, thus rendering weak associations nearly impossible to detect. Also, concerns about uncontrolled confounding become especially prominent in situations where the anticipated effects of occupational exposures are small.

Refined quantitative exposure-risk information is sometimes of scientific interest without being necessary for prevention. A case in point is the uncertainty about the relative carcinogenic potentials of the various asbestos fiber types. An association between amphibole asbestos fibers (e.g., crocidolite) and malignant mesothelioma is widely accepted. However, there has been a long-standing debate as to whether mesothelioma can be induced by

chrysotile, the principal commercial type of asbestos, or whether contamination with other fibers (amphiboles) is the ultimate cause (Cullen, 1996; Stayner et al., 1996). Regardless of the answer to this question, prevention of asbestos exposure is unquestionably the appropriate public health action. Experimental and epidemiologic research into the relative toxicities of asbestos fiber types may ultimately reveal insights into carcinogenic mechanisms of fibers and the pathogenesis of mesothelioma.

Determining the potentially harmful effects of occupational exposures typically involves estimating relative risks or changes in physiologic function in relation to exposure types and levels. Dose-response estimation may then be undertaken to characterize the magnitude of risks across a range of exposures. Some studies test previously specified hypotheses, whereas others seek to identify new associations. For example, population-based case-control studies in British Columbia of cancers with established workplace associations—mesothelioma, bladder cancer, and nasal cancer—were designed to estimate the causal contributions of known risk factors and to identify previously unsuspected hazards (Teschke et al., 1997a, 1997b). In the analysis of bladder cancer (Teschke et al., 1997b), previously unsuspected associations with employment as sheet metal workers, miners, and gardeners were detected. Occupational health surveillance studies, which we will discuss in Chapter 8, are designed to monitor effects from known or suspected toxic agents, as well as to identify new hazards. Surveillance may be restricted to a particular occupational cohort or may be more broadly applied to the population at large, as in the case of the surveys by Kennaway and Kennaway (1936).

The process of occupational hazard identification can be complicated in situations when multiple associations are examined. For example, relative risks for some 50 to 60 diseases may be estimated in a single cohort study. Likewise, population-based case-control studies often seek information on lifetime work experience, which can reveal many possible exposure-disease associations. Some findings may agree or disagree with prior expectations, and others may be unprecedented findings. In these situations, one must be wary of positive associations resulting from a large number of factors studied (Thomas et al., 1985). Corroboration of results by other epidemiologic studies and consistency with findings from toxicologic research may be required to separate real from chance associations.

### Causal Inference

Ultimately, the data derived from occupational epidemiology research are used for decision-making. Regulatory agencies rely heavily on epidemiologic data when they propose occupational and non-occupational exposure limits. Medico-legal attribution of risk for individual cases and population

predictions of the future occurrence of disease in exposed workers are other common uses for these data.

Decisions about causation require evaluations of the composite of evidence from epidemiologic and other research. In its most elementary form, an evaluation of scientific evidence can be reduced to the question, "Does the exposure cause the disease?" An acute workplace illness or injury that occurs in close temporal and physical proximity to an obvious hazard can be linked unambiguously to occupational exposure. Moreover, some conditions, such as the pneumoconioses, are, by definition, attributable to occupational exposures. However, much of occupational epidemiology research addresses the relative contributions of workplace exposures on health outcomes that have both occupational and non-occupational causes. Lung cancer, obstructive lung disease, spontaneous abortion, and nervous system symptoms are examples that fit this description. In such situations, a simple cause-effect relation is difficult to establish. It should be emphasized that causation is always a judgment, not a certainty. Complicating matters for the occupational epidemiologist is the possibility, or even likelihood, of interactions between occupational exposures and host factors or non-occupational disease determinants. For example, accelerated loss of lung function among a cohort of underground coal miners may only be observable among cigarette smokers, suggesting a modification (potentiation) of the effect of coal dust by smoking. Does this imply that coal mining alone is not a cause of lung damage? No—prevention of dust exposures among miners would, presumably, improve their health. Irrespective of whether this benefit would accrue only to smoking miners or to all miners, the data would suggest the existence of an occupational respiratory hazard.

Epidemiologists have devoted considerable attention to the issue of causation (Rothman, 1988). Criteria for causal inference, such as those proposed by Hill (1965), can offer guidance. Among these, only the temporality criterion, requiring that exposure must precede disease, is essential. The extent to which other criteria—minimal bias, strength of the association, consistency of findings with those from previous research, consistency of findings within a study, and dose-response relation—are satisfied can vary greatly from study to study. Thus, for example, an observed adverse effect of an occupational exposure that is unlikely to be an artifact of confounding or other biases may indeed be causal, regardless of the magnitude of the effect estimate. A statistically precise dose-response gradient and coherence with other research would add further support for a causal link.

It is important to realize that a single epidemiologic study of occupational exposures (or other factors) can seldom provide a conclusive answer to the question of causation. Replication of research, one of the hallmarks of the experimental sciences, in a strict sense is not possible in epidemiology

because populations and exposure circumstances always differ among studies. Epidemiology is, for the most part, an observational rather than experimental science. Nevertheless, the inherent variability among epidemiologic studies may be advantageous insofar as examination of the consistency of findings from epidemiologic studies conducted at various times and locations, and on demographically different populations, can be a powerful empirical test of a causal hypothesis.

## REFERENCES

- Becklake MR (1991). The epidemiology of asbestosis. In: Liddell FDK, Miller K (eds.). *Mineral Fibers and Health*. Boca Raton, FL: CRC Press, pp. 103–119.
- Boffetta P, Jourenkova N, Gustavsson P (1997). Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control* 8:444–472.
- Boffetta P, Andersen A, Hansen J, et al. (1999). Cancer incidence among European man-made vitreous fiber production workers. *Scand J Work Environ Health* 25:222–226.
- Case RAM, Hosker ME, McDonald DB, et al. (1954). Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry: Part I. *Brit J Ind Med* 11: 75–104.
- Checkoway H, Demers PA (1994). Occupational case-control studies. *Epidemiol Rev* 16:151–162.
- Checkoway H, Eisen EA (1998). Developments in occupational cohort studies. *Epidemiol Rev* 20:100–111.
- Cooke WE, McDonald S, Oliver T (1927). Pulmonary asbestosis. *Brit Med J* 2:1024–1027.
- Corn JK (1980). Historical aspects of industrial hygiene: silicosis. *Am Ind Hyg Assoc J* 41:125–132.
- Creech JL, Johnson MN (1974). Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150–151.
- Cullen MR (1996). The amphibole hypothesis of asbestos-related cancer: gone but not forgotten. *Am J Public Health* 86:158–159.
- Decouffe P (1982). Occupation. In: Schottenfeld D, Fraumeni JF (eds.). *Cancer Epidemiology and Prevention*. Philadelphia: W.B. Saunders, pp. 318–335.
- Doll R (1952). The causes of death among gas-workers with special reference to cancer of the lung. *Brit J Ind Med* 9:180–185.
- Doll R (1955). Mortality from lung cancer in asbestos workers. *Brit J Ind Med* 12:81–86.
- Dreesen WC, Dalla Valla JM, Edwards TI (1938). *A Study of Asbestosis in the Asbestos Textile Industry*. Public Health Bulletin, no. 241. Washington, DC: U.S. Government Printing Office.
- Eisen EA, Kriebel D, Wegman DH, et al. (1991). An epidemiologic approach to the study of acute reversible health effects in the workplace. *Epidemiology* 2:263–270.
- Gorell JM, Johnson CC, Rybicki BA, et al. (1997). Occupational exposures to metals as risk factors for Parkinson's disease. *Neurology* 48:650–658.
- Hamilton A (1925). *Industrial Poisons in the United States*. New York: Macmillan.
- Hill AB (1965). The environment and disease causation: association of causation? *Proc R Soc Med* 58:295–300.
- Hunter D (1978). *Diseases of Occupations*, 6th ed. London: Hodder and Stoughton.
- Kennaway NM, Kennaway EL (1936). A study of the incidence of cancer of the lung and larynx. *J Hyg* 36:236–267.
- Kukul WA, Larson EB, Bowen JD, et al. (1995). Solvent exposure as a risk factor for Alzheimer's disease: a case-control study. *Am J Epidemiol* 141:1059–1071.
- Lee DHK, Selikoff IJ (1979). Historical background to the asbestos problem. *Environ Res* 18:300–314.
- Liou HH, Tsai MC, Chen CJ, et al. (1997). Environmental risk factors for Parkinson's disease: a case-control study in Taiwan. *Neurology* 48:1583–1588.
- Marsh GM, Youk AD, Stone RA, et al. (2001). Historical cohort study of U.S. man-made vitreous fiber production workers: I. 1992 fiberglass cohort follow-up: initial findings. *J Occup Environ Med* 43:741–756.
- Merewether ERA, Price CV (1930). *Report of Effects of Asbestos Dust on the Lungs and Dust Suppression in the Asbestos Industry*. London: Her Majesty's Stationery Office.
- Mundt KA, Dell LD, Austin RP, et al. (2000). Historical cohort study of 10,109 men in the North American vinyl chloride industry, 1942–72: update of cancer mortality to 31 December 1995. *Occup Environ Med* 57:774–781.
- Murray M (1907). *Report, Department, Commission on Compensation of Industrial Disease*. London: Her Majesty's Stationery Office.
- National Research Council [NRC] (1999). *Health Risks of Exposure to Radon (BEIR VI Report)*. Washington, DC: National Academy Press.
- Pearce N, Beasley R, Burgess C, Crane J (1998). *Asthma Epidemiology: Principles and Methods*. New York: Oxford University Press.
- Pearce NE, Matos E, Vainio H, et al. (eds.) (1994). *Occupational Cancer in Developing Countries*. Lyon: International Agency for Research on Cancer.
- Peller S (1939). Lung cancer among miners in Joachimsthal. *Hum Biol* 11:130–143.
- Pirchan A, Sikl H (1932). Cancer of the lung in miners of Jachymov (Joachimsthal). *Am J Cancer* 15:681–722.
- Pott P (1775). *Chirurgical Observations*. London: Hawes, Clarke, and Collins.
- Rehn L (1895). Blasengeschwulste bei Fuchsin-arbeitern. *Arch Klin Chir* 50:588–600.
- Rom WN (1992). The discipline of environmental and occupational medicine. In: Rom WN (ed.). *Environmental and Occupational Medicine*, 2nd ed. Boston, MA: Little-Brown, pp. 3–6.
- Rothman KJ (ed.) (1988). *Causal Inference*. Chestnut Hill, MA: Epidemiology Resources.
- Seidler A, Hellenbrand W, Robra B-P, et al. (1996). Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology* 46:1275–1284.
- Slutsky M, Levin JL, Levy BS (1999). Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries. *Int J Occup Environ Health* 5:116–122.

- Smith AR (1928). Chronic benzol poisoning among women industrial workers: a study of women exposed to benzol fumes in six factories. *J Ind Hyg* 10:73-93.
- Stayner LT, Dankovic DA, Lemen RA (1996). Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health* 86:179-186.
- Steenland K, Stayner LT (1997). Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control* 8:491-503.
- Teschke K, Morgan M, Checkoway H, et al. (1997a). Mesothelioma surveillance to locate sources of exposure to asbestos. *Can J Public Health* 88:163-168.
- Teschke K, Morgan M, Checkoway H, et al. (1997b). Nasal and bladder cancer surveillance to locate sources of exposure to occupational carcinogens. *Occup Environ Med* 54:443-451.
- Thomas DC, Siemiatycki J, Dewar R, et al. (1985). The problem of multiple inference in studies designed to generate hypotheses. *Am J Epidemiol* 122:1080-1095.
- Veys CA (1969). Two epidemiological inquiries into the incidence of bladder tumors in industrial workers. *J Natl Cancer Inst* 43:219-226.
- Waldron HA (1983). A brief history of scrotal cancer. *Brit J Ind Med* 40:390-401.
- Waxweiler RJ, Stringer W, Wagoner JK, Jones J (1976). Neoplastic risk among workers exposed to vinyl chloride. *Ann NY Acad Sci* 271:40-48.
- Whorton D, Krauss RM, Marshall S, et al. (1977). Infertility in male pesticide workers. *Lancet* ii:1259-1261.
- Wright WC (1964) (Trans.). *De Morbis Artificum (Diseases of Workers)*, B. Ramzaaini. New York: Hafner.