Occupational Cancer

Michael Alderson

Occupational Cancer

Michael Alderson
Chief Medical Statistician, Office of Population Censuses and Surveys, London

Butterworths London Boston Durban Singapore Sydney Toronto Wellington

First published 1986

British Library Cataloguing in Publication Data

Alderson, Michael
Occupational cancer.
1. Cancer 2. Occupational diseases
I. Title
616.99'4071 RC262

ISBN 0-407-00297-9

Library of Congress Cataloging in Publication Data

Alderson, M. R. (Michael Rowland)
Occupational cancer.

Bibliography: p.
Includes index.
1. Cancer. 2. Occupational diseases. 3. Carcinogens —Environmental aspects. 4. Industrial toxicology.
I. Title. [DNLM: 1. Carcinogens, Environmental.
2. Neoplasms—chemically induced. 3. Occupational Diseases. QZ 202 A362o]
RC262.A376 1985 616.99'4071 85-19030
ISBN 0-407-00297-9

Typeset by Scribe Design, Gillingham, Kent
Printed in Great Britain by The Garden City Press Ltd, Letchworth, Herts

Preface

This book provides an up-to-date review of the occurrence and causes of occupational cancer. The intention has been that the text should assist all those involved with the health of workers (including medical and safety staff, management, and health and safety representatives). The material should be of particular interest to those mounting studies on the health hazards of specific work processes and the carcinogenicity of the work environment.

Chapter 1 provides a description of the main classes of epidemiological study that can be used to investigate any potential cancer hazard to which a group of workers is exposed. This is (*a*) to enable the reader to have sufficient understanding about the advantages and disadvantages of the various methods so that he can judge the weight to be placed upon any specific findings, and (*b*) to guide those planning specific studies.

Chapter 2 provides a detailed review of present knowledge on the causes of occupationally induced cancers; the sections are restricted to specific chemical or physical agents, for which there is evidence of an association with increased risk of cancer. A major contribution of this chapter is from the tables which provide a synoptic view of reported studies on workers exposed to these specific agents. The text mentions evidence from animal and other laboratory tests of carcogenicity, where these have provided guidance in the absence of relevant epidemiological data. The main thrust of the reviews is on epidemiological studies (and case reports) that have clarified knowledge of the actual situation. The general issues of toxicology and product safety are beyond the scope of the present work. However, it must be remembered that plant engineering to reduce worker exposure may be crucial in removing a potential hazard from cancer, although actually being carried out for the more immediate aim of avoiding discomfort or toxic effects.

Chapter 3 complements the preceding one on carcinogenic agents, with a review of those industries in which an increased incidence or mortality from cancer has been reported. Industries are included when there is no obvious non-occupational confounding factor operating and also no indication that the increased cancer is associated with exposure to any specific agent in the work environment. Again synoptic tables are provided when a number of studies have been reported. The text also concentrates on epidemiological studies and case reports. Should the reader, in searching for discussion of a particular topic, not immediately find an entry where expected, the index should be consulted, where generous cross-reference is provided. Many topics are indexed under several synonyms, as well as under both the agent and the industry in which this occurs.

Chapter 4 provides a brief note of the major known causative agents of malignant disease at each main site. In the space available only limited discussion is provided, but key references are provided. The intention is that anyone concerned about the occurrence of a particular cancer in a group of subjects can readily check on the present knowledge of aetiology. This should help consideration of whether there may be some non-occupational factor leading to excess risk of the cancer.

The final chapter discusses the general approaches to prevention of occupational cancer. Sections deal with the contribution from research, the general approaches suitable for prevention, the impact of legislation, and the contribution from national and international bodies. The final section discusses action taken to control a number of specific carcinogens.

The initial work on the reviews of occupational cancer was carried out when the author held the

Cancer Research Campaign chair of epidemiology at the Institute of Cancer Research Grateful thanks are due to the Campaign for the generous funding of this post. The work has been extended and revised; it is now presented as a personal view of the published literature on the subject.

Michael Alderson
Southampton

Abbreviations

BCME	bis(chloromethyl)ether
BLV	bovine leukaemia virus
CEC	Council of European Communities
Ci	curie (old unit of radiation activity)
CL	confidence limits
CME	chloromethyl ether
CMME	chloromethyl methyl ether
CNS	central nervous system
2,3-D	dichlorophenoxyacetic acid
DBCP	dibromochloropropane
DDT	dichlorodiphenyltrichloroethane
DNOC	dinitro-*o*-cresol
E	expected (deaths)
FLV	feline leukaemia virus
GRO	General Register Office
Gy	gray (absorbed dose of radiation)
HCH	hexachlorocyclohexane
HLA	histocompatibility antigens
HSC	Health and Safety Commission
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ILO	International Labour Organisation
LET	linear energy transfer
MCPA	chloromethylphenoxyacetic acid
NHSCR	National Health Service Central Register
NIOSH	National Institute of Occupational Safety and Health
nm	nanometre (10^{-9} m)
O	observed (deaths)
OPCS	Office of Population Censuses and Surveys
OSHA	Occupational Safety and Health Administration
P	probability
PAH	polyaromatic hydrocarbons
PCBs	polychlorinated biphenyls
PMR	proportional mortality ratio
ppm	parts per million
PRR	proportional registration ratio
PVC	polyvinyl chloride
rem	rem (old unit of radiation dose equivalent)
RES	reticulo-endothelial system
RR	relative risk
SE	standard error
SMR	standardized mortality ratio
SRR	standardized registration ratio
STT	short-term tests
Sv	sievert (new unit of radiation dose)
2,4,5-T	trichlorophenoxyacetic acid
TCDD	tetrachlorodibenzo-*p*-dioxin
TCP	trichlorophenols
TLV	treshold limit value
TWA	time-weighted average
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
UK	United Kingdom
US	United States
UV	ultraviolet light
VC	vinyl chloride
VCM	vinyl chloride monomer
WHO	World Health Organisation

1

Epidemiological method

Epidemiology is one of the disciplines that can help in the investigation of occupationally induced cancer. It can contribute to (*a*) identifying possible hazards, (*b*) testing hypotheses on cause, (*c*) quantifying dose–response relationships, and (*d*) evaluating preventive measures. Studies on these aspects utilize the conventional methods of epidemiology, but certain adaptations are required for this particular field of cancer epidemiology. The present chapter, in the space available, can only provide an introduction to the methods used; standard texts on the subject should be consulted for further detail. (A list of recommended reading is given at the end of the chapter.) However, the following should provide a basic guide to the principles involved. This should be sufficient to assess the results from studies reported in the literature, and provide enough information to mount preliminary studies.

Though this chapter deals with method, the consideration of occupational mortality and incidence statistics is supplemented by an appendix on national publications of such statistics.

1.1 Different types of study

This section describes briefly 8 different types of study. These studies are in an order that goes from simple use of routine data through analytical studies of increasing complexity to prospective studies (the latter being the studies of longest duration and usually the definitive studies prior to preventive action).

1.1.1 Routine occupational mortality and incidence statistics

This section describes the development of regular analyses of occupational mortality. The section covers the generation of statistics from the national system of death notification, with or without the use of census statistics, to provide estimates of the population at risk within different occupations. Some countries extend the method to the data available from population cancer registries. A brief comment on the background for presenting statistics is given, followed by a discussion of some of the method issues of use, analysis and interpretation of the data, validity of the material, and possible extensions of the basic method.

In introducing a brief glimpse of the historical aspects of occupational mortality statistics, it is worth remembering that Paracelsus—the first to describe an industrial disease—said: 'Science cannot look back to the past'. Hunter (1957) recorded that Rammazzini wrote in the eighteenth century about disease occurring in over 60 occupations. Increasing attention was paid to the effect of occupation on health in the early part of the nineteenth century. Thackrah (1832) published his work *The Effects of Arts, Trades and Professions on Health and Longevity*. Chadwick (1842) stressed in his report on the sanitary condition of the labouring population of Great Britain the need for the collection and examination of facts. A few years later, Engels (1845) wrote of the condition of the working class in England. Farr (1875) pointed out that these previous writers employed methods which could render no precise results except in cases where the influences they dealt with were very powerful.

It was a major advance when the Registrar General (1855) first collated such information from the 1851 census with the mortality returns for that year. He wrote:

> 'The previous investigations of the various rates of mortality in the districts of the Kingdom have shown how much the health and life of the population are affected by fixed local influence.

> The professions and occupations of men open up a new field of enquiry on which we are now prepared to enter, not unconscious, however, of peculiar difficulties that beset all enquiries into the mortality of limited, fluctuating, and sometimes ill-defined sections of the population.'

Subsequent analyses of occupational mortality have been produced following each decennial census. In recent decennial reports, the mortality data have been based on deaths in 5 or 3 years around the time of the census, in order to provide a larger number of deaths in any individual occupation. The occupation used for the numerator in calculating the rates is the final occupation recorded at death registration. Enhancement of the method has been by:

(*a*) Selection of well-defined jobs for examination.
(*b*) Combination of allied or easily confused occupations.
(*c*) Cross-classification of job by geographical region.
(*d*) Use of occupation and industry to provide increased specificity.

The first detailed discussion of the problems involved in the interpretation of occupational mortality data was by Ogle (1885); he gave a clear description of the selection process into and out of occupations. Further attention was paid to this problem of selection into and out of occupation by Tatham (1902; 1908). Stocks (1938) presented evidence suggesting that variation in male mortality in England and Wales was influenced by housing, and to a lesser extent by social class and latitude. Attempts were made to distinguish the influence of a man's work, the industry in which he worked, and his general environment. Separate analyses of mortality by occupation and industry were carried out. The 1930–32 Decennial Supplement attempted to permit examination of the influence of job, independently of industry and locality, by presenting cause-specific mortality for wives. It was suggested that the study of the direct influence of occupation was possible from comparison of the standardized mortality ratio (SMR) of men and their wives. For example it was suggested that the influence of selection might be responsible for farmers having a lower SMR than their wives, rather than from benefit of their actual work.

Alderson (1972) indicated the following problems by using the following data:

(*a*) The validity of the cause of death—does knowledge of the job bias the wording of the certificate?
(*b*) Validity of occupation recorded at death registration—does the informant inflate the importance of the job of the deceased?
(*c*) Use of denominator from a different source—how is someone temporarily out-of-work from sickness or redundancy or prematurely retired classified?
(*d*) Selection biases—into and out of certain occupations in relation to physique, mental stamina, health.
(*e*) Use of last-held occupation, instead of job held longest.
(*f*) Relation of occupation to work environment—is there dilution due to aggregation of very different types of work?
(*g*) Confounding with non-occupational factors—do individuals in certain jobs smoke more, eat foods with high fat content etc.?

One of the problems that has had most attention devoted to it is the concern of the validity of the denominator; this is discussed further in 1.1.1.3.

1.1.1.1 Uses of occupational mortality statistics

Initially the statistics may be used for descriptive purposes: to indicate the numbers of deaths and the patterns of mortality for different categories of workers. The material may also be used to look at the variation in mortality from one occupation to another, or variation in one occupation from earlier periods in time. An extension of the simple descriptive use of statistics is as a source of fresh hypotheses ('fishing' for variation that stimulates some line of thought about possible aetiology). A very different application is the calculation of incidence or mortality by specific occupation in hypothesis testing. In general, descriptive and hypothesis generation studies will involve relatively broad categories of work, whilst hypothesis testing will be related to specific groups of workers—wherever possible identifying those exposed to a specific agent and preferably distinguishing categories of workers with variation in degree of exposure (both intensity or level and duration of exposure).

Hunches may be derived from clinical experiences, from other direct experiences, from laboratory investigation and from epidemiology. A milestone in the identification of carcinogenic factors was the work of Pott (1775), who identified the relationship between scrotal cancer and chimney sweeping. There are many other examples in the field of malignant disease where clinicians have been the first to suspect a hazard. It is important to acknowledge that laboratory investigation has contributed as much to the identification of fresh hazards as has epidemiology. In the past, epidemiology has usually relied on analysis of routine national statistics in the generation of fresh leads, although as the following sections indicate, fresh approaches are now being explored.

Stevenson (1923) pointed out that the influence of occupation on health could be indirect, as well as via the direct influence of a hazard upon mortality risk. He began the use of comparison of husbands' and wives' mortality, in order to distinguish the extent of the indirect component, i.e. where the SMR of both husbands and wives was greater than 100, the indirect component could be gauged by the excess of the female SMR over 100. However, Fox and Adelstein (1978) pointed out that (*a*) the percentage of wives aged 15–64 economically active and retired had risen from about 10% in 1931 to nearly 50% in 1971, and (*b*) many working wives will be in a job related to that of their husband and thus exposed to similar work and home environment. Fox and Adelstein (1978) go on to suggest that social class standardization of the occupational SMRs can assist by (*a*) allowing for general social class differences in mortality that are independent of work environment, (*b*) adjusting for specific patterns of behaviour such as smoking that show a clear social class gradient, and (*c*) distinguishing area from social class contributions to certain diseases.

Fox and Leon (1982) reviewed the use made of the 1970–72 report for England and Wales (Registrar General, 1978). Enquiry to potential users suggested the material was of value (*a*) as reference on occupation hazards, (*b*) for collation studies, (*c*) in consideration of health risks, (*d*) to distinguish occupational and non-occupational effects, (*e*) to generate hypotheses. However, the authors do not provide a single example where the latest or an earlier report has been the first lead to the identification of a fresh occupation hazard.

The *Lancet* (1983a) appeared to suggest that insufficient effort is devoted to following up clues about occupational cancer generated by routine statistics. It fails to discuss the relative advantages and disadvantages of this use of routine statistics. Moriyama (1984) suggested that there was ample evidence to show that occupational mortality data do not shed much light on occupational risk. He said that their chief use had been to present mortality differentials by social class, but it was not possible to make inferences about occupational risks from these data. He argued that if every death certificate had been occupation and industry coded, analytical studies could not produce risk factors from the data. Frazier *et al.* (1984) agreed with Moriyama's point that the occupational mortality did not permit a direct inference about disease or workplace hazard.

1.1.1.2 SMR and proportional mortality ratio (PMR)

There is a close relationship between age of an individual and the probability of dying. Thus when comparing observed mortality in two occupational groups with different age structures, some method is required to take account of this age effect. One approach to this problem is to examine the mortality by specific age groups. Although this enables direct comparisons to be made irrespective of any variation in age distribution, it can result in the presentation of a large amount of material (if, for instance, the age-specific mortality rates for 15 5-year age groups are examined). This creates a problem in the preparation and presentation of the material, and the sheer number of separate sets of data creates difficulties in interpretation.

Standardization is a technique that may be used for producing an index of mortality, which is adjusted for the age distribution in the particular occupational group being examined. One approach is to apply the age-specific rates for a 'standard' population to the age-specific numbers of individuals in the study population and then to derive an expected figure for the numbers of deaths.

When the denominator comes from a different statistical system (such as the census), there are major differences in the circumstances of recording the occupation. This has long been recognized as a problem in the method used by the Registrars General in England, Wales and Scotland. For a study in the United States (US), Stocks suggested the use of a PMR as a screening device, to identify SMRs that were not raised because of numerator/denominator biases (*see* Guralnick, 1962). The same type of approach was discussed by Logan (1982), who used two indices that were comparable to a PMR for comparison against the SMR.

Wang and Decoufle (1982) derived the algebraic relationship between the SMR and and PMR. This showed that the validity of the PMR depended upon the homogeneity of the age-specific overall SMRs and the value of the average SMR. They related this to a number of epidemiological studies and pointed out that incomplete death ascertainment can lead to biased estimates.

As indicated in the worked example (*see* 1.5.5), the SMR can be based upon any chosen age range. Doll and Cook (1967), when discussing presentation of data on cancer incidence, advocated (*a*) the use of a truncated age-standardized index, with different age ranges and weights depending upon the age-specific incidence of the particular cancer, and (*b*) the use of the ratio of the rates at ages 55–64 : 35–44 as an index of the rate at which the incidence increases with age.

1.1.1.3 Validity of occupational mortality and incidence statistics

Three rather different aspects need to be considered: (*a*) the validity of the cause of death on the certificate, (*b*) the validity of the occupations recorded for the denominator and numerator, and (*c*) the effect of small numbers especially when using the material for hypothesis generation.

Cause of death

Some general points of the validity of this item are discussed and then the possible specific biases in relation to occupational mortality. The cause of death is a crucial item of occupational mortality statistics, and the main statistic examined in historical prospective studies (*see* 1.1.7); the following general note on validity is equally applicable to this other use of the material on cause of death.

Any routine data collection system is liable to inaccuracies. This problem is best discussed by considering the separate steps in the chain leading to the production of mortality statistics, which are:

Conversion of basic information about the patients into the diagnosis by the clinician → Completion of the death certificate → Transcription onto the death notification → Classification of underlying cause of death → Coding → Processing → Analysis → Interpretation of the statistics.

A number of studies have examined the accuracy of the diagnostic information available at the time of death; usually this has been compared with data derived from autopsy. A major study was sponsored by the General Register Office (GRO) (Heasman and Lipworth, 1966). Alderson (1981a) has reviewed the literature on this topic, and pointed out that some studies indicate a worrying degree of variation between autopsy and clinical diagnoses. Other recent studies using this approach were by Busuttil, Kemp and Heasman (1981), and Cameron and McGoogan (1981).

Another approach has been to use 'dummy' case histories and obtain 'mock' death certificates from clinicians, e.g. Reid and Rose (1964), McGoogan and Cameron (1978), and Gau and Diehl (1981).

Others have compared death certificates with a review of detailed case histories (*see*, for example, Moriyama *et al.*, 1958; Alderson, 1965; Puffer and Griffith, 1967; Alderson and Meade, 1967; Pole *et al.*, 1977; Clarke and Whitfield, 1978).

Wingrave *et al.* (1981) compared the coding of the death certificates for 205 deaths by staff in (*a*) a Royal College of General Practitioners research unit, and (*b*) the Office of Population Censuses and Surveys (OPCS) and GRO Scotland.

It is generally accepted that mortality statistics, because of these problems, must be interpreted with caution. Obviously there are some conditions where the medical knowledge and facilities for diagnosis have altered markedly over time, or may vary from place to place. This will have a major impact on interpretation of the data—similar to situations where there have been major alterations in the International Classification of Diseases (ICD) with splitting or amalgamation of various cause groups. It has been suggested that approximately 20% of coded causes of death involve relatively minor errors and 5% major errors (where a major error is a change from one chapter of the ICD to another, which generally implies alteration from one body system to another).

The possibility that knowledge of an occupational risk might influence certification in workers was discussed by Mole (1982) and Kneale and Stewart (1982)—the former suggesting that doctors near a plant might 'overcertify' and the latter that doctors further away might 'undercertify' a particular cancer. No hard evidence to support either contention was presented.

Occupation recorded for numerator and denominator

Heasman, Liddell and Reid (1958) carried out a study which provided some facts relevant to a discussion of the accuracy of occupational mortality data, though this work was restricted to a survey on the accuracy of job descriptions on records used for the calculation of indices of occupational mortality and morbidity in the mining industry. These authors comment on errors in the descriptions of occupations used in the numerator and denominator of the occupational mortality rates, including errors introduced by the coding system. Following the 1961 census a postenumeration survey was carried out for the first time to check the accuracy of the information collected at the census; results of this are provided in the General Report of the 1961 Census (General Register Office, 1968). Some of the occupation questions had been differently phrased, and thus comparisons between the census and the postenumeration survey are difficult to interpret; however, the survey did support the earlier suggestions that there was overstatement of the number economically inactive. The second study discussed in the General Report of the 1961 Census concerned the matching of the information recorded at the death registration with the census schedule for a sample of deaths occurring shortly after the census. Out of 2196 males, 63% were assigned to the same occupation unit at death registration and, at census, 10% were assigned to different units within the same occupational order, whilst 27% were assigned to different orders.

Alderson (1972) has reported a study amongst a representative sample of males dying in Bristol during 1962–63. A chronological history was obtained of all occupations held since leaving school for each deceased person in the study; this information was obtained by interview with the next of kin. These occupation histories have been coded, and compared with the coding of the occupations recorded at death registration. Comparison showed that there was complete agreement between the two sets of data regarding the final occupation for 79% of the subjects; there were negligible discrepancies for 6%, minor discrepancies at unit level for 5% of the subjects, and major discrepancies for 10% of the subjects.

Where an individual has developed a fatal chronic disease (whether or not occupationally induced) and has had to change his occupation because of impaired ability, mortality will be shown against the final occupation. Should the change of job have been due to onset of occupationally induced disease, this will not be reflected in the mortality rate for the principal occupation; there will also be an erroneously high mortality rate for the final occupation.

Swanson, Schwartz and Burrows (1984) compared occupation and industry obtained from (*a*) 2000 death certificates, (*b*) 2000 cancer registrations, (*c*) 352 interview results in Detroit in 1980–81. The death certificates had data completed on occupation for a higher proportion than the registration material. The death certificate occupation and industry were an exact match with the interview data for 76%.

Number of events

Though there were 273 129 deaths in males aged 15–64 in England and Wales in 1970–72, when the topic of interest is a relatively rare cancer, in a small occupational unit the number of observed and expected deaths may be very low. For example, the SMR for laryngeal cancer was 146, but this was based on the observed deaths (O) = 16, and the expected deaths (E) = 10.96, which were not significantly different.

When scanning tables of SMRs, some approach is required to indicate the likelihood of the value differing from 100 by chance. A simple test which calculates chi-squared (χ^2) is described in 1.5.6. It is suggested that a conservative test, when scanning many hundreds of results, should only identify those where the probability (P) < 0.01 and O ≥ 20. *Table 1.3* sets out the associated values of O, E, and the SMR to identify such significant results.

1.1.1.4 Extensions of the basic method: extended occupational history

It is sometimes suggested that the value of occupational mortality statistics would be enhanced by the collection of an extended occupational history at death registration. For example, this point is included in the Royal College of Pathologists and Physicians (1982) report on death certification; it was one of the recommendations made by the House of Lords select committee on occupational health (Gregson, 1984). However, there are a number of points that need to be borne in mind in considering this suggestion: (*a*) the informant at death registration may be distressed by the recent bereavement, may not know the details of the occupations held by the deceased, and may inflate the importance of the job held by the deceased; (*b*) this collection of detail will not necessarily overcome the issue of the numerator/denominator bias in the statistics; (*c*) the effort involved in the data collection and more detailed analysis may not be justified in relation to other ways of monitoring the health of employees.

One alternative to the collection of the information at death registration was selected in the US, as part of the Third National Cancer Survey. In this study, information was collected from all patients with cancers of sites, except superficial skin, for 9 geographical locations in the US in 1969–71. The population covered was just over 21 million (10% of the US population). Details were obtained from medical records for 181 027 incident cancers; this was supplemented by interviews with 10% of the patients, at which details such as occupation and smoking were obtained (Williams, Stegens and Goldsmith, 1977).

Combined use of PMR and SMR

Reference has already been made to the use of the PMR as a tool for searching for those SMRs that are raised and do not reflect numerator/denominator bias in the data. This can be extended by the use of the SMR to determine the overall force of mortality of an occupation, and weight the PMRs for specific diseases, so that the all-cause PMR is not 100, but the value of the SMR. This might have the advantage that the SMRs could be generated every decade, or be based on a sample of deaths, whilst the cause-specific PMRs (from which large numbers of deaths are required) could be based on continued coding of all deaths.

This suggestion would utilize the power of the linked studies to obtain a valid all-cause SMR without bias, and the value of the PMRs for exploring specific causes. This should overcome the defect of the PMR that in general use one cannot distinguish, from an internal examination of the material, whether a value is genuinely raised, or reflects a decrease in the force of mortality from some other major cause of death.

1.1.2 Record linkage

A more powerful probe of an occupational influence may be provided by record linkage. One example is the longitudinal study carried out in England and Wales, which permits linkage of job details provided at census to subsequent patterns of mortality through national linkage (Office of Population Censuses and Surveys, 1973). A recent report (Fox and Goldblatt, 1982) presented a wide range of results from mortality of the 1971 cohort over the period 1971–75. Chapter 12 of this report provided results by occupational order; there are marked overall differences from the decennial supplement, with the linked study showing relatively low rates for all occupational orders and a high SMR for men unoccupied at the time of the census. The relatively low SMR for the occupational orders is due to the 'selection' of those fit for work and is another aspect of the 'healthy-worker effect' (*see* 1.3.9). Comparison between occupational orders showed some with relatively high SMRs, which were in agreement with the direction of the differences found in the decennial supplement. Though the longitudinal study overcomes the numerator/denominator biases, insufficient deaths have accumulated to permit examination of cause of death for occupational units (Fox and Leon, 1982). The national systems described for Canada, Denmark, Norway and Sweden all depend on record linkage. The former links occupational data from social security records to deaths, whilst the Scandinavians are all linking census to cancer incidence and mortality (*see* Appendix).

Instead of organizing record linkage as a routine, and then periodically using the linked file for special studies, an alternative approach is to carry out a specific record-linkage study in order to probe a particular problem. Mancuso and Coulter (1959) described how the US Bureau of Old-age and Survivors Insurance records could be used to identify individuals with specific long-term work histories. Linkage with deaths from vital records permitted examination of the mortality patterns of those in particular occupations. Alderson (1980a) arranged for OPCS staff to link records from the 1961 census with subsequent mortality. The census files were searched for codes compatible with an occupation as hairdresser. This enabled the census staff to identify the original census schedules, check the occupation and abstract full identification particulars for each individual. About 2000 men were identified (a 10% sample of the occupation in 1961); the identification particulars were used to trace each individual on the National Health Service Central Register (NHSCR), and thus find the death entries for those who had died. These data were used to calculate expected mortality and contrast this with observed numbers of deaths for 5 malignancies which other studies had suggested might be associated with exposure to hair dyes.

The main conceptual difference of an *ad hoc* study of this nature is that the effort of linkage is devoted solely to the individuals of particular interest, rather than using routine record linkage for the total population. Also it was possible to go back to the 1961 census, because the computer records that still existed for this could provide the cross-index to the hard-copy original schedules for all hairdressers.

A special example of record linkage is the establishment of registers of patients with specific rare cancers that may be of occupational origin—such as registers of hepatic angiosarcoma or mesothelioma patients. The use of the latter is discussed in 2.31.9.4 and 2.31.13. Falk and Baxter (1981) reviewed the use of hepatic angiosarcoma registries and pointed out: (*a*) the lengthy time to establish the register, (*b*) the effort required to confirm diagnoses, (*c*) the difficulty of getting information from next-of-kin spread across the country, (*d*) the absence of retrievable job records, (*e*) the constraint from lack of a control group. They emphasized the need to obtain information from several sources; death certificate review was inadequate without review of pathology.

1.1.3 Collation studies

A less precise probe, but one readily carried out, is to compare the distribution of cancer mortality (or incidence) with that of indices of variation in occupation geographically or over time. For example, cancer mortality by specific site was prepared and mapped for the counties in the US for 1950–69. At the same time these counties had been classified by industrial activity. Blot *et al.* (1977) compared 39 petroleum industry counties with 117 counties matched for geographical region, population size and various demographic indicators. The definition of a petroleum county was one where (*a*) at least 100 persons were employed in the industry, and (*b*) at least 1% of the county's population was estimated to be petroleum employees. Age-adjusted mortality rates during 1950–69 for 23 cancer sites were calculated for white residents. Males in the petroleum industry counties experienced significantly more cancer for 7 sites of malignancy: stomach, rectum, nasal cavity and sinuses, lung, testis, skin including melanoma, brain. The excesses for cancer of the stomach, rectum and testis occurred in the more highly populated petroleum industry counties. The paper commented that other industries are generally to be found in the same location as the petroleum industry, but no attempt was made to define which other industry, if any, might have contributed to the high mortality from various disease groups.

1.1.4 Proportional mortality analysis

A relatively simple check of an issue can be carried out where records are available that identify the cause of death in a group of workers. The analysis merely requires the following information for each individual who had died: sex, date of birth, date and cause of death. The technique tests whether the proportion of deaths from the cause of interest is greater or less than one would expect in relation to deaths from all causes. The expected figure is usually calculated by applying the proportion of deaths by cause for the county as a whole to the distribution of actual deaths, taking age, sex and calendar period into account.

Boyd and his colleagues (1970) cross-checked the initial observations of a pathologist in Cumberland that iron-ore miners appeared to have a higher prevalence of lung cancer at autopsy than one would expect (bearing in mind the relative frequency of this as a cause of death in males in England and Wales). They had access to the death certificates issued for all males dying in Cumberland in 1948–67. These were sorted to identify all decedents recorded as being iron-ore miners; the deaths of all other individuals were used as the comparison group. Taking age and calendar period into account, the relative proportion of deaths from lung cancer, other cancers, respiratory disease and all other causes were examined. They observed 42 deaths from lung cancer in the miners, with an expected of 27.7 based on national data and 28.8 based on local mortality.

Their results thus supported the initial observations of the pathologist, though no definitive cause of the malignancy was identified. (A suggestion was made that the atmosphere in the mine was contaminated with radon, which might have accounted for the enhanced risk, rather than this being due to the dust from the iron-ore.)

Although an identical technique may be used to examine cancer registrations, it may not be so easy to identify all diagnoses of cancer. In a workforce, there may not be any employer or union mechanism for recording such material, and there may be great difficulty in obtaining particulars for those who leave the industry or retire. In addition, not every country has available national cancer registration statistics that can be used for calculation of the expected events.

For a condition that is relatively common, it may be possible to use local rather than national statistics in order to estimate the expected distribution of events; this may have an advantage of correcting for any regional, social class, or other local factor that influences the pattern of mortality other than that possibly due to the specific occupation.

A brief description of the statistical technique for handling such data is provided in 1.5.2.

Ad hoc studies using this technique have usually obtained the event data for the occupation being investigated from (*a*) company records, (*b*) union records, (*c*) insurance schemes (including those operated by companies or unions), (*d*) professional societies or registers of accredited professionals and (*e*) details recorded at death or cancer registration in a defined locality. Routine national systems may also use this approach, where there is doubt about the validity of estimates of the exposed population, e.g. in England and Wales for annual analyses of cancer registrations by occupation.

1.1.5 Cross-sectional studies

It is a relatively simple matter to identify subgroups of workers in industries where irradiation or benzene exposure may have occurred, and to classify the groups by extent of exposure. Samples of the men may then be approached and, in addition to collecting data on non-occupational factors causing chromosome abnormality, the men may be requested to give an appropriate sample so that detailed chromosome analyses may be carried out. Such a study was carried out on workers exposed to benzene; the initial findings of a highly significant excess of abnormalities in the benzene workers was not confirmed in a follow-up study, which showed an even higher abnormality rate in the control population selected (Tough and Court Brown, 1965; Tough *et al.*, 1970). The prevalence of chromosome aberrations was determined in the peripheral blood lymphocytes of dockyard workers exposed to mixed neutron γ-radiation. Exposures were mostly below the accepted permissible level of 0.05 gray (Gy) per year, but a significant increase in chromosome damage was noted with increased exposure (Evans *et al.*, 1979).

Such cross-sectional studies are only suitable for investigating carcinogenesis when there is some valid measure of a precursor of malignant neoplasms. Surveys of chromosome aberration, *in situ* cancer, or prevalence of benign lesions may be suitable. The prevalence of cancer will usually be so low that it would be impossible to mount an adequately sized survey of an exposed and non-exposed workforce to obtain interpretable results.

1.1.6 Case-control studies

Conventional case-control studies may be used to probe for occupational exposures with cancer. There are two conceptually different approaches: type 1 chooses one or more sites of malignancy and explores a range of aetiological factors including occupation, searching for differences between the cases and the controls. Type 2 is much more focused on one site of malignancy, estimating the risk for those exposed to a particular occupation.

Type 1 study

In the United States Third National Cancer Survey interviews were obtained from 7518 persons with cancer in 8 areas (a response of only 57%). Information was collected on alcohol and tobacco use as well as on employment history. The analyses consisted of two-times-two tables of counts of persons with/without a particular cancer against having/not having a specific employment; with 29 sites and 202 employment categories, this generated 5858 comparisons. This use of 'intercancer comparisons' has the problem that a cancer in the control group may be exposure-biased (under or over-represented); unless this cancer was more than a small proportion of the total, this effect would be minimal. Williams, Stegens and Goldsmith (1977) suggested that a major advantage of the study was that it permitted use of smoking, alcohol and socio-economic status as control variables.

Type 2 study

Damber and Larsson (1982) identified 604 males dying from lung cancer in northern Sweden, an equal number dead from other conditions, and 467 living controls. History of occupation and smoking were obtained from next-of-kin. The particular focus of interest was the influence of work underground in the local iron-ore mines, and the relative effect of such work and smoking on risk of lung cancer.

The important point in distinguishing between these two approaches is that the former (study 1) is an exploratory or 'fishing' study, which can only be used to generate hypotheses for further study, whilst the latter (study 2) may quantify the risk or evaluate aspects such as dose–response.

A more restricted study may only collect data from a sample of index patients, and then compare the distribution of occupation reported with those published from the census. Though this involves a lower cost per case than in conventional case-control studies, there may be bias in the two sources of information. Lee, Alderson and Downes (1972) used this approach in a study of scrotal cancer and Acheson, Cowdell and Rang (1972; 1981) in studies on nasal cancer.

1.1.7 Historical prospective studies

Rushton and Alderson (1981a) used industry records to identify men employed for at least a year in 8 oil refineries in the UK in the period 1950–75. Those who had left their company's employment and retirees whose vital status was not known were traced through central Social Security and the NHSCR records. All deaths were thus identified, the causes obtained, and compared with the calculated expected value based on national mortality rate with adjustment for regional variation. A statistical test was then applied to the comparisons between O and E. The results are presented in *Table 3.5*.

Where there are available records of individuals' work histories, with a complete file of data on mortality that has occurred among these individuals, it should be possible to relate the data on the 'population at risk' to the identifiable outcome, i.e. mortality. The occupational records are used to identify each individual in the study. It is essential to know the following: each individual's date of birth (or age at starting work), the date of entry to the occupation, some indication of potential environmental exposure, the follow-up status. The latest date known to be alive should be obtained for all individuals, including those still in the workforce and those who have retired. Individuals who have left the industry should be traced in order that their status can be obtained. Such leavers are likely to be different in a number of ways from those staying in the industry; without follow-up information on such individuals, the statistics may produce an incomplete or biased result. Rushton (1982) compared the results from a study which included tracing all those leaving the industry prior to retirement with results excluding this group. There were no appreciable differences and it was pointed out that avoidance of the lengthy and costly tracing should be considered, bearing in mind the age of these premature leavers, their length of service, and the proportion of deaths they are likely to contribute to the study results. For all deaths that have occurred in the study population, the date of death and cause of death is required. This material can be manipulated in a standard fashion to generate 'person-years at risk', which are tabulated by age and calendar period (*see* 1.5.3). By applying national age, sex and calendar period cause-specific mortality rates, the expected numbers of deaths by cause may be calculated. A comparison is then made between the respective numbers of observed and expected deaths for particular causes; the statistical aspects of this comparison are discussed in 1.5.4.

This approach can be used to explore the risk of a specific cancer, or to examine patterns of mortality of the workers in more general terms.

Occasionally, full details of each member of the workforce are not available, but company records may be able to provide estimates of the numbers of employees and pensioners by age group over the period for which death details are available. Using such material, Dean *et al.* (1979) were able to calculate expected deaths by cause and to compare these with observed deaths for the blue-collar workers at a Dublin brewery in 1954–73. This technique is less precise than using the calculated person-years at risk based on data for each individual, but it provided a sounder statistic than proportional-mortality analysis.

There are three 'types' of cohort that may be followed in such studies: (*a*) a group in post at a particular point in time (which will usually include individuals of varying age, and mixed duration of exposure), (*b*) a study confined to new entrants to a workforce over a defined period, (*c*) a combination, with staff in post supplemented by new entrants over succeeding years. These different approaches introduce appreciable differences in the age structure of the study population, the duration of exposure, and the time periods at which exposure occurred. If there have been major changes in the environment of the plant over time, there will be confounding between duration and intensity of exposure.

Many studies fail to distinguish these aspects both in description of the study and in the interpretation of the data.

1.1.8 Prospective studies

In 1953 the National Coal Board began a survey of working coal miners; in 1953–58 men at 24 collieries in the UK were interviewed and had a chest X-ray. Subsequent surveys involved medical examination and assessment of respiratory function, and respondents completed a questionnaire on respiratory symptoms and smoking habits. Work histories and measurements of respirable dust concentrations permitted calculation of cumulative exposure for individuals. Analyses of mortality in relation to these factors were reported by Miller, Jacobsen and Steele (1981). As an example, there were 19 550 men in England and Wales for whom reliable information on cumulative exposure to mine dust was available; the exposures were divided into 4 groups. Because older men predominated in the higher exposure categories, analyses were by age group at first survey. Two tables provided mortality from stomach and other digestive organs; there was a significant trend in mortality with increasing dust exposure. However, there was also a close association between dust exposure and pneumoconiosis, and between pneumoconiosis and mortality from digestive cancers. It was not possible to distinguish between a direct effect of dust or an indirect effect via pneumoconiosis on risk of these cancers.

The distinction from historical prospective studies is that, after the study design has been confirmed, *ad hoc* arrangements are made to collect detailed data on (*a*) exposure to agents in the work environment, (*b*) confounding factors, (*c*) long-term outcome. Rather than retrieve details of occupation held by individuals and relate this to subjective assessment of exposure, the work environment is surveyed at intervals to quantify 'dose'.

During the study design phase, the important confounding factors should be listed and consideration given to collecting relevant data from the subjects in the study. This is especially important for an aetiological factor known to play an appreciable part in the cause of the cancer, or where there is suspicion of interaction between the occupational environment and this second factor.

1.2 Principles of occupational studies

The following subsections discuss some of the general aspects of occupational studies. In addition to the points made here reference should be made to a textbook on epidemiological method to obtain more information, e.g. Alderson, 1983.

1.2.1 Who is at risk of an occupational hazard?

It is not only workers involved in primary production who may be at risk of cancer from exposure to carcinogens. An obvious example of the chain is that associated with asbestos; this involves those working in the mines, handling the 'raw' asbestos in factories, applying asbestos as in lagging and insulating, even stripping insulation out of various articles at breakers' yards etc. In addition to this chain of exposures, it has been shown that the families of workers and those living in the vicinity of an asbestos factory had an increased mortality from mesothelioma (Newhouse and Thompson, 1965). This was thought to be due to (*a*) contamination of the workers' clothes which then exposed the wives who washed these, and (*b*) contamination of the locality surrounding the factory with fibres transmitted in the air. This indicates the expanding ring of contacts who need to be considered when assessing any hazard from a particular industrial process.

Rather more difficult to investigate is the possibility that the next generation may be at risk—from fetal loss, excess stillbirths, congenital malformations, or cancers. This has been tackled in 1.4.6.

1.2.2 Which individuals are eligible for inclusion in a study?

A number of points of eligibility need to be considered in planning a study. It is often desirable to exclude workers with a minimum duration of employment (to restrict those transients with limited relevant exposure). This may be excluding those who have worked for only 1 month, 3 months, 1 year or perhaps 5 years. It is recommended that individuals with employment over the minimum (such as a year) should be included, even though their exposure is relatively limited, as they help provide estimates of a dose–response relationship.

If a hazardous agent is extremely potent and the latent interval for generating the hazard is less than 20 years, then an adequate indication of this may come by studying just those in employment. However, if the condition is rare, and the latent interval is long, then it is unlikely that the hazard will be clearly identified in those under the age of 65. If the turnover in the occupation is high, then it is even more important that not only pensioners, but also those leaving prior to retirement, are followed up. It is usually possible to organize retrieval of vital status for pensioners, but it is much more expensive to trace the leavers. However, if the number who have worked on a particular plant or process is small, it may be crucial to trace these individuals in order to obtain enough numbers of events for statistical analysis. Rather different is the point that, if the workers who leave the industry are a biased group of those who have been exposed to risk, it is extremely important to trace them—for example were they the dirty workers who had a higher than average exposure? Were they individuals who were in some way sensitive to the environment? In the past, many studies of occupational hazards have excluded women, because of the small numbers involved. However, with the advent of legislation against sexual discrimination, the inclusion of women becomes more appropriate. It is also possible that the exposure and reaction to exposure differs between the sexes and again this argues for inclusion of women. One particular aspect of this is if the hazard influences the risk, not to the exposed person, but to the next generation; ionizing radiation may, for example, have an effect on the pregnant woman which it cannot have on the exposed male.

In many industries, contractors may come onto the site and have an environmental exposure entirely different from that of the normal plant operators. However, because the organization of their employment records is different, it is often difficult to include contractors' personnel in an occupational study. Rather different are 'visitors'—for instance in some fields of work it may be customary to have individuals coming from abroad to work for a limited period of months or years. It is an important issue to consider whether such individuals also need to be included in the study.

Other reasons for difficulty in studying specific groups of men are: (*a*) maintenance staff, who have not only the exposures specific to their craft, but work in many parts of a plant, often with higher potential exposure than process workers; (*b*) management systems with flexible manning and workers moving between plants of different environments; (*c*) movement of staff in complex installations from plant to plant, for increasing experience or on promotion; (*d*) progression of long-stay workers from the 'dusty or dirty' end of a process, to more popular jobs with lower exposure levels.

1.2.3 Factors influencing initiation of a study

With finite resources and the likelihood of a stream of fresh leads to consider, it is not possible to launch a definitive study on each 'hunch'. Less tangible issues may be critical to the decision, such as the enthusiasm of the research workers, the degree of collaboration available for the project, or even the very implausibility of a new and previously unsuspected health hazard. Having selected the appropriate research topic, there is then need to ensure that appropriate research facilities are available; these may be the techniques, the ideas, the equipment, and other facilities required. Providing the facilities are available, there must be access for the study to be carried out. The specific points requiring clearance will depend upon the design of the study, but many require access to retrievable records, or the investigation of individuals. As far as retrievable records are concerned, this may need access to (*a*) personnel records, (*b*) environmental data and (*c*) follow-up data on individuals who have left the industry. Such access requires the approval of management and union, with permission to disclose the identity and release information required to trace individuals who have left the industry. The tracing of leavers raises the issue of confidentiality of personal records; the Medical Research Council (1973) has provided guidelines for research in this field. The Faculty of Occupational Medicine (1982) has also produced notes of guidance on the ethics for occupational physicians.

1.2.4 Tracing individuals

Particularly with historical prospective studies, there is a need to trace subjects to determine their vital status. The actual approach used will depend on the employer's records, and the avenues open in different countries.

As far as employer's records are concerned, the study may initially identify all men ever employed. The tracing will usually be required for (*a*) those leaving prior to retirement, and (*b*) at least some of the retirees, i.e. those not known to the pension fund to be alive or dead. In the United Kingdom (UK), it is possible to trace individuals through the central Social Security records to identify the fact of death, or through the NHSCR to obtain fact and cause of death. The former is simpler if the National Insurance Number is known; the latter is facilitated by the NHS number and has the great advantage that once a group of workers have been identified on the register, their entries can be 'flagged' and the research worker informed as future deaths occur. For either system, identification must include surname, forenames, and date of birth in order to distinguish individuals in these national files.

Transfer of the names from the industry, via the researcher, to the central registers must comply with accepted ethical agreements on confidentiality of such information. Since 1971 in England and Wales and also in Scotland, cancer registrations have been annotated on the NHSCR. With appropriate safeguards on confidentiality, this information may be released to the research worker for workers who develop cancer.

Equivalent systems exist in Scandinavia, whilst the newly established death index in the US will provide an alternative source. In other countries *ad hoc* local follow-up is required.

1.2.5 Validity

This section covers a number of points that are particularly relevant to studies of occupational cancer. However, there is an extensive literature on general aspects of validity of the different types of occupational study (*see* Alderson, 1983, for review).

1.2.5.1 Bias in subjects studied

A preliminary consideration is whether all employees 'at risk' were covered in the study. Marsh and Enterline (1979) stressed the importance of independent check of the completeness of occupational cohorts. In a validation of records for 6 plants in the United States, additional records for 21% further subjects were found by cross-checking against Inland Revenue records. The reason for the emphasis on requiring a complete cohort is the worry that those missing are atypical in respect of exposure, other risk factors, or development of disease.

Rather different is the consideration of the selection process involved; Ogle (1885) gave a clear description of some of the biases associated with selection into and out of occupations. For example, some jobs can only be done by the physically strong and active; these characteristics of the workforce may determine their patterns of morbidity and mortality, rather than any aspect of the work environment. An associated aspect is the influence of non-occupational factors on risk of disease that may also be linked to work. For example, many occupational studies have involved examination of the (potential) hazard of lung cancer—a lung cancer for which there is a known major behavioural risk factor (smoking). If smoking habits have not been recorded for the employees in a specific occupation, it is always questionable whether variation in smoking could account for any difference in lung cancer mortality in the workers. Of course, if information is available on intensity and duration of chemical exposure and a dose–response relationship is found with lung cancer, this is less likely to be due to confounding with smoking; however, such results do not rule out a multiplicative or interactive effect between the smoking habits of the workers and their occupational environment.

1.2.5.2 Dilution of environmental effects

When a work hazard only directly affects a restricted group of individuals, the impact of this may be diluted or lost by studying a broader group of the workforce. In general terms this was well recognized over 100 years ago (Registrar General, 1855); it is a point that warrants consideration whenever it is not known precisely what is the specific hazard responsible for the health problem being studied. Without clear definition of the discrete group of workers 'exposed to risk', there may be loss of precision in the study; this may also be an inevitable consequence of those studies using routine or retrievable data, when job titles cover broad categories of workers.

1.2.5.3 Validity of exposure data

There is bound to be considerable difference in the quality of exposure for the different types of study. Occupational mortality and incidence statistics rely on job descriptions obtained at one point in time and processed in a routine statistical system (with potential bias between the numerator and denominator for rates, and SMRs). Very different is the quality of data that are collected in prospective studies. It also appears that in the past the degree of recording has been higher when physical measures are involved (asbestos, dusts in general, irradiation) rather than levels of chemicals in the work environment.

With a process involving a single suspect agent, it may be satisfactory merely to document whether or not exposure was likely to have occurred. More suitable data for analysis are provided by the quantification of the intensity of exposure and the duration of exposure. It may be difficult to gauge in which broad category of exposure level individual workers should be placed; in many industries, no records exist of environmental or personal monitoring for specific chemicals. This difficulty is exacerbated where a complex chemical works has many plants and workers move from one plant to another. Sometimes the range of chemicals involved in some of the plants and processes might be unknown, let alone their levels in the environment monitored. Indirect assessment of potential exposure of process workers may be possible. This becomes much more difficult, if not impossible, for maintenance staff who move throughout a site; often, because of the nature of their work, exposure may be very difficult to gauge and very different from that of the normal working of the plants. Smith, Waxweiler and