

Occupational Cancer

A guide to prevention, assessment and investigation

AFOM Working Party on Occupational Cancer



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PREFACE

There is scientific consensus that some occupational exposures can cause cancer. Many current cancers are the result of past occupational exposures. Moreover, although significant progress has been made in preventing occupational cancer, some members of the workforce are still being exposed to agents which increase their likelihood of developing cancer.

Like most occupational diseases, occupational cancer is preventable. For this reason and because cancer is such a serious disease, it is to be expected that occupational cancer prevention would be a high public health priority and that clear guidelines would be available to compensation jurisdictions so that cancers caused by occupational exposures can be correctly identified. Unfortunately neither is the case. Although the National Occupational Health and Safety Commission (NOHSC) has identified and classified several exposures as carcinogenic, cancer control initiatives by industry or by State governments - who have legislative responsibility in this area - have been limited. In New Zealand the Ministry of Health, in its 2002 Cancer Control Strategy, has listed occupational cancer as a priority area, and the Department of Labour (OSH) has formed a Cancer Panel.

In the case of identifying current occupational cancers, Australia has no guidelines for assessing workers' compensation claims. The result is that claims could be determined according to which expert witness is the most credible. Credibility does not necessarily coincide with scientific judgement, particularly when no "expert" witnesses with competence in the relevant field are called. Moreover, the judgement of expert witnesses can be influenced by factors such as which party to the disputed claim seeks their opinion. This differs markedly from current practice in clinical medicine, in which clinicians are increasingly required to base their decisions - on diagnosis, prognosis and treatment - on scientific evidence.

The Australasian Faculty of Occupational Medicine (AFOM) has prepared this document primarily for physicians, particularly those who advise industries and unions, to help them identify industries, occupations and exposures which may be associated with cancer. It will help them prepare advice on the actions required for primary prevention, and measures to take to ensure that such preventive actions are effective, so that workers can be assured that their health is being protected.

This document is also intended as a resource for compensation jurisdictions, and the physicians who advise them, to provide principles and guidelines for identifying which cancers are attributable to work.

EXECUTIVE SUMMARY

There is widespread scientific agreement that many current cancers are caused by occupational exposure, and that occupational cancer is preventable. Yet preventing occupational cancer has not been a high public health priority and there are no clear guidelines available to the compensation courts on how to correctly assess claims.

This guide is intended to assist physicians who advise industries and unions in identifying occupations and industries associated with occupational cancer and putting in place preventative measures to minimise exposure and risk. It is also a guide for physicians advising compensation jurisdictions seeking to identify which cancers are attributable to work.

Chapter 1 examines the role physical and chemical agents play in causing cancer and how carcinogens are identified. It points out that most environmental and occupational carcinogens are difficult to identify because of the long time delay in cancers being diagnosed, and the combination of factors that cause cancers. Occupational cancers are indistinguishable from those unrelated to work. Carcinogens are therefore classified as known or suspected, and there can only be cautious estimates of the number of occupational cancer cases and their proportion to all instances of cancer.

It is concluded that most future occupational cancers will either be respiratory, related to past exposure to asbestos, or non-melanoma skin cancer from solar radiation. While occupational exposures are probably responsible for a small proportion of cancers in the general population, within particular workgroups carcinogenic exposure is still a significant concern. Because it is impossible to say with certainty which agents are carcinogenic and which individual cancer is occupationally caused it is best to treat all chemicals as potential carcinogens.

Chapter 2 sets out the primary steps to prevent occupational cancer, which is a statutory requirement on employers in all Australian states and territories and in New Zealand.

If it is impossible to eliminate the carcinogenic agent, the object should be to limit the number of workers exposed and to minimise the duration of exposure for those who are. Two important principals must be borne in mind:

- measures are best considered at the design stage rather than waiting to modify the plant once installed
- “passive controls”, that is measure which do not require the active cooperation of workers are more effective than those needing behavioural change on the part of every individual worker.

The chapter reviews practical measures to isolate the carcinogenic agent, minimising the number of workers exposed and exposure times, reducing the intensity of exposure and contingency plans for system failure.

The authors also review strategies for pre-placement screening of high risk individuals. While, for example, there is a synergistic effect from the combination of smoking and exposure to asbestos so that placing smokers away from work where there is any likelihood of occupational lung cancer would reduce risk, they conclude that placement measures should not be viewed as a substitute for preventing exposure.

They also conclude that with the present state of genetic knowledge, exclusionary employment practices based on genetic screening are unlikely to significantly reduce cancer risk compared with eliminating or controlling exposure.

Where workers have had past exposure to carcinogens a number of measures should be considered including avoiding exposure to other carcinogens. The underlying principle is that workers must be provided with all relevant information.

Chapter 3 details the surveillance regime that may be put in place to monitor workers who are exposed to carcinogens in the workplace, with a view to ensuring control systems are working to minimise exposure and to detect early signs of disease. These include measuring the amount of chemical in the work environment, monitoring the measurement of chemicals in body tissues and fluids.

Monitoring the workplace environment and work methods are essential in identifying potential sources of exposure, while personal monitoring is more useful for predicting risk. Comparing exposure to recommended exposure standards should ensure that most workers are protected. However any exposure to carcinogens, no matter how small, should be regarded as bearing some risk. Consequently the target level should be the lowest level of exposure that is reasonably achievable, rather than simply meeting recommended standards.

Biological monitoring involves tests on blood or urine for chemicals or their metabolites and can be an important adjunct to environmental monitoring where a valid measure exists. Tests to detect interaction between chemicals and DNA are mainly research tools at present. Caution is required in interpreting the results of such monitoring, which is most useful as an aid to estimating exposure rather than predicting future effects. Tests to detect genetic or chromosomal damage require great care in execution and in interpretation as they are also mainly research tools and require matched controls for comparison. They have no place in predicting whether a particular individual will develop disease.

Caution is also necessary when screening individuals for early cancer or premalignant states, since the timing of screening is crucial. Most screening programs are done by employers yet most cancers are likely to develop long after the worker has ceased employment at the workplace where exposure occurred. The establishment of a State or national register of workers with past exposure to carcinogens is desirable.

When identifying current occupational cancers Australia has no guidelines for assessing workers compensation claims, so that claims can be determined on the basis of the credibility of competing expert witnesses. Yet credibility does not necessarily coincide with scientific judgement. Chapter 4 seeks to supply those guidelines.

Unlike infectious disease, cancer in a patient previously exposed to a cancer causing agent cannot readily be attributed to that agent. Consequently these cases must turn on the probability that the agent caused the cancer.

To assess that probability 7 questions must be considered:

- Is the agent carcinogenic to humans?
- Could the exposure have led to the uptake of the agent?
- What was the intensity and duration of the exposure?
- Is the agent associated with cancer at this site and of the same histological type?
- Is the site of the cancer consistent with the route of uptake of the agent?
- Was the time from exposure to disease onset consistent with the induction latency period of the agent?
- Were there other factors that might have contributed to the risk of cancer in this person?

After examining these questions the probability that the cancer was caused by the exposure must be quantified. This decision can be aided by deriving an arithmetic function called the probability of causation (PC) such that

$$PC = (RR-1)/RR$$

where RR = relative risk, ie the cancer rate in an exposed population compared to an unexposed population. If RR exceeds 2 the balance of probabilities favours the claimant.

The RR can be determined by consulting the epidemiological literature, though it may also be necessary to adjust the estimate of PC for other causal factors, eg smoking.

While the PC model has the advantage of simplicity, though, there are problems. The PC will fall onto a continuum between 0%, where we can be certain that the exposure was not causal and 100% when we can be certain it was. Determining causality according to whether the PC is above or below 50% will lead to errors in some cases. An "all or nothing" threshold could be regarded as harsh, and legislative adjustments could be made to give the claimant the benefit of the doubt. This though is a matter for political decision making.

Asbestos exposure is the commonest cause of work related cancer. Chapter 5 summarises the main issues in assessing the probability of causation.

If asbestosis is present the assessment is relatively simple and no quantitative estimate of exposure is required. Furthermore this judgement can be made irrespective of smoking history.

If asbestosis is not present the decision on whether the cancer is caused by asbestos is a matter of continuing debate, and it is unlikely that consensus will be reached in the near future on whether asbestos exposure can cause lung cancer in the absence of asbestosis. If it is held that asbestosis is not a necessary precondition for asbestos related cancer the criterion for accepting a compensation claim should be whether the individual has received a doubling dose of asbestos: ie whether the cumulative exposure is sufficient to cause an RR of lung cancer greater than 2.

Assessments of mesothelioma are simpler because, unlike lung cancer, nearly all cases are asbestos related. In industries where there is a history of asbestos exposure mesothelioma can be confidently ascribed to exposure, even where that exposure has been light or transient.

A recent rise in the incidence of mesothelioma in women in Australia suggests the disease can arise from asbestos levels close to the low background levels all urban dwellers are exposed to. As achieving zero exposure to removal workers even under strict controls is unrealistic, consideration should be given to alternatives to removal, such as sealing or encapsulation.

An issue for occupational medicine is the occurrence of clusters in a workplace or the surrounding community. Unlike epidemics clusters are difficult to confirm, and can occur by chance. Nevertheless clusters should be investigated with a mind receptive to the existence of a cluster. Such investigations should involve the interested parties in the workplace, be open, and the results openly communicated to these parties.

Chapter 6 outlines the specific steps such an investigation should work through. The diagnosis of the initial cases that lead to concerns that a cluster might exist should be confirmed, whether there is an excess of cancers, a suspected causal factor and whether the excess is work related. Even where a cluster is not found to be more than chance such investigations can point to improvements in workplace conditions and may lead to the recognition of new hazards.

1 INTRODUCTION

The role of physical and chemical agents in cancer causation

Cancer is now believed to develop as a result of a series of steps, many of which involve genetic changes. If the genetic material (DNA) in a cell is damaged or altered and not repaired, the alteration can be passed on to successive generations of cells when mitosis occurs. Mutation is the term applied to such a heritable change in the DNA. Subsequent division of an affected cell can lead to a cell population in which all cells carry the mutation. A further mutation in any one cell in that cell population can lead to yet another new cell population with two mutations and so on. Such changes in the DNA structure can lead to changes in function, particularly in the regulation of cell division and cell death. Cancer can be the result of a sequence of such mutations, in which cells divide in an unregulated manner. For example, cancerous tissue fails to recognise tissue boundaries, and invades surrounding tissues and organs.

A number of physical and chemical exposures have been shown to cause genetic changes either by direct damage to the DNA or by causing tissue damage which in turn leads to DNA damage. The practical significance is that exposure to these agents can be responsible for human cancers, ie they are human carcinogens.

Not all carcinogenic substances are genotoxic however. The cancer-causing mechanisms are not fully understood, but it is likely that factors that increase the rate of cell division increase the likelihood of mutations. An example is alcohol, which leads to toxic damage to liver cells followed by rapid cell division during the process of repair. Some medical conditions associated with rapid cell proliferation (eg uterine hyperplasia) are associated with increased cancer risk.

Because several steps are involved in the development of cancer, there is often a lag period of many years, even decades, between exposure to a carcinogenic agent and the diagnosis of cancer. The period between exposure and onset of the cancer is called the latency period (or the induction latency period) of the agent.

A substance defined as carcinogenic is a contributing cause of cancer in some individuals. It does not mean that it can cause cancer on its own. In fact cancers usually occur as the result of exposures to a combination of causal factors.*

Moreover to define a substance as a carcinogen does not mean that it is causal in all cases of such cancers. Unlike the measles virus for example, which is a requisite for the occurrence of measles, most carcinogens are not *necessary* causes of cancer. Even cigarette smoking, which is strongly associated with lung cancer, is not a necessary cause of that condition: lung cancer can occur in lifelong non-smokers, even in the absence of passive smoking. It follows that since lung cancer can occur in the absence of smoking, cigarette smoking need not necessarily play a causal role in every lung cancer, even in those with a smoking history.

How carcinogens are identified

Some occupational carcinogens have been recognised for many years. For example, the aromatic amines beta-naphthylamine and benzidine were easily recognised as carcinogenic in the late 19th and early 20th centuries because a high proportion of workers using these agents in the chemicals industry developed bladder cancer.¹ Vinyl chloride monomer is another agent readily identified as a carcinogen, because of the unique cancer type - angiosarcoma of the liver - associated with its use.

However, most environmental carcinogens, including those in the occupational environment, are difficult to identify, for a number of reasons:

- The responsible exposures are likely to have occurred years, even decades, before the cancer is diagnosed. The exposures are often poorly documented and may even have been unrecognised at the time.
- Cancers are usually caused by a number of factors acting in combination or in sequence, and different combinations of factors may be responsible for particular cancer types in different individuals.
- Work-related cancers are usually indistinguishable in their histology and natural history from similar cancers which are unrelated to work. For example, a bladder cancer caused by exposure to an aromatic amine is indistinguishable from a bladder cancer due to another cause.

* A sufficient cause of a disease is one which will cause the disease in all who have that trait or exposure, and no other risk factors need be involved

The last of these reasons means that individual cases of cancer cannot readily be attributed to a particular environmental carcinogen. Carcinogens may be identified by epidemiological studies, which aim to compare the incidence of cancer in an exposed population with the incidence of cancer that would occur in that population in the absence of exposure.

The possibility of other factors causing the cancer complicates such studies. Ideally the effect of an exposure should be measured by comparing two populations which are identical in all respects except that one is exposed and the other is not. This ideal can be achieved in animal studies but not usually in human studies.

Animal studies can be carried out under experimental conditions, which the experimenter can completely control. The exposed and non-exposed animals are comparable, sometimes even genetically identical, and exposures are measured precisely. Unfortunately, the findings in animals of such studies do not necessarily apply to humans. Different animal species can handle foreign substances differently, and outcomes can be specific to the species under study; for example some substances are carcinogenic to mice, but not to rats. Moreover animal studies usually involve larger exposures, relative to body size, than the exposures workers are likely to incur, and it cannot be assumed that effects on exposed workers can be inferred by extrapolating from effects observed in animal experiments. Nevertheless, animal studies are an important guide in identifying human carcinogens. The application of animal studies in evaluating chemicals for carcinogenicity is discussed in Appendix 1.

The evaluation of human carcinogenicity should if possible be based on evidence which includes human studies. However, for obvious ethical reasons, experimental studies are not possible on human subjects. Reliance must therefore be placed on *observational* studies, in which measurements are made of exposures (or estimates of past exposures) which workers happen to have experienced, and their cancer incidence or cancer mortality is compared with those of persons not exposed. Thus the person conducting the study not only has no control over the exposures, but is usually limited in the availability of a suitable non-exposed population. Ideally the non-exposed should be comparable to the exposed in all respects except for the exposure. Where comparability cannot be achieved in the study design, adjustment may be required in the analysis. However, it may not be possible to identify all the ways in which the exposed and unexposed populations are different. One of the major difficulties in epidemiological studies is to ensure that observed differences in cancer rates due to unrecognised differences in the two populations (eg in relation to lifestyle) or differences in the completeness of identification of disease, are not wrongly attributed to the exposure under study.

Another major difficulty is the long lead-time between exposure and the onset of cancer. The task of identifying and measuring exposures that may have occurred many years ago is fraught with uncertainties: adequate documentation of past exposures is rarely available. The lead-time in epidemiological studies is in fact an important drawback; they require the occurrence of cancers or cancer deaths before carcinogens can be identified. For this reason there has been extensive research in recent years to identify valid biological markers of cancer risk in exposed workers, so that further exposure may be prevented in time to prevent cancer onset. Some of these biological markers are discussed in Chapter 3.

In practice there are limited epidemiological data to support the evaluation of most suspected carcinogens. Epidemiological studies are expensive and logistically complex, thus limiting the number of studies and the scope of those that are undertaken.

Classification of carcinogens

Because of these difficulties, there is uncertainty and dispute as to which agents can cause human cancer. Several agencies and organisations provide listings of chemicals that have been evaluated according to specific criteria and have been identified as carcinogens. For example, the International Agency for Research on Cancer (IARC), a body sponsored by the World Health Organization (WHO), attempts to resolve differences by assembling scientific working parties to examine available evidence and to seek consensus on particular agents. The outcome is that each agent is assigned a classification, for example carcinogenic to humans, probably carcinogenic, possibly carcinogenic.

The criteria by which carcinogenicity is assessed are described in all IARC monographs and the IARC specifically notes that the information provided in these assessments will be used in different ways by different users (such as scientists, regulators and physicians). A description of the IARC classification protocol is given in Appendix 1. IARC evaluations are primarily concerned with identifying carcinogens, from which risk assessment and public health measures may follow. They are not concerned primarily with attributing individual instances of cancer to particular exposures.

Classification tends to be reliant on epidemiological studies, which present difficulties in separating the effect of occupational exposures from that of other possible causes. An important example is smoking, which is a powerful

cause of many cancers that are also caused by occupational exposures. The findings of epidemiological studies can be misleading if there are differences in the smoking patterns between the population with exposure to occupational agents and the comparison population. The differences may not be simply in the proportion of smokers in the two populations: there may be differences in the amount smoked and in the number of years since quitting, both of which have profound effects on the relative risk of cancers, particularly lung cancer.

The application of epidemiological findings to IARC classification criteria is a matter for scientific judgment of IARC panel members. Although IARC classifications are widely accepted, they have sometimes been based on split decisions, and some decisions have been contentious. Examples from recent years are the categorisation of cadmium, beryllium and silica as human carcinogens.²⁻¹⁶ Conversely, some decisions have been criticised for undue influence from industry.¹⁷ Thus an IARC classification does not necessarily mean that the matter is beyond dispute.

In Australia the National Occupational Health and Safety Commission (NOHSC) classification includes: Category 1 carcinogens - substances known to be carcinogenic to humans, and Category 2 carcinogens - substances regarded as if they are carcinogenic to humans. Chemicals classified as carcinogens by NOHSC are listed in Appendix 2a

New Zealand has three categories of carcinogens: A1 - confirmed human carcinogens, A2 - suspected human carcinogens, and A3 - confirmed animal carcinogens with unknown relevance to humans. A1 and A2 carcinogens are listed in Appendix 2b.

How many cancers are work related?

The estimate of the proportion of cancers attributable to occupational factors is therefore hampered by uncertainties over which agents are cancer-causing.

Individual cases of occupational cancers are usually clinically indistinguishable from cancers unrelated to occupation. Hence there are no registers of occupational cancers (with the exception of mesotheliomas, discussed below) which allow estimates to be made of the proportion of cancers caused by work. Reliance has to be placed on population estimates based on epidemiological studies, rather than on registers of particular cases.

Caution is required in applying findings from epidemiological studies to assess the number of occupation-related cancers in current Australian conditions. Several chemicals are scheduled as "human carcinogens" on the basis of studies in overseas countries in previous decades, where there were many heavily exposed workers. Such heavy exposures are not common in the Australian workforce (although heavy exposures no doubt occur in other countries, particularly countries without the rights of organised labour which are taken for granted in democracies). Therefore in assessing current risk, information is needed on current exposure levels and exposure-response relationships.

Moreover the presence of a chemical in the work environment does not automatically mean that workers are exposed. There is no risk of disease unless an agent either becomes airborne and is then inhaled, or is absorbed through the skin or ingested. For example a number of therapeutic substances used for cancer treatment are themselves carcinogenic and, while this is a concern for those cancer patients who are deliberately administered these agents by mouth or by injection, it is only a concern to those who dispense or administer these agents if they become airborne and are inhaled. Under current conditions it is unlikely that significant exposure is occurring.^{18,19}

A number of estimates of the burden of cancer due to occupational exposures have been attempted, and the most widely cited is the study by Doll and Peto published in 1981, in which an estimate of the fraction of each cancer type attributable to occupation was applied to the number of deaths from the corresponding cancer in the US in the year 1978.²⁰ The resulting overall estimate was that between 2% and 8% of all cancers in the US were attributable to occupation, with a best estimate of 4-7% in males and 1% in females. An estimate of the occupational cancer burden in Australia, using the same methodology, was published by Winder and Lewis,²¹ with the conclusion that about 1000 cancers per year are work-related. The method was again used, with minor modifications, in a report for Worksafe Australia in January 1994.²²

It is likely that the most important work-related contributor to current cancers is from asbestos exposures, which are responsible for nearly all mesothelioma cases. In 2000, the most recent year for which national data are available, there were 490 registered cases of pleural mesothelioma in males, and the number of such cases is continuing to increase.²³

In 1995 an estimate was made of the most significant contributors to the incidence of occupational cancer in South Australia.²⁴ It was estimated that between 3% and 26% of lung cancers were work related, with the most likely figure being about 8%; it is likely that many lung cancers have occurred from past asbestos exposures,

although whether these are still occurring is not known. (The latency period between asbestos exposure and lung cancer is probably less than for mesothelioma.) In the same South Australian study, it was estimated that up to 29% of leukaemias and 30% of lip cancers may be work-related. Cancers of the lip are commoner in outdoor workers, due to exposure to solar radiation. This exposure is also responsible for many skin cancers. The incidence of non-melanotic skin cancers is not recorded in State Cancer Registries, although a study published in 1998 showed high and increasing rates of these cancers, particularly squamous cell carcinoma, which is the skin cancer most strongly linked to occupational exposure to solar radiation.^{25,26} Fortunately, these cancers are not often fatal.

In the South Australian study an estimate was made of the future cancers being generated from current occupational exposures. For the purposes of this estimate, only substances or occupations for which the IARC has concluded that there is sufficient evidence of human carcinogenicity (ie Category I carcinogens) were included. It was estimated that as a result of chemical exposures experienced by people presently in the workforce at current exposure levels, 93 cancers would occur annually. Assuming that the total cancer incidence in South Australia stays the same as at the time this estimate was made, this number would constitute about 1.35% of all cancers. Bearing in mind that most occupational cancers would occur in men, a better estimate would be 2.44% of cancer in males, and 0% cancers in females. This estimate did not include occupational cancers from non-chemical exposures, for example non-melanotic skin cancers and lip cancers from solar radiation, cervical cancer in sex workers, liver cancer from occupationally acquired Hepatitis B and C in health care workers.

In New Zealand it has been estimated that 600 cases of occupational cancer occur each year, although only 138 cases of occupational cancer were notified and confirmed by OSH in the four years to June 1996 (ie 34 cases per year on average).²⁷

Recent overseas estimates of the burden of cancer due to occupation vary considerably. A recent Finnish study, conducted as a part of the WHO Global Burden of Disease study, concluded that work-related cancers were responsible for 8.3% of deaths in Finland in 1996. This study included an estimate of 29% of lung cancers in males caused by occupational exposures, of which one-half were caused by asbestos.²⁸ On the other hand a review of avoidable future cancers in the US has included an estimate that fewer than 1% of cancers would be avoided by removing occupational pollution.²⁹

Overall, it is likely that most occupational cancers in future will be respiratory cancers related to past asbestos exposure and non-melanoma skin cancer from solar radiation. Otherwise, occupational exposures are probably responsible for only a small proportion of cancers in the general population. However, *within particular workgroups*, carcinogenic exposures are still a significant concern: they require adequate prevention and control measures, and surveillance of the workforce.

Practical implications

It is therefore likely that the proportion of future cancers attributable to current work exposures is quite low. However, the possibility remains that many exposures, including some not yet identified, may each be partly responsible for cancers in numbers too small to be detected by observational epidemiological studies, and that collectively these may add up to a significant number of cancers.

Accordingly, it is a wise precaution to treat all occupational chemicals as potentially dangerous to health. Measures should be taken to prevent chemicals from becoming airborne and inhaled, and skin contact should be avoided. The subject of primary prevention of occupational cancer is addressed in Chapter 2.

For those workers in industries where carcinogens or suspected carcinogens are in use, careful monitoring of the work environment and the workers themselves is imperative. The surveillance of workers in such industries is discussed in Chapter 3.

In addition to any current exposures to carcinogens, cancers are occurring as a legacy of past exposures. The most significant of these is the continuing occurrence of mesotheliomas caused by past asbestos exposures. It is important that cancers occurring now are assessed for possible work-relatedness, both to ensure that just compensation is awarded, and to identify any exposures which are still inadequately controlled.

To define an exposure as carcinogenic merely indicates that the likelihood of cancer in an exposed individual or a population is greater than it would have been had there been no exposure. Conceptually those with cancer in the exposed population fall into two groups:

- those who would not have developed the cancer but for the exposure
- those who would have developed the cancer even had if there had been no exposure.

Since it is not usually possible to distinguish which of the two groups to which an exposed person with cancer belongs, the task of determining whether a cancer was work caused in an individual case is based on probabilities, taking into account all known factors that might affect the probability of causation in the individual case. These factors are discussed in Chapter 4.

Because so many occupational cancers are asbestos related, these cancers are specifically considered in Chapter 5.

Health and safety practitioners may occasionally be confronted with a cluster of cancers in a workplace or an industry. Chapter 6 is a guide on the investigation of such clusters.

Considered together, the chapters of this booklet will assist health professionals in their understanding of the estimation of risks associated with occupational carcinogen exposures, and this will further enhance the development of practical measures adopted to reduce these exposures.

2 PRIMARY PREVENTION OF OCCUPATIONAL CANCER

Prevention of occupational cancer depends on preventing exposure to any substance, mixture of substances, conditions or processes in the workplace that has the potential to increase the incidence of cancer in workers. The range of prevention measures detailed in this chapter constitutes primary prevention. Secondary prevention is prevention of disability arising from a disease, and would include screening for indicators of early cancer or incipient cancer (see Chapter 3).

Primary prevention is of course a statutory requirement on all employers, and all states and territories of Australia have hazardous substances legislation that imposes obligations on employers and employees. State legislation is based on the National Occupational Health and Safety Commission (NOHSC) documents *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC: 1005(1994)], *National Code of Practice for the Control of Workplace Hazardous Substances* [NOHSC: 2007(1994)], and *National Code of Practice for the Control of Scheduled Carcinogenic Substances* [NOHSC: 1011(1994)]. These documents describe a strategy for the safe use of chemicals, including carcinogens, in the workplace.

In New Zealand relevant legislation includes the *Health and Safety in Employment Act 1992*, the *Hazardous Substances and New Organisms Act 1996* and the *Health and Safety in Employment (Asbestos) Regulations 1998*.

Elimination of carcinogenic exposures

The ideal control method is to eliminate the use of the carcinogenic agent by using alternative technology or agents. If this is feasible decisive government action may be required. An example of such action is the case of crocidolite (blue asbestos) which all Australian governments have banned from use. On the other hand, the NOHSC has drawn up a Schedule of Carcinogens prohibited except for use in research.¹ Most State and Territory governments have not enacted these recommended controls. In New Zealand there is a short list of substances subject to severe restriction.

In practice, it is unlikely that eliminating the cancer-causing process or chemical will be feasible in most cases, and the health and safety practitioner will therefore have to consider which options are the most effective and cost-effective for minimising exposure.

The risk of an individual developing an occupational cancer increases with increasing exposure. Exposure is often expressed as cumulative exposure, which is the product of exposure duration and average exposure concentration.

The population risk of occupational cancers occurring also increases as more workers are exposed.

Thus, when the use of a carcinogen cannot be eliminated, control measures must minimise exposure duration, exposure concentration and the number of persons exposed.

In considering measures to prevent exposures to carcinogens, two important principles should be borne in mind.

Firstly, elimination of the hazard is best considered at the design stage, rather than waiting until plant has been installed. It may be uneconomical to modify or replace plant if it has already been installed and still has some years of productive use.

Secondly, it is preferable wherever possible to institute “passive controls”, that is, measures which do not require the active cooperation of workers. Measures requiring behavioural change on the part of every individual worker are less likely to prevent every worker from being protected all the time.

Identification of carcinogenic exposures

Carcinogens may be identified by reference to the sources described in Appendix 2. Many chemicals used in the workplace in relatively small quantities have not been classified for their carcinogenicity to humans. If it is suspected that an unclassified workplace chemical has carcinogenic potential some guidance is available in the NOHSC Standard *Approved Criteria for Classifying Hazardous Substances; Appendix 1, Carcinogenic effect*.² For example, suspicion may arise about an unclassified chemical that belongs to the same chemical group that contains known carcinogens such as aromatic amines or polycyclic aromatic hydrocarbons.

In some cases there is an excess incidence of cancer in particular industries or occupations, although we do not know the actual agent responsible. For example foundries are classified as causing lung cancer, although the responsible agent (or agents) is unknown. Similarly working in coke ovens or aluminium reduction plants, or as a painter, are all considered to be cancer risks although there is uncertainty about the causal agents and mechanisms in each case.

Minimising the exposure

Isolating the agent or process

Isolation means separating the process so that people not directly involved in the process are not exposed, as in the following examples.

- Areas of asbestos removal are completely masked, with the air pressure in the enclosure slightly negative with respect to atmospheric.
- The ethylene oxide facility in the sterilisation department of a hospital is installed as a dedicated enclosure that has a dedicated exhaust system ducted to the exterior of the building and air pressure in the enclosure slightly negative with respect to atmospheric.
- Polyvinyl chloride, made from polymerisation of the potent carcinogen vinyl chloride, is manufactured under enclosed conditions.

Minimising the number of potentially exposed workers

The number of workers exposed should be minimised without increasing the average exposure of each individual worker. An example of how this was achieved is shown by the measures taken to reduce the risk from ethylene oxide exposures in South Australia:

- The State Health Commission centralised sterilisation units, so that only two remained to service the entire metropolitan area. The other hospitals closed their ethylene oxide facilities and sent their equipment to one of the two centralised facilities for sterilisation. Economies of scale from the large capacity of the centralised unit meant that that no more than three sterilisation cycles were required in 24 hours.
- Access to the dedicated facility was restricted to personnel directly involved in the gas sterilisation process.

For a given degree of exposure, such reductions in the number of exposed workers can reduce the likely number of resultant cancers to zero, as shown by the following example.

Supposing the average cumulative exposure to a carcinogen is at such a level that the average risk of cancer attributable to the exposure is 1 in 1000, and that overall there are 2000 exposed workers. The probability that one or more occupational cancers will occur in this population is 86%.

If steps are taken to reduce the number exposed to 100, the probability of one or more resultant cancers occurring is reduced to 10%.

Thus with the reduced number of workers exposed, it is now more probable than not that not even one case of occupational cancer will occur.

Minimising the time of potential exposure

Workers should only enter the dedicated area when it is essential.

Separating the exposure from workers and others in time or in space

Only essential personnel should be present when there is potential for exposure and, if possible, no personnel should be present when exposure is possible, as in the following examples:

- Asbestos removal or work on asbestos in buildings should only be conducted when the building is unoccupied, for example at weekends.
- In the ethylene oxide facility, maintenance personnel were only permitted to enter the plant room when the facility was not in operation.

Reducing the average intensity of exposure

The most common measures for minimising exposure are the installation of dedicated exhaust systems and personal protective equipment. Details of these controls are beyond the scope of this document.

Another important control is the institution of a double locker system in which two locker rooms - an outer room for street clothes and an inner room for work clothes - are separated by a shower. Such facilities are common in lead work, asbestos removal operations and in mining of uranium.

Repair and maintenance procedures

It is quite common to find that exposures are well controlled in normal production processes, but comparatively little attention is paid to other operations such as cleaning, repairs and maintenance. These matters are especially likely to escape attention if they are undertaken after hours or by contractors. Accordingly the most significant (and hence the most economically efficient) reductions in exposure may often be made by attention to these operations. In the manufacture of polyvinyl chloride from vinyl chloride monomer, a potent cancer-causing agent, the production has always been fully enclosed. Up to the 1970s, however, maintenance workers were in danger of significant exposure when they entered the vessel containing significant quantities of monomer. The cleaning process is now automated and performed under full enclosure.

Contingency plans for system failure

Where possible, alarm systems should be in place to warn of system failure or unanticipated exposure. An example is the monitoring of an area for radiation in uranium mining and milling.

Contingency plans are essential for evacuation and for containment of spills and escapes in such a way as to avoid exposure.

Work practices, personal protective equipment and personal hygiene

Work practice control measures are placed at the lower end of the hierarchy of controls for good reason: they require the conscious cooperation of all workers at all times. Although it is desirable to avoid sole reliance on worker behaviour, such measures are an important supplement to engineering controls.

Worker induction and training

Workers potentially exposed to carcinogens must be informed of the identity and location of the substances. They must be fully informed of the ways in which exposure can occur, and of safe operating procedures implemented to avoid inhalation, ingestion or skin contact. (Skin contact can lead to systemic absorption either through the skin or by transfer from the hands to food or cigarettes, leading to ingestion.) When it is necessary to perform work with the potential for exposure to carcinogenic substances or processes, workers must be able to comply with the requirements to minimise exposure to themselves and to other people in the workplace. It is therefore essential that selected workers are capable of being trained to the appropriate level and are able to demonstrate their ability to perform safe work procedures. Induction training should be documented and signed off by the worker with appropriate periodic revision procedures.

Workplace monitoring

Workplace monitoring ensures that the opportunity for exposure by inhalation of airborne agents, or by skin contact or ingestion is minimised.

These measures are the province of the occupational hygienist but the essential measures are as follows:

- Inspect the processes where the carcinogen is in use, to ensure that control systems such as exhaust ventilation are functioning correctly.
- Take quantitative measurements of airborne levels, by area monitoring or personal sampling in the breathing zone of the operator.
- Ensure that safe operating procedures are observed.
- Ensure that personal protective equipment (eg respirators) is appropriate, individually fitted, tested for efficacy and properly maintained by competent personnel.
- Ensure good personal hygiene such as avoidance of eating or smoking in a designated area or before hand washing.
- Measure valid biological indexes of exposure (eg presence of a substance or a metabolite in urine or blood) if possible. This is particularly important for agents which can be absorbed through the skin, as the uptake of agents from this route cannot be predicted from airborne levels. The role of such biological monitoring and of health surveillance is discussed in Chapter 3.
- Initiate and maintain appropriate recording, notification and review processes.

Pre-placement screening of high risk individuals

Some non-occupational factors can increase the risk of occupational cancer. For example there is a synergistic effect from the combined exposures of smoking and asbestos, and of smoking and inhalation of radioactive dust, so that smoking increases the risk of these occupational lung cancers.

Lung cancer is a rare disease among individuals who have never been active smokers: placement of all smokers away from any work where there is any likelihood of occupation-related lung cancer would reduce the incidence of such diseases to a low level. An alternative would be to allow individuals who had long since quit smoking to work in such locations, since the risk of lung cancer falls off very sharply in successive decades since quitting, relative to those who continue to smoke.³

Nevertheless the primary means of cancer prevention is to eliminate or control exposure to carcinogens. Placement of smokers should not be viewed as a substitute for preventing exposure.

Genetic screening

Genetic variation plays a central role in determining the response of humans to carcinogenic chemical exposures. Future growth in our understanding of the genetic bases of cancer raises the likelihood of future pre-employment genetic screening of prospective employees to estimate their susceptibility to occupational cancer.

Increased genetic susceptibility to cancer can be due to changes in a range of genes, including those that influence activation or inactivation of carcinogens, DNA repair, cell cycle control and, possibly, immune function.^{4,5} For example, reduced activity of genes coding for the glutathione-S-transferase (GST) or N-acetyltransferase (NAT) families of enzymes can reduce the rate of metabolic inactivation of some carcinogens and has been shown to be associated with an increase in risk of a number of cancers.⁶ The purpose of screening is to identify prospective employees who, by their genetic makeup, are more susceptible to cancers that result from particular occupational exposures.

The question of genetic screening would not arise if hazardous exposures could be eliminated. Given that this is not always achievable, there could be a number of motivating factors for genetic screening programs. An employer may consider the duty of care as including identification of high-risk individuals. Similarly an employee could assert a right to know of any genetic factor which might put him/her at increased risk of cancer. The Australian Law Reform Commission has recently suggested that employers should be able to collect and use genetic information for the purpose of protecting workers' health and safety.⁷

However the role and justification for genetic screening is not straightforward. The very complex events leading to the development of clinical cancers make it extremely difficult to determine with any certainty one individual's susceptibility compared to others. For example individuals with the NAT2 slow genotype, which confers a phenotype of slow acetylation of arylamines, have been found to have an increased risk of bladder cancer from exposure to these agents.⁸ While this genotype may mean increased susceptibility, it is not possible at present to identify which *individuals* with that genotype would develop cancer. Occupational cancers are relatively rare events and the odds ratio for the observed effect between various polymorphic groups is generally small, for example, less than a 2-fold increase may be seen. The implications of these considerations are that most individuals who were excluded from certain work situations on the basis of genetic screening would not have developed cancer even had they been employed; while on the other hand some workers who pass the test and are accepted could develop the cancer anyway.

Thus genetic screening could lead to an applicant being refused employment on the basis of a test which is not only an invasion of privacy, but is limited in its ability to discriminate those at risk from those who are not. Moreover, there is the risk that employers could form the comfortable but incorrect view that the screening program will prevent work-related cancer and will relax efforts to reduce exposure of the workforce.

Despite these concerns, a role for genetic screening cannot be totally discounted. In an individual with a genetic trait for cancer with a high penetrance (ie many people with the trait develop the disease), the risk from even very low exposures may be significant. There is evidence, albeit inconclusive, of some women having a genetic variation leading to increased lung cancer risk from passive smoking.⁹ For individuals with an increased background risk, reduction of exposures to safe levels may be difficult to achieve. We may then speculate that the marginal benefits of increasingly stringent controls will be small, being ineffectual against subgroups such as those vulnerable to familial cancers. At the same time, such stringent controls may be redundant in preventing cancers in most people, in whom genetic repair processes can cope with a moderate volume of mutagenic insults. There may be a case for identifying such high-risk individuals so that they are not only protected from any occupational exposures, but

that they avoid all other sources of exposure also. For example individuals with the condition xeroderma pigmentosum, who are at high risk of skin cancer from ultra-violet radiation, should be identified so that they not only avoid outdoor jobs, but they also avoid exposure to solar radiation at all times.

There are also significant legal issues, addressed in the *Disability Discrimination Act 1992* which is administered by the Human Rights and Equal Opportunities Commission (HREOC). This Commonwealth legislation prohibits exclusionary employment on the basis of disability, unless the person cannot meet the requirements of the job, or the job cannot be reasonably altered to accommodate the disability, or that occupational health and safety or public health laws would be contravened. However the Act does not specifically address the question of genetic screening. In New Zealand the relevant legislation is the *Human Rights Act 1993*.

Although this document cannot resolve these complex ethical and legal questions, the following principles are proposed:

- The primary means of prevention of occupational cancer is elimination or containment of the causal exposure so as to prevent inhalation, skin contact or ingestion.
- With the present state of knowledge, exclusionary employment practices based on genetic screening are unlikely to make any significant reduction in cancer risk in comparison with elimination or control of exposure.
- Where there is a demonstrated association between genetic variation and cancer risk, employees have the right to be informed of the association and of the availability of appropriate testing.*
- Where genetic testing is undertaken, it should be voluntary, that is, not a precondition for employment.
- Screening programs should be under the control of a physician with a high level of competence in genetics and the relevance of testing in workers. The physician would have to explain the tests and their implications at the beginning of the program, and to explain the significance of results to individual workers.
- Informed consent, protection of privacy and confidentiality, and provision of independent counselling would also be necessary prerequisites to such screening. Test results should be available to the employee, whose decision it would be to convey information, if any, to the employer.

Management of workers with past exposure

For workers who have had past exposure to carcinogens, a number of measures should be considered.

The underlying principle is that workers must be provided with all relevant information. The employee's work history should be reviewed and, if requested, the worker should be provided with their documented exposure record together with a realistic estimate of risk. If the exposure level is low the cancer risk is low also. Another prognostic factor is the efficacy of treatment. Some cancers have a high cure rate; for example the 5-year survival rate in males with bladder cancer is 61%.¹⁰

Measures should be taken to ensure that no further exposure to the carcinogen occurs.

It is also important to ensure that other carcinogenic exposures are avoided. This is particularly important in the case of tobacco-related cancers. Smoking amplifies the carcinogenic effects of a number of other exposures, for example asbestos, ionising radiation and arsenic. Moreover, as discussed above, the risk of lung cancer falls off sharply with increasing decades since quitting smoking. Workers who have been exposed to carcinogens, especially lung and bladder carcinogens, should therefore be advised to stop smoking. Advise workers of appropriate periodic screening procedures and provide them with a statement of past exposure on work separation.

Screening for pre-clinical cancer or for pre-cancerous lesions is warranted where there are valid screening tools and where effective intervention is available if the disease is detected (see Chapter 3).

Also consider the value of dietary modification to reduce the likelihood of cancer. Epidemiological studies have consistently shown an association between consumption of fruit and vegetables and lowered risk of many cancers.¹¹ Research to date has not enabled identification of many specific micronutrients for cancer prevention. One clinical trial of beta-carotene was halted because it not only showed no benefit, but subjects in the beta-carotene arm of the study had significant increases in lung cancer incidence and in cardiovascular and total mortality.¹² Nevertheless a number of individual studies have showed that there may be a significant potential for dietary modification of cancer risk.¹³⁻¹⁵

The employer concerned should be reminded of the legal obligation to retain all exposure records for 30 years from the last entry in the record.

* A recommended reference is the AFOM publication Australian Faculty of Occupational Medicine Genetic Screening and Occupational Medicine: a position paper. AFOM, 1995.

3

SURVEILLANCE OF WORKERS EXPOSED TO CARCINOGENS

Workers exposed to chemicals may be monitored using several methods:

- Exposure monitoring (or ambient monitoring) strategies measure the amount of chemical in the environment to which workers are exposed. This is usually in the form of air sampling and analysis but may include measurement of chemicals on surfaces, clothing, protective equipment and other points at which chemical contact may occur.
- Biological monitoring is the measurement of chemicals or their metabolites in tissues or fluids, such as urine, blood, exhaled air, hair or other media. This permits an estimate of the uptake of chemical by workers.
- Biological effect monitoring involves the measurement of some biochemical, physiological, or other end-points that may be affected by chemical exposure, without necessarily being associated with disease. The monitoring of workers exposed to carcinogens include
 - detecting evidence of interaction between the carcinogen and the subject's DNA
 - detecting structural change or damage to DNA.
- Health surveillance provides a method of evaluating clinically important changes that are associated with disease processes, and may provide opportunities for early intervention and the reduction of disease severity.

The toxicological principle underpinning the use of these monitoring approaches is one of dose-related effects: higher levels of exposure are associated with higher risks of disease development. Lower levels of exposure may be below the effect threshold for toxicity and may be tolerated by exposed workers without ill effect. However, where a job involves an exposure which is believed to be carcinogenic, it is prudent public health practice to assume that there is no threshold below which there is no risk of cancer attributable to the exposure. Repeated exposures, especially at high concentrations, carry a greater risk of causing a carcinogenic event than single, sporadic or occasional low level exposures. The most important response is primary prevention. If the exposure cannot be eliminated it should be controlled sufficiently to eliminate any health risk. There is also a role for secondary prevention - monitoring workers for any exposure to carcinogens or for any effects of such exposure.

The aims of the monitoring and surveillance strategies described are complementary, and may permit different levels of investigation of worker chemical exposures. These aims can include:

- ensuring that physical control systems are working effectively in minimising exposure
- detecting early signs of disease or pre-clinical disease in individual workers.

There is a special need for health surveillance of workers exposed to carcinogens, not only because of the serious outcome of many cancers, but because of the long latency period between exposure and disease onset. One of the greatest problems with cancer epidemiology is that results are not apparent until there is a "body count". By the time an excess risk is found many workers will have been exposed with risk of future cancers. For example although asbestos use has been highly regulated since the 1970s, there is likely to be a continuing incidence of asbestos-related cancers for at least a further decade as a legacy of past exposures. Because of this limitation of conventional epidemiology, there has been a great deal of research into identifying factors predictive of cancer, which if detected can lead to preventive action.

A number of monitoring measures is now possible at different stages along the path from exposure to the carcinogen to the development of cancer. Detectable chemical or genetic effects from carcinogenic exposures are commonly called *biomarkers*.

Successive stages of cancer development following exposure to carcinogens are schematically represented in Figure 1. Although cancer is now believed to result from the cumulative effect of several mutations, this model is simplified to include only a single mutation in the pathway to cancer formation.

Some form of monitoring is possible at all of these stages, as indicated in Table 1.

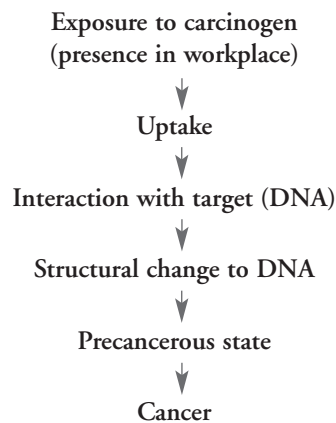


Figure 1. Successive events following carcinogenic exposure giving rise to opportunities for monitoring

It is important when interpreting the results of the tests to realise their limitations. Some of the tests are more useful as indices of exposure rather than as predictors of disease, and some are the reverse. Some of these limitations are described below.

Environmental monitoring

Identification and measurement of exposure in the workplace is an essential part of the process of ensuring that control systems are effective. A detailed account of environmental monitoring is beyond the scope of this document but those responsible for health surveillance should ensure that exposure and risk are assessed with the assistance of concurrent environmental measurements.

Environmental monitoring should begin with an inspection of the workplace and work methods, taking note of the potential for substances to become airborne through evaporation, aerosolisation, combustion, grinding etc. The effectiveness of the natural ventilation and any supplied dilution or local exhaust ventilation may need to be assessed. Simple tools, such as air current tubes (smoke tubes), may assist this preliminary evaluation. However, more complex assessments of environmental chemical exposures may require specialised equipment and the assistance of occupational hygiene professionals.

Table 1. Types of monitoring of workers exposed to carcinogenic substances

Effect	Monitoring and testing
Exposure	Inspection Testing ventilation Area monitoring Personal monitoring
Uptake	Measurement of carcinogen or its metabolites in blood or urine
Biological effect monitoring and interaction with non-target tissues	Identifying biochemical or other non-target tissue biological effects that are associated with exposure and uptake Identifying evidence of carcinogen-protein binding as surrogate indicator of carcinogen-DNA binding
Interaction with target tissue	Identifying evidence of carcinogen-DNA binding
Structural change	DNA strand breaks and crosslinks Chromosome aberrations Sister chromatid exchanges Micronuclei Gene deletions Loss of heterozygosity
Precancerous change	Carcinoma in situ Dysplastic lesions
Cancer	Diagnosis

Quantitative monitoring of atmospheric contaminants may be required, and either area or personal monitoring can be undertaken. Areas are monitored at fixed locations at a workplace, measuring the level of contamination from a particular source (eg industrial process) and examining the likely dispersion characteristics. Personal monitoring, on the other hand, requires the monitoring device to be attached to the worker, usually in the breathing zone, so that an integrated measure of that worker's chemical exposure is obtained. This concentration of chemicals may then be related to the various tasks performed throughout a work shift.

Personal monitoring is the more useful for predicting risk, since it estimates time-weighted average exposure over periods ranging from minutes to hours each day. Repeated sampling as part of a detailed monitoring program provides further information on the day-to-day and longer term patterns of chemical exposure. Area monitoring is of greater use for identifying potential sources of exposure within a workplace and for identifying workers to whom personal monitoring programs should be targeted.

Recommended exposure *standards* have been established for many, although not all, workplace contaminants.¹ By measuring the levels in a workplace and comparing them to the exposure standard, we have a means of ensuring that most workers are protected. However, in the case of carcinogens any exposure levels should be regarded as predictive of some risk, however small, even if there is compliance with the standard. Since the likelihood of resultant cancer will be reduced with reduced exposure levels, the target level should be *the lowest level which is reasonably achievable*.

If the agent is absorbed through the skin, the potential for skin contact should be noted. There may also be a potential for skin contact to lead to an agent coming into contact with food or cigarettes, leading to ingestion.

Biological monitoring of uptake

The most elementary step in a health surveillance program is to determine whether there has been uptake of a chemical into the body. This is particularly important where different work patterns or work rates, or the level of worker exertion, may contribute to greater potential for inhaling airborne chemicals. It is also important where uptake is not solely from inhalation (eg some chemicals are absorbed through the skin). The most common measures of uptake are of the chemical itself or of its metabolites in the blood or urine. It is clear that knowledge of the metabolism and distribution of the indicator chemical is a prerequisite of appropriate sampling regimes and chemical analytical techniques.

Caution is required in interpreting the results of such monitoring. One elementary precaution in urine testing is to ensure that the measurement is standardised for urinary volume. A high concentration of a substance in the urine may be merely due to a low urine output. A common means of standardisation is to measure the absolute urinary output from a 24-hour collection. Since this may not be convenient or acceptable to workers, an alternative approach is to take a "spot" urine sample and standardise according to urinary creatinine concentration, which is an indicator of dilution (a high creatinine level indicates concentrated urine).

It is also important to record the time of last exposure and time of urine sample collection, or the elapsed time since last exposure, especially for carcinogenic agents having a short clearance time from the body. MOCA [4,4' methylene bis(2-chloraniline)], classified as a probable carcinogen, has a half-life of about 24 hours so that a sample of urine collected more than a week after exposure would be unlikely to contain any MOCA even with high exposures.

The most useful result of biological monitoring is to estimate exposure rather than to predict future effect. Even as an index of exposure it is important to consider sources other than the occupational exposure. For example an individual with elevated urinary hydroxypyrene levels (an index of polycyclic aromatic hydrocarbon exposure) may have derived the excess from smoking rather than from occupational exposure.

Another example is that of urinary 1-hydroxypyrene (1-OHP) levels in coke oven workers. 1-OHP is a urinary metabolite of pyrene, one of the polycyclic aromatic hydrocarbons (PAHs) which are a carcinogenic hazard in industries where organic substances are burnt. A worker with a relatively high levels of urinary 1-OHP may have incurred PAH exposure from the coke oven; on the other hand it may be partly derived from smoking or from contaminated urban air. It is preferable to interpret biological monitoring and environmental monitoring data together.²

It is possible to be more confident in interpreting an overall excess of exposure in *groups* of workers. If a group of coke oven workers has a significantly higher mean urinary 1-OHP level than a group not working near PAHs, it is most likely that the excess is occupation related. Detection of such an overall excess would be a clear indication

that control measures should be upgraded, and consideration given to following up exposed workers with biological effect monitoring and medical screening.

Caution is required in using such a response as a predictor of future risk. Consider the hypothetical example of urinary 1-OHP levels in coke oven workers in Figure 2.

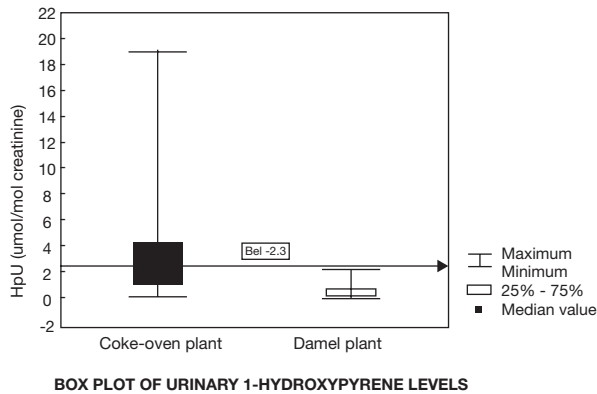


Figure 2. Plot of urinary 1-hydroxypyrene levels in oven-top workers and other coke oven workers (Reproduced with permission of the American Industrial Hygiene Society. Source: Reference 3)

On average, the urinary 1-OHP exposures have clearly been higher in the oven-top workers than the others, and indicate the need for more stringent controls. However individual levels are not necessarily predictive of individual cancer risk. Some individual oven top workers have lower 1-OHP levels than the average in the other group, and some in the latter group have levels above the average of the oven top workers. While using the results to promote preventive action, it is important to prevent undue anxiety by explaining that higher individual levels do not necessarily indicate a higher cancer risk in that individual.

The measurement of internal dose by biological monitoring documents whether any uptake of chemical has occurred. The option should therefore always be taken to find out whether an index of uptake actually exists. Observation or personal recollection of exposure can be quite unreliable, as has been demonstrated in studies of Vietnam veterans working with Agent Orange: TCDD (dioxin) level measures in veterans' adipose tissue showed no significant association with four surrogate measures of probable exposure.⁴

For some substances there are recommended biological exposure guidelines. For example, ACGIH[®] (the American Conference of Governmental Industrial Hygienists) has developed Biological Exposure Indices (BEIs[®]) for selected substances as indicators of uptake of those substances. The BEIs[®] are guideline values, and represent the levels of chemicals in specimens (commonly urine, blood or exhaled air) from healthy workers that typically correlate with inhalation exposures at the ACGIH[®] Threshold Limit Values for those substances.⁵ For example, following airborne xylene exposures at 100 ppm, one may expect end-of-shift urinary methylhippuric acid concentrations of 1.5 g/g creatinine. (The exceptions are BEIs[®] where biological monitoring is desirable because of additional routes of entry, eg skin.) Hence BEIs[®] may be considered as the biological equivalents of environmental exposure guidelines. However, while they may be useful guides to achieving acceptable exposure levels, their interpretation is not one that identifies safe levels of exposure. The relationships between airborne concentrations of chemicals and the corresponding biomarker have been established using data collected from published studies. The variation in data inherent in varying experimental designs means that the derived relationships are not exact. For example, a worker whose biomarker value does not exceed the BEI[®] may well have experienced an airborne exposure significantly greater than the workplace atmospheric exposure standard. Conversely, a biomarker value above the BEI[®] may occur with exposures below the exposure standard.

BEIs[®] are not formally cited in Australian law. In New Zealand, they are cited as guidelines in the Workplace Exposure Standards.

Table 2 indicates some carcinogens and suspected carcinogens which have recommended standards for biological exposure.

* The Australian Workplace Exposure Standard (WES) for xylene is 80 ppm and the corresponding BEI would be 1.2 g/g creatinine

Table 2. Some carcinogens and suspected carcinogens which have Biological Exposure Indices (Reproduced by permission of the ACGIH®)

Chemical	Determinant
Aniline	Total p-aminophenol in urine Methaemoglobin in blood
Arsenic, elemental and soluble inorganic compounds	Inorganic arsenic plus methylated metabolites in urine
Benzene	S-phenylmercapturic acid in urine t,t-muconic acid in urine
Cadmium	Cadmium in blood Cadmium in urine
Chlorobenzene	Total 4-chlorocatechol in urine Total p-chlorophenol in urine
Chromium (VI), water-soluble fume	Total chromium in urine
MBOCA	Total urinary MBOCA
Nitrobenzene	Total p-nitrophenol in urine Methaemoglobin in blood

In the United Kingdom the Health and Safety Executive (HSE) has set a number of health guidance values (HGVs) which are conceptually similar to BEIs®. It has also set a number of benchmark guidance values (BGVs) for chemicals that are inappropriate for a HGV, such as for genotoxic carcinogens. If there is considered to be no level of exposure that is protective of most workers, BGVs have been established as a means of reducing exposure to achievable levels. A BGV is set at around the 90th percentile of available validated data, provided by a cross-sectional study of workplaces with good occupational hygiene practices. It is thus a level which exceeds 90% of the data, and can be achieved by most industries with good work practices.⁶ BGVs have been set for lindane, MOCA and MDA (methylene dianiline), and another is proposed for urinary 1-hydroxypyrene, a marker for workers exposed to polycyclic aromatic hydrocarbons.

Non-quantitative indices of exposure

For some carcinogenic exposures, biological effects unrelated to the cancer process may serve as a marker of current or past exposure. For example, exposure to chlorinated compounds such as the phenoxyacetic acid herbicides (eg 2,3,7,8-TCDD) can cause chloracne^{7,8}; and aluminium reduction plant workers who have skin contact with coal tar pitch may develop skin photosensitivity.

Asbestos exposure can cause pleural plaques. Plaques are different from the previous examples in that they do not occur for many years after initial exposure, and are therefore of limited use as checks on current control systems. If some individuals in a group of workers with past exposure to asbestos are found to have pleural plaques, the group as a whole is at increased risk of asbestos-related cancer. Whether the presence of plaques is an indicator of individual risk is a matter of dispute. A 1997 autopsy-based study suggests that plaques are a risk indicator.⁹

Identifying interaction with DNA

Most environmental carcinogens are believed to act by chemical interaction with DNA (genotoxic carcinogens), resulting in structural alteration and altered genetic function. Some substances found to be carcinogenic bind covalently with DNA to form so called DNA adducts (addition products). For example benz[a]pyrene binds with DNA to form benz[a]pyrene-DNA adducts.

Methods for the detection and quantification of chemical adducts of DNA have been developed and applied to occupational and non-occupational carcinogen exposures.¹⁰

Tests such as these have the same limitations as the direct measurements of uptake described above. The first is that we cannot be certain that such adducts are the result of occupational exposure. Adducts between the polycyclic aromatic hydrocarbons (PAHs), of which benz[a]pyrene is an example, and DNA can occur regardless of the source of the PAH. Thus coke oven workers may have benz[a]pyrene DNA adducts from their occupational exposure to benz[a]pyrene. Equally however they may be the result of smoking or pollutants in urban air or may even be dietary in origin.

Second, the presence of such adducts is not a predictor of future cancer in an individual. Such tests should be regarded as markers of exposure, not necessarily as an indicator of future disease. They should be interpreted on a group basis, so that if on average the level of DNA adducts found in workers in a particular process is higher than in a control group, the process may require an improvement in controls. Individuals with consistently elevated adduct levels may be at increased risk, relative to others with consistently lower levels, either because of higher exposure or increased susceptibility to adduct production or persistence.

Sometimes it is expedient to test for the binding of reactive chemicals to proteins instead of DNA. These protein adducts may be used as a surrogate index of the binding of chemicals to DNA as the ultimate genotoxic target. The advantage of using proteins such as haemoglobin as quantitative markers of DNA binding is that large quantities of haemoglobin may be extracted from human blood samples.

Most of these studies have been experimental and it is hoped that this research will give insights into the biology of cancer formation. However testing for these biomarkers is not readily available in Australia for surveillance of workers exposed to carcinogens.

Tests for structural change or damage to DNA

An alternative to searching for adducts of DNA with specific carcinogens is to look for microscopic evidence of structural changes to the DNA. Unlike tests for DNA adducts, which are research tools, tests for structural DNA changes are available for surveillance of potentially exposed workers. Unfortunately they have the disadvantage of being non-specific, as they may arise from many types of chemical insults such as air pollutants, smoking, dietary factors, prescription drugs or occupational chemicals.

Some examples of these tests are:

- **DNA breaks:** In vivo repair of DNA adducts, cross-links and other lesions may give rise to transient breaks in DNA as a part of the DNA repair process. Other genotoxic chemicals may induce DNA breaks without forming adducts. DNA breaks may be visualised in a range of tissues using a variety of analytical techniques. One such test, the single-cell gel electrophoresis test, or comet assay has emerged to become a simple, robust, and quantitative method for the analysis of DNA breaks both in vitro and in vivo.¹¹ This test has the advantage that it may be applied to a variety of accessible tissues, including peripheral blood lymphocytes, exfoliated urothelial cells in urine, and buccal mucosal cells. The selection of the appropriate test tissue may depend on the likely target for toxicity of the chemical under investigation.
- **Chromosome aberrations (CA):** These represent a variety of changes to chromosomes, including gaps, breaks, loss or addition of centromeres, and other changes. Specialised expertise is required in interpretation and scoring of CA.
- **Sister chromatid exchanges (SCE):** These represent the exchange of DNA between chromatids of the same chromosome following chromosomal damage, although the specific mechanism is not fully understood. The advantage with this method is that SCEs are more easily visualised and scored than CA.
- **Micronuclei:** These occur when genetic injury results in either chromosome damage or damage to the spindle apparatus of the cell, so that when the cell divides, either a DNA fragment or a whole lagging chromosome is not incorporated into daughter nuclei but appears in the cytoplasm.

All of these tests need great caution in interpretation because they are associated with a wide variety of chemical insults. Moreover, to visualise these changes, laboratory culture of lymphocytes is needed. This may itself contribute to elevated observed frequencies, requiring concurrent analysis of unexposed or control groups. Therefore, it is necessary to compare the average frequency of aberrations in a *group* of workers with an exposure of interest with the frequency in an unexposed group. They should not be regarded as useful tests for individuals, since other factors, such as viral infection, recent x-ray and other chemical exposures (eg diet, hobby or pastime, or unidentified chemical exposure) may affect cytogenetic outcomes.

Studies of chromosome aberrations in subjects exposed to chemicals have shown that the endpoint (such as increased rate of SCEs) returns to normal after exposure ceases and damaged cells are repaired or cleared from the body.¹² This has implications for communication of results to subjects. Positive outcomes in these tests indicate that some forms of DNA damage have occurred and there is an implicit risk if exposure continues. There is continuing research and debate on the prognostic significance of such findings. It has been claimed that some studies have found a higher risk of cancer in those groups in whom the frequency of biomarkers is raised but the increased risk is unrelated to occupational exposures.¹³ Irrespective of current uncertainties, it is important to note that tests for increased frequency of biomarkers are not valid for predicting whether a particular individual or individuals will develop disease.

Screening for pre-clinical cancer or early cancer

Screening tests for early cancer or for premalignant states are of limited use as checks on control systems, because such changes are unlikely to be detected until several years have elapsed since initial exposure. Such screening is worth undertaking in workers with past exposure to carcinogens if the detection of an abnormality can be followed by action which effects cure or prolongs survival time. Survival time is the time from onset of disease to death, not time of diagnosis to death. If early diagnosis merely lengthens time from diagnosis to death by achieving a correspondingly shorter time from disease onset to diagnosis, nothing has been gained.

The utility of screening varies with the cancer type. In general this depends on the effectiveness of treatment of the particular cancer. Cervical cancer is an example where screening can lead to treatment resulting in an increase in cure rate in the population screened. On the other hand a Mayo clinic study on lung cancer concluded that the benefit of screening by sputum cytology or chest x-rays is insignificant.¹⁴ Some recent studies have claimed a potential benefit^{15,16} but a Cochrane review has failed to find support for chest radiography or sputum cytology.¹⁷

The advent of CT scanning has presented a potential advance in screening. CT scanning can detect very small lung tumours, and some recent evidence concluded that CT-based screening (as opposed to plain x-ray) enhanced detection of lung cancer at earlier and more curable stages.¹⁸ Randomised trials are needed to demonstrate the extent to which screening of individuals at risk will improve cure rates and survival times.

Before a screening measure is undertaken for detecting future disease, consideration must be given to whether the test is a valid predictor of that disease. An example where this condition has been ignored is a past recommendation from the US for blood examination of workers exposed to ethylene oxide, which is believed to cause leukaemia. There are no warning signs of incipient leukaemia evident from haematological studies, so such a test is at best invalid and at worst liable to engender a false sense of security to workers who are still exposed.

The performance of a screening test should be judged by its ability to identify persons who have or will develop cancer. Firstly, there needs to be a high probability of a positive test in someone who has or will develop cancer. Secondly, it is desirable that most subjects without the disease will test negative, since a high rate of false positives can generate much groundless anxiety. Nevertheless tests may be justified if (i) they are highly sensitive and (ii) a positive result can be followed promptly by further investigation to exclude false positives. An example is urine dipstick testing for haematuria in workers exposed to aromatic amines, many of which can cause bladder cancer. Such screening programs are worthwhile because the results of treatment are often excellent. Dipstick testing for haematuria is sometimes positive from causes other than cancer or precancerous states - indeed probably a minority of positive tests are due to these causes, but this cheap and simple test is justified since positive test cases can readily be followed up to identify cancers and premalignant states.

The timing of screening programs is crucial. Most occupational screening programs are undertaken by employers, yet most cancers are likely to develop long after workers have ceased employment at the workplace where exposure occurred. For those responsible for the surveillance of workers exposed to chemicals, every effort must be made to ensure that screening programs are undertaken at a time when they most useful. This means that employers should maintain a roll of previous employees and notify those on the roll when their next test is due.

A more desirable solution would be to establish a State or national register of workers with past exposure to carcinogens. Some programs already exist for workers with past exposure to mineral dusts but very little attention has been given to other carcinogenic exposures. Only a government authority could undertake this program effectively and unfortunately there appears to be little interest in any such programs on the part of any Australian jurisdictions.

Table 3 lists possible clinical screening tools for various cancer types. Most of these tests are recommended by the National Occupational Health and Safety Commission, although some measures (eg skin examination) await proof of efficacy.

Table 3. Possible clinical screening tools for subjects at risk of occupation-related cancer

Cancer type	Test	Comment
Lung	X-ray	Population studies have shown possible improvement in cure rate or survival time ¹⁵⁻¹⁷
Lung	Spiral CT scanning	Costly, but consider for workers at risk of lung cancer ¹⁸
Lung	Sputum cytology	No demonstrated increase in cure rate or survival time ¹⁷
Mesothelioma, asbestos-related lung cancer	Chest x-ray, HRCT scan	Detection of pleural plaques indicates past asbestos exposure; detection could lead to need to avoid further exposure, quitting smoking, possible dietary advice
Silica-related lung cancer	Chest x-ray, HRCT scan	Detection of silicosis indicates need to avoid further exposure, quitting smoking, possible dietary advice
Bladder	Clinical testing for haematuria	Simple to perform but low specificity – most test-positive subjects will not be cancer cases
Bladder	Urine cytology	Tumours may shed abnormal cells intermittently
Skin	Clinical examination	Simple to perform; should be undertaken in all sun-exposed workers and those exposed to skin carcinogens; false positives common however
Leukaemias	No test available	No known identifiable predictors which could lead to effective intervention
Liver	α -foetoprotein	

Ethical and legal considerations

Tests such as those described here test healthy people not because they have presented to a medical centre for attention but only because they happen to work at a particular location. Thus the usual element of implied consent to undergo testing in a medical context is absent. Certain ethical considerations are therefore important in designing a program of health surveillance or biological monitoring.

- The right to privacy should be respected. This means that results should be obtained and interpreted by a person independent of the employer, and results withheld from the employer unless the worker gives informed consent for them to be passed on. As discussed above, the appropriate manner of reporting to the employer should be by work area, so that problem areas - rather than problem individuals - can be identified. South Australian law prohibits access by employers to company medical records. Individual results must be accessible only to medical personnel, even where the company itself runs the medical service.
- The results of the testing should not result in any discrimination, such as loss of employment, loss of pay or any other victimisation. Workers in some industries have longstanding concerns over medical screening programs because the employers' response has been to blame the victim rather than address the problem of the working conditions which caused the problem.

In some jurisdictions there may be a statutory requirement for performing health surveillance or biological monitoring. For example, New South Wales regulations require employers to provide biological monitoring for an employee if there is a reasonable likelihood that the employee could be exposed to levels of a hazardous substance that could be a risk to health and an effective procedure for the biological monitoring of those levels is available. Some jurisdictions have scheduled certain substances for which biological monitoring or health surveillance is required if there is significant risk to the health of the employee from the scheduled substance and there are valid techniques for detecting indications of the disease or other effects on health.

However, the regulations do not address issues of consent, termination of employment or redeployment.

The following provisos should apply to biological monitoring or health surveillance programs:

- They should be part of a prevention program.
- Consent should be given without coercion, and should be fully informed, including information on evidence for efficacy, sensitivity and the consequences of a false positive test result.
- In general, individuals should have the right to refuse to participate. However in some circumstances biological monitoring may be essential to ensure the efficacy of control measures, in which case employers could require such testing to fulfil the legal duty of care. In such circumstances employers should make clear their policy on participation in biomonitoring programs and should seek employee consent to participate in the program before job placement.
- Individuals should be provided with their own results.
- There should be skilled medical advice available to provide interpretation of the results to workers. (It should not be assumed that all doctors possess the necessary skills.)
- Results should not be passed to a third party (eg the employer) without the individual's consent.

Conclusion

For those with a duty of care to workers handling carcinogens, the first priority must be to eliminate or control exposure. If exposure cannot be eliminated entirely, a monitoring program must be in place to reassure workers that they being protected against the risk of occupational cancer.

The best evidence that workers are protected is in environmental monitoring indicating that the immediate environment of workers is free of contamination.

It is often desirable to supplement environmental monitoring with biological monitoring. Environmental monitoring usually consists of monitoring for airborne substances but atmospheric concentrations are imperfect predictors of the amount of contaminant inhaled. Furthermore some chemicals, including some carcinogens, are absorbed through the skin, and there may be some possibility of ingestion also. The most valid index of uptake therefore is from assay of blood or urine, which integrates exposure by all routes and over time. The main inferences to be drawn are whether there is significant uptake in the exposed groups compared with controls, rather than on the prognostic significance of results in individual workers. Indeed workers should be reassured that a raised level of such metabolites does not in itself imply an increased cancer risk.

Biological testing for effects of exposure, such as adducts of DNA with carcinogens, has the same limitations as testing for urinary metabolites. Such testing is still regarded as a research tool, and is not readily available for routine surveillance.

Similar limitations apply to tests for chromosomal aberrations, which are even less exposure-specific.

Health surveillance for incipient disease or early disease is useful if it can lead to cure or to increased survival time. This varies for different cancers. It is important that any screening program is sustained beyond the period of actual exposure, as cancer from an occupational exposure may not occur for many years.

Where to go for biological monitoring

A number of laboratories provide tests described in this chapter. Appendix 3 lists the addresses of professional bodies of consultants who can give advice and assistance on monitoring programs.

EVALUATING WHETHER AN OCCUPATIONAL EXPOSURE HAS CAUSED CANCER IN AN INDIVIDUAL CASE

This chapter outlines the procedure for evaluating whether an occupational exposure has contributed to the occurrence of cancer in an individual. The main application of such evaluations is in compensation or litigation.

The notion of causation of occupational cancer is different from that of infectious disease. If a person presents with the clinical manifestations of malaria, and the malaria parasite can be found in the person's blood, it can be said with confidence that the patient's condition is caused by the malaria parasite. On the other hand the occurrence of a cancer in a person previously exposed to a cancer-causing agent cannot readily be attributed to that agent, since work-related cancers are usually indistinguishable, histologically and in natural history, from similar cancers unrelated to work. A decision on whether an exposure was causal in development of cancer is based on factors such as whether exposure occurred, the extent and timing of exposure, and consideration of the balance of probabilities in the light of current scientific evidence. This chapter sets out the successive steps required to ensure that all relevant factors are considered in making the ultimate judgement. The risk of cancer from asbestos exposure has been extensively studied and is discussed in Chapter 5.

The suspected cause of the cancer may be:

- a specific chemical or another exposure such as ionising radiation
- employment in a particular occupation or industry, without any chemical or other exposure being specified.

If a specific chemical or other exposure is suspected, the analysis follows the steps below. If an occupation or industrial process is being evaluated, general reference to work practices in a particular industry may be necessary to determine specific substances to which the individual in question may have been exposed. If one or more chemicals are identified as suspect causes of the cancer, each would then be evaluated by the steps below. However, even if no particular exposure is specified, investigation of the particular occupation or process can still proceed, to determine whether there is empirical evidence of causation, regardless of what the particular causal agent may have been.

In assessing the probability that a cancer is causally related to a chemical exposure (or industrial process or occupation), the following questions should be addressed:

- Is the agent carcinogenic to humans?
- Could the exposure have led to uptake of the agent?
- What was the intensity and duration of the exposure?
- Is the particular agent associated with cancer at this site and of the same histological type?
- Is the site of the cancer consistent with the route of uptake of the agent?
- Was the time from exposure to disease onset consistent with the induction latency period of the agent?
- Were there other factors that might have contributed to the risk of cancer in this person?

If the answers to these questions indicate that the agent could have been responsible for the cancer in that person, the probability that the exposure was causal in that person must then be estimated.

Is the agent carcinogenic to humans?

A number of bodies have evaluated the carcinogenicity of occupational and environmental agents. The International Agency for Research on Cancer (IARC), an agency of the World Health Organization, undertakes such evaluations, which are carried out by committees of scientists selected from different countries on the basis of their knowledge of the agent being evaluated. In Australia a committee of the National Occupational Health and Safety Commission (NOHSC) evaluates carcinogenicity. The committee evaluations are usually similar to those of the IARC, although the classification system is somewhat different. The NOHSC schedule of carcinogens is given in Appendix 2a and the New Zealand schedule in Appendix 2b.

In many instances the agent or occupation will have already been subject to a formal evaluation by a body such as IARC. The agents studied have been classified by IARC according to the strength of evidence of carcinogenicity, using a set of formal criteria (see Appendix 1). The IARC schedule can be viewed on its website at www.iarc.fr.

Information on carcinogenicity is given on material safety data sheets (MSDSs) but it is preferable to directly refer to a scientific or regulatory source. MSDSs are produced by a number of different bodies, private and public, and vary greatly in quality. If an agent has been assigned a classification by a body such as NOHSC or IARC, the supporting documentation should be consulted.

However, some other steps should also be taken.

Firstly, examine and evaluate any epidemiological or experimental studies published since the classification was made as to whether they affect the basis of that classification sufficiently to change it. Pay close attention to the date when authoritative reviews or evaluations were made. Search the more recent literature to establish whether new data have rendered the earlier assessment invalid. Additional data should be evaluated by a person skilled in cancer epidemiology.

Secondly, consider the strength of the evidence on which the classification is based. A classification of carcinogenicity may have been based on limited evidence, such as a single epidemiological study, and may not necessarily be justified for the purpose of assessing a claim. It may well, however, be justified as a precautionary measure to ensure that workers are given adequate protection.

Thirdly, ask whether the classification has been subject to dispute. Some IARC classifications (eg on beryllium and silica) have been the subject of continuing debate.

If there has been no formal evaluation of the carcinogenicity of the agent, a judgement will have to be based on a review of the available scientific evidence. Refer to a cancer epidemiologist for such a review.

What was the intensity and duration of the exposure?

If the exposure could have led to uptake, it is necessary to determine the total effective exposure.

The primary evidence of “exposure” is generated from an occupational history, which is best recorded by an experienced occupational health physician or occupational hygienist. The history will record start and finish dates for each job held. Each job should be described by actual duties performed as well as job classification. Record all aspects of the work environment including, for example, whether particular workplaces were adequately ventilated. Record individual workplace and out-of-work hygiene practices, such as the need for washing to remove adherent material from skin or clothing. All aspects of “safety” may be relevant. The availability and use made of protective clothing or related matters is a crucial aspect of the history.

Wherever possible make a quantitative estimate of exposure using exposure records from the person’s work if they are available. If not an estimate may be made from knowledge of the industry concerned. Such estimates may require the help of an occupational hygienist, and would take into account the process, control methods in use at the time and whether personal protective equipment was used. Evidence of personal exposure may be inferred from the necessity to clean safety equipment (eg remove deposits, replace filters). Obviously if safety equipment is not available or is inadequately maintained, this will be relevant to any discussion of exposure. Individual experience of the workplace, as documented in the occupational history, may provide evidence of exposure such as awareness (and persistence) of odour, the need to wash hands, face or other skin free of material, and the need to wash clothing.

Biological evidence of exposure may be available. Direct evidence stems from documented detection of the compound or its metabolites in body tissue or fluids, and may exist if determinations of blood or urinary levels were made at the time of exposure. In some circumstances biological indices of exposure may still be found when the cancer has been diagnosed. For example some pesticides are highly stable in the body and the levels found at the time of cancer onset may be used as an index of past exposure. Blood dioxin levels have been measured in Vietnam veterans formerly exposed to phenoxyacetic herbicides (of the Agent Orange type). In fact previous estimates of dioxin exposure (based on exposure history or chloracne) correlated poorly with the blood dioxin levels, and scientists concluded that the latter enabled them to make a more valid estimate of the relationship between exposure and disease.^{1,2}

Some metals (eg cadmium) have a long half-life in the body enabling current body burden to be used for estimating past exposure.³

A record of employment duration in the particular job is usually obtainable relatively easily, either from the subject or from employment records. Both experimental and epidemiological data indicate that risk of cancer increases with increasing duration of exposure. Most instances of occupational cancer involve exposure periods of at least five years. The possibility of a causal relationship cannot be excluded for lesser periods, though many epidemiological studies exclude individuals whose exposure was less than six months.

These considerations should lead to an estimate of *cumulative exposure*, which is the product of time-weighted average exposure and the duration of exposure.*

Cumulative exposure is essential as an indicator of the probability that the exposure caused the disease. The higher an individual's cumulative exposure to a human carcinogen the greater is the probability that it contributed to the causation of the cancer. A low cumulative exposure does not exclude a causal role but makes it less likely.

Could the exposure have led to uptake of the agent?

There are a limited number of ways in which a chemical agent can be taken up: inhalation, ingestion and absorption through the skin. Uptake from at least one of these routes must occur if the agent is to cause cancer. The potential for each of these routes must be carefully explored by somebody familiar with the principles of occupational hygiene.

If the agent was solid, it must have become airborne in respirable form. If the cancer under consideration is the lower respiratory tract (lung or bronchial cancer) the dust must have been respirable (ie less than 10 microns in diameter).

Volatility of liquids is an important factor. If an agent is volatile, the vapour can be inhaled. Even non-volatile liquids can still be inhaled through aerosolisation.

Many substances can be absorbed through the skin, and it is therefore important to know both whether the agent can be absorbed percutaneously and how readily. If skin absorption can occur it is important to ascertain whether there was an opportunity for skin contact.

Ingestion is less common in the occupational environment but can occur from smoking or eating with contaminated hands.

In the special case of radiation exposure, the type of radiation is important. Alpha particles cannot penetrate intact skin, and can only have a biological effect if inhaled or ingested, whereas gamma-radiation and x-rays can be effective whether the source is internal or external. Therefore, where there is a history of radionuclide exposure, it is important to know the type of radiation emitted.

Is the particular agent associated with cancer at this site and of the same histological type?

Most cancer epidemiology has associated particular exposures with cancers of a specific site or a number of specific sites. For example tobacco smoking is associated with cancers of the lung, larynx, bladder, cervix, pharynx but not other cancers such as cancers of the brain. It is important to ascertain that the cancer site is consistent with the target organs identified in the epidemiological studies. Some of the more common exposures and the target organs are listed in Table 4.

It may also be helpful to identify the tumour type in some detail. Some carcinogens can cause tumours of different histological type. Examples are wood dust with the associated sinonasal cancer adenocarcinoma; vinyl chloride with angiosarcoma of the liver; benzene with acute myeloid leukaemia; ionising radiation with acute myeloid leukaemia and chronic myeloid leukaemia; and inorganic acids with intrinsic carcinoma of the larynx.

It is sometimes necessary to characterise the exposure in further detail. For example sinonasal cancer has been identified with working with hardwoods (the evidence being weak or absent with softwoods). Mesothelioma is most strongly associated with blue asbestos (crocidolite), although it has also been associated with exposure to other species of asbestos. This consideration may be important where a person with mesothelioma has been exposed to different asbestos types in different jobs.

* Cumulative exposure is the exposure estimate most commonly used, and a number of exposures have been confirmed as carcinogenic on the basis of increasing risk with increasing cumulative exposure. However, there may be other dimensions of exposure which are important in determining risk, such as the frequency or intensity of exposure peaks.

Table 4. Common carcinogenic exposures and their target cancer sites

Exposure	Cancer site
Asbestos	Mesothelium (pleura/pericardium, peritoneum), lung
Passive Smoking	Lung
Silica	Lung
Shoe manufacturing/repair	Nasal epithelium
Aluminium reduction	Bladder, lung, skin
Coal gas/coke production	Lung, kidney
Furniture/cabinet making	Sinonasal epithelium
Iron and steel founding	Lung
Rubber industry	Various
Painting	Lung, leukaemias
Arsenic	Lung, skin, bladder
Chromium	Lung
Benzene	Leukaemia
Nickel	Sinonasal epithelium, lung
Coal tar and coal tar pitch	Larynx, lung
Inorganic acids	Larynx, lung
Mineral oils	Bladder
Radon daughters	Lung
Wood dust	Sinonasal epithelium

Is the site of the cancer consistent with the route of uptake of the agent?

It is useful to consider whether the cancer has occurred at a site to be expected from the route of uptake.

The route of uptake of carcinogens influences the site of the resulting cancer. Carcinogens taken up by inhalation, such as tobacco smoke and asbestos, are usually associated with lung cancer. Whether they can cause cancer at other sites will depend on whether they are absorbed systemically from the point of entry. Some constituents of tobacco smoke are absorbed, so that smoking is also associated with a number of internal cancers, such as bladder and cervix uteri. On the other hand asbestos has a long residence time in the lung and is rarely associated with cancers at remote locations. (A relatively uncommon exception is abdominal mesothelioma, which can be caused by asbestos exposure.)

Lung cancer can result from exposure pathways other than inhalation. Although lung cancer has been causally associated with inhaled arsenic, a strong link has been identified between lung cancer and raised arsenic levels in drinking water.⁴

Skin cancer is commonly associated with substances which have come into contact with the skin, but there is some evidence that it can result from exposure from other routes as well. For example cases of skin cancer have been reported following arsenic ingestion.⁵

It is also possible that skin contact can lead to internal cancers as well. Some aromatic amines, for example, are absorbed through the skin and thus may be responsible for some cases of bladder cancer in exposed workers.

Was the time from exposure to disease onset consistent with the induction latency period of the agent?

The transformation of normal cells to malignant cells is understood to be a multi-step process. Although all cancers are believed to be monoclonal in origin (ie derived initially from a single mutant cell), a number of

successive mutations, each followed by a period of reproduction of the mutant cell (clonal evolution), must occur before a malignant cell is finally produced leading to cancer. An environmental agent can contribute to cancer formation by directly causing a mutation or by promoting rapid growth of cells thereby increasing the probability of a mutation. The period between exposure to an environmental carcinogen, usually measured from the date of initial exposure, and the onset of cancer is known as the latency period of the agent. Epidemiological studies indicate that most such carcinogens have a latency period of several years.

Therefore before attributing a cancer to a past exposure, an estimate should be made of the period between the exposure and cancer onset to ensure that at least the minimum latency period has elapsed. Most epidemiological studies tend to exclude cancers within 10 years of first exposure and, because of the number of steps in the transformation from a normal cell to malignancy, greater confidence can be placed in a causal association with longer periods following exposure. There is good evidence on the latency period of asbestos exposure in causation of mesothelioma, as discussed in Chapter 5. There is evidence that the latency period for benzene and radiation-induced leukaemia may sometimes be less than 10 years.⁶⁻¹⁰ However, evidence is scant on the minimum latency period for most cancers. Therefore in the absence of good data, latency periods of less than 10 years cannot be totally ruled out.

Were there other factors that might have contributed to the risk of cancer in this person?

It is important to search for other factors which may affect the risk of cancer, such as smoking, age, other carcinogenic exposures and genetic factors.

Smoking has a strong causal role in many cancers, accounting for over 90% of lung and laryngeal cancers, 50% of pancreatic cancers and less than 10% of gastric cancers. For these cancers the smoking history should be quantified. Smoking history is measured in pack-years, that is number of years smoked multiplied by average number of packets per day. A record of the number of years since quitting, where applicable, is also relevant.

However, a history of smoking does not necessarily diminish the probability that the cancer was occupation related as well. It is clearly established that multiple factors can contribute to tumour formation, and there is a broad range of human cancers where causation includes the combined impact of two or more factors, particularly when each agent can cause the same tumour type. If that is the case, the risk of cancer is greater - and possibly multiplicatively greater - than would have been the case if the exposure was to each of the agents separately. Examples extend from the synergism exhibited between cigarette smoking and a number of carcinogens - asbestos, radon daughters and arsenic - as contributing to lung cancer. These considerations may be important in determining the balance of probabilities in a particular case and are discussed in the following section.

Assessing the probability that the exposure was a contributory cause of the cancer

If the exposure is considered to be carcinogenic, if the cancer is of a type consistent with the chemical agent and its route of exposure, and if the minimum latency period has been exceeded, it remains to quantify the probability that the cancer was caused by the exposure.

The greater the total exposure, the greater the likelihood that it was causal.

Ultimately the decision on causation is which is the more probable of the following two alternatives:

- the cancer would have occurred in this person even if there had been no exposure
- the cancer would not have occurred in this person but for the exposure.

Deciding causality is thus a matter of resolving the balance of probabilities - whether it is more probable than not that the exposure contributed to the cancer. Most legal compensation jurisdictions make decisions on the balance of probabilities. Such decisions can be aided by deriving an arithmetic function called the probability of causation (PC).

Probability of causation

In general terms, the PC is derived thus:

$$PC = (RR - 1) / RR$$

where RR = relative risk, that is, the cancer rate in an exposed population compared with the rate in an unexposed population.

Where the RR exceeds 2, the probability in any single case that the exposure is causal is greater than the probability that it is not. Where the RR is less than 2, the reverse is true.

On the basis of this reasoning, the balance of probabilities favours the claimant if RR exceeds 2.

The exposure corresponding to a RR of 2 is sometimes called the doubling dose, meaning the exposure at which the risk is double that of the general population.

The examples in Box 1 explain the basis of the probability of causation function.

Box 1. The basis for using the probability of causation function

Consider a population exposed to a carcinogen which causes a doubling of the incidence of bladder cancer, and suppose that the annual rate of bladder cancer in the general unexposed population of comparable age and sex is 10 cases per 100,000. The bladder cancer rate in the exposed population is therefore 20 per 100,000, that is, the RR in the exposed population is 2. Of the subpopulation of workers exposed to the agent who developed bladder cancer, one-half will have developed the cancer as a result of the exposure, whereas the other half would have developed the cancer even in the absence of exposure. With a sample of, say, 20 subjects randomly chosen from this subpopulation, 10 will have developed the cancer as a result of the exposure, whereas the other 10 would have developed the cancer even in the absence of exposure. (In reality, because of sampling variation the numbers might not be exactly 10 and 10. The numbers would be exactly equal only with an infinitely large number of subjects.) It is not possible to know which individual subjects belong to which category. It is only possible to say that in each subject the probability that the cancer is causally related to the exposure is on average equal to the probability that it is not. The probability of causation in any individual case is 50%.

If instead the exposure causes a trebling of the cancer rate, that is the RR is 3, then it can be said that of a sample of 30 exposed cancer cases, 20 will have developed the cancer as a result of the exposure, whereas the other 10 would have developed the cancer even in the absence of exposure. In each subject it is more probable than not that the cancer was causally related to the exposure, and the probability of causation is equal to 20/30, or 0.67.

Conversely, if the exposure increases the cancer rate by one-half, that is the RR is 1.5, then of 15 cases with a history of exposure, only 5 would be caused by the exposure. In each subject it is more probable than not that the cancer was not related to the exposure, and the probability of causation is thus 5/15, or 0.33.

Estimating relative risk

The probability of causation is thus seen to be dependent on the RR, that is, the ratio of the incidence rate of cancer in a population exposed to the agent to the incidence in an unexposed population. Since RR increases with increasing exposure, the critical question is *whether the cumulative exposure was sufficient to cause more than a doubling of the risk, that is, whether the RR exceeds 2 in a population exposed to the estimated cumulative exposure*. If it does, then the balance of probabilities favours causation.

To determine the RR it is necessary to consult the epidemiological literature to identify whether the person's cumulative exposure has been associated with a RR greater than 2. Some studies have computed the dose-response relationship between cumulative exposure and RR, in which case the decision is comparatively simple.

Unfortunately, for several carcinogenic agents the relationship between exposure and risk has not been measured. In such cases all that can be done is to decide whether the exposure of the affected individual was similar to that recorded in epidemiological studies of the agent. The RR is best estimated where the person's job description coincides with that which served as a basis for epidemiological study; for example, where an individual worked as a house painter, reference can be made to the RR in studies of occupational cancer risk in house painters. If the circumstances are different, judgement will be required on whether the RR is different. Thus a garage mechanic may be exposed to the same petroleum products as refinery workers, but the processes and work practices may differ, in which case judgement is required on whether the exposure and hence the RR is different. (Generally large capital-intensive organisations such as oil refineries are able to control exposures better than small workplaces.) Similarly employment as an instructor on automotive spray painting under ideal conditions is not the same as working in a vehicle repair shop.

Some epidemiological studies which lack an estimate of RR of cumulative exposure nevertheless have estimates according to duration of employment. Thus a study of bladder cancer in the aluminium industry may have shown an RR of 1.5 in those employed for up to five years, and an RR of 2 in those employed from six to 10 years. In such a hypothetical case, workers who had performed similar work to that of the population in the study for more than 10 years would have a RR of bladder cancer greater than 2, and in an individual with bladder cancer the PC would be greater than 50%.

Usually there is little difficulty in deciding which epidemiological study to consult to determine the relationship between risk and exposure, because the number of relevant epidemiological studies is usually quite small. Sometimes the IARC may have made a classification of human carcinogenicity on the basis of a single study. Where there is more than one relevant study, it is best to select a study where the exposure occurred in the same or a similar industry to that of the case in question. If a choice must be made, consult review articles on the subject or the series of IARC monographs on carcinogens, which tabulate all the available epidemiological studies.

Adjusting for other causal factors

For cancers associated with occupational exposures that are also caused by smoking it may be necessary to adjust the estimate of PC, depending on whether there is any synergistic effect from the combination of smoking and the occupational exposure. The interaction of the two may have a multiplicative effect as in the following hypothetical case of exposure to a chemical agent:

RR	Not exposed	Exposed
Non-smoker	1	2
Smoker	10	20

The RR from exposure alone is 2, from smoking alone 10, and from both $2 \times 10 = 20$ (approximately), that is, the effect of the two factors combined is multiplicative. Note that the RR from the occupational exposure is 2 in both smokers and non-smokers, that is the RR due to occupational exposure applies regardless of smoking history. Thus where the combined effect of exposure and smoking is multiplicative, no adjustment is needed for smoking. Where the effect is not multiplicative, the PC will have to be adjusted according to the nature of the interaction (eg additive) and whether the person smoked and how much.¹¹

Similar adjustments may be required for the age of the person in cases where risk following exposure is dependent on age and the combined effect is other than multiplicative.

Limitations of the model

The PC model has the merit of simplicity but there are a number of associated problems, some of which various jurisdictions have sought to overcome by statute.

The estimate of PC is a continuous estimate lying anywhere between 0% and 100%. Reducing this percentage estimate to one of two alternatives - causal or non-causal - necessarily means that some errors will occur. Between 0%, where we can be certain that the exposure was not causal, and 100%, where we can be certain that it was, the determination of causality according to whether the PC is less than or greater than 50% will lead to errors in some cases (see Box 2).

Box 2. How errors can occur in assessing causation

Let's return to the examples in Box 1. Where it is found that a particular exposure causes a RR of 3, it can be said that of a sample of 30 exposed cancer cases, 20 will have developed the cancer as a result of the exposure, whereas the other 10 would have developed the cancer even in the absence of exposure. In each subject it is more probable than not that the cancer was causally related to the exposure, and the probability of causation is equal to 20/30, or 0.67. If all 30 cases were awarded compensation, one third will have received an award to which they were not really entitled, but it will not be known which 10 of that 30 they were.

In the other example where the exposure increases the cancer rate by one-half, that is the RR is 1.5, then of 15 cases with a history of exposure, only 5 would be caused by the exposure. In each subject it is more probable than not that the cancer was not related to the exposure, and the probability of causation is thus 5/15, or 0.33. If all 15 cases were denied compensation, 5 would have been unjustly treated, but it is not known which of the 15 individuals they were.

In summary, if all cases are decided according to the balance of probabilities an injustice will be done in a proportion of cases, either to the plaintiff or the defendant. (The situation is thus different from the criminal law where it is held that "it is better that 100 criminals go free than that one innocent person shall hang".)

The existence of this “all or nothing” threshold could be regarded as harsh, particularly to those claimants in whom the PC just falls short of 50%. Some jurisdictions have sought to overcome this by instituting a system of part payments for such cases.^{11,12}

Other legislative adjustments could be made by statute to give the claimant the benefit of any doubt. An example is the use of the upper limit of the 95% confidence interval to assess RR as proposed by the Canadian province of Quebec.¹¹ The confidence interval is a statistical estimate of the possible error in the estimated RR due to limitations in the size of study populations on which the RR is based. The smaller the sample population on which the RR estimate is based, the larger the potential for error and the greater the confidence interval. For example, if a given cumulative exposure were found to cause an RR of 1.60 with a 95% confidence interval of 1.30 to 2.10, under the system described above a person with that cumulative exposure would fail in his claim because the RR (ie the point estimate of RR) is 1.60, which is less than 2. However, if there were a rule that the upper limit of the 95% confidence interval (in this case 2.05) were to be the basis of the estimate, the claim would succeed since it exceeds 2.

Such departures from the use of the conventional balance of probabilities could be justified by the uncertainties involved in accurately assessing exposure history of individuals and in deriving exposure-response relationships. However, such rules would require enactment in law and are therefore a matter for political decision making.

Another concern is that the adjustment for co-factors such as age and smoking, as discussed, can sometimes involve complex computations.

Further complexities are certain to arise in the future in relation to the role of genetic factors in cancer development, and the effect of exposure in people with different genotypes. For example people with the slow n-acetyl transferase 2 (NAT-2) genotype who are exposed to certain aromatic amines appear to have a greater risk of bladder cancer than those similarly exposed but who lack that genotype. Such genetic factors influence the metabolism of some chemical agents, and may thus vary the risk of cancer in either direction.

Even more difficult to evaluate is the occurrence of some uncommon hereditary conditions associated with defective DNA repair. An example is the condition xeroderma pigmentosum, where the person has a greater than 1000-fold increase in sunlight-induced skin cancers. As in the previous example, solar radiation is critical in the formation of skin cancers in such patients, but so great is the risk due to the genetic disposition that such a cancer is almost impossible to avoid, however well the person's job is designed to provide protection from sunlight. Where genetic factors produce a large increase in risk, cancer could be regarded as almost inevitable regardless of the work history. It is likely that attention will be required in the future on whether and how PC will need to be adjusted for such factors.¹³

What if the exposure is found not to be causal?

The question is often asked: why did the cancer occur in this person at this time. When it is concluded that the exposure was not causal, many people find it difficult to accept the absence of any obvious cause. However, an explanation is lacking for most individual cancers, excluding tobacco-related cancers. Knowledge of causation for most tumour types is fragmentary, with many cancers still being categorised as “spontaneous”. An argument that a particular exposure caused an individual cancer cannot be sustained simply on the basis that no other cause can be found.

Conclusion

Assessment of causation in particular cancers can be summarised in the following steps.

- Determine whether it is possible that the agent (or process or occupation) could be a contributory factor in the cancer. This is decided on the basis of what the agent is, whether there was uptake by inhalation, ingestion or by other means, the timing of exposure in relation to cancer diagnosis and the cancer site and histological type.
- Assess the total exposure.
- Consult the relevant scientific data to determine whether the exposure exceeds the level found to cause a doubling of the risk of the cancer.

5 ASBESTOS-RELATED CANCERS

Asbestos exposure is the commonest cause of fatal work-related cancer, and is likely to continue to be so for some decades. The epidemiology of asbestos-related cancer has been studied intensively and only a summary of the main issues is presented here.

Is asbestos carcinogenic to humans?

The association between asbestos and human cancer is established beyond any reasonable doubt.

Which cancers are associated with asbestos exposure?

The cancers associated with asbestos exposure are lung cancer and mesothelioma, the latter usually affecting the mesothelium of the parietal (ie outer layer of) pleura but occasionally affecting other sites of mesothelium such as the peritoneum.

Some epidemiological evidence suggests that asbestos exposure can cause colonic cancer, although a review of 30 cohort studies up to 1993 found that there was not a consistent elevation of relative risk.¹ A recent study has suggested up to a 4-fold increase in risk in highly exposed workers, although the authors concluded that confirmation is needed from other studies before it can be accepted that there is an excess risk of colonic cancer from asbestos exposure.² Laryngeal cancer has also been identified as being possibly caused by asbestos in some cases but the supporting evidence is not strong.³

What is the route of exposure?

In nearly all cases the likely route of asbestos exposure is inhalation. Occasionally the question of ingested asbestos may arise, since some water supplies are reticulated in asbestos-cement pipes. Some ingestion could also occur following inhalation. Conclusive evidence of carcinogenicity of ingested asbestos is lacking.⁴⁻⁶

Assessment of probability of causation: lung cancer

The evaluation is dependent on whether the subject has asbestosis.

If asbestosis is present, the assessment of probability of causation can be relatively simple, since the association between asbestosis and lung cancer is strong and unequivocal. If a diagnosis of asbestosis is established no quantitative estimate of exposure is required: epidemiological evidence shows that if asbestosis is present the relative risk (RR) of lung cancer from asbestos exposure is well above 2, so that the probability of causation (PC) can be confidently assessed as above 50% whenever asbestosis is present.^{7,8} Furthermore this judgement can be made irrespective of smoking history.

The diagnosis of asbestosis is usually made by detection of lung opacities on radiological examination. Other conditions can give a similar appearance, so that diagnosis should be corroborated by a clear history of asbestos exposure. Further corroboration may be obtained if pleural plaques are present. Plaques are not always asbestos-related and the diagnosis is a matter of clinical judgement supported by skilled radiological services.

Even so, plain x-rays of the chest have been found to miss 20% of cases of asbestosis confirmed histologically.⁹ Therefore if there is a history of occupational asbestos exposure, high-resolution CT scanning should be undertaken before excluding a diagnosis of asbestosis. If a biopsy or surgical specimen has been obtained, sections of lung should be examined for the presence of asbestosis: the presence of any asbestos bodies at all, together with diffuse interstitial fibrosis, should be regarded as diagnostic.¹⁰

If asbestosis is not present, the decision on whether the cancer is caused by asbestos is a matter of continuing scientific debate. There is strong controversy as to whether the fibrotic changes of asbestosis are a necessary pathway from asbestos exposure to lung cancer. In theory, there is no reason to presume that fibrosis is a necessary precursor to malignant change following asbestos exposure. After all, pleural mesothelioma more often than not occurs in the absence of pleural fibrosis. However, consensus is lacking on the question of whether the risk of lung cancer is increased from asbestos exposure in the absence of asbestosis.

Some evidence points toward an absence of excess lung cancers in the absence of asbestosis. The two studies cited which have shown excess lung cancer risk have failed to show any excess in the absence of asbestosis.^{6,7} An autopsy study of insulation workers found parenchymal fibrosis in every one of the 138 cases where there was a tissue

specimen for histological study.⁸ A review of seven cohort studies in which there were no cases of asbestosis found a significant lung cancer excess (RR = 1.37, 95% CI 1.02-1.81) in one cohort but overall there was no excess (RR = 1.00, 95% CI 0.88-1.14).¹¹ However some observers are unconvinced and have criticised these studies on the grounds of bias or insufficient statistical power.¹²

Other studies have been claimed to show that asbestos exposure per se can cause lung cancer in the absence of asbestosis. Some population-based studies, in which asbestos fibre counts in lung tissue or radiological evidence of pleural plaques have been used as markers of exposure, have found excess lung cancers after all cases with asbestosis were excluded.^{13,14} These studies have in turn been criticised on the grounds of bias.^{15,16}

Realistically, it is unlikely that consensus will be reached in the near future on whether asbestos exposure can cause lung cancer in the absence of asbestosis.

If it is held that asbestosis is not a necessary precondition for asbestos-related cancer, the criterion for acceptance of a claim should be whether the individual has received a doubling dose of asbestos; that is, whether the cumulative exposure is sufficient to have caused an RR of lung cancer greater than 2.

Cumulative asbestos exposure is expressed as the product of duration of exposure (in years) and the mean exposure concentration (measured in fibre/mL over the period of exposure. Cumulative exposure is thus measured in fibre/mL year.

It is therefore important to estimate the cumulative asbestos exposure. Exposure records should be examined if available, or the likely exposure can be estimated, preferably by an experienced occupational hygienist.

In the absence of asbestosis, and if asbestosis is held not to be a precondition for asbestos-related lung cancer (either by statute or on the basis of evidence presented), the probability of causation is contingent on the following:

- **Asbestos exposure history:** The issue is whether the asbestos exposure exceeded the *doubling dose*, which will depend on the type of asbestos exposure. For reasons given in Box 3, the estimates shown in Table 5 are suggested.
- **Lung fibre count:** An alternative method of assessing past exposure is from fibre burden. If the asbestos fibre burden in a surgical or biopsy specimen of lung is available, a level of 5 million fibres/g of dry lung, detected by scanning electron microscopy, is approximately equivalent to a doubling dose in a subject without asbestosis.¹³
- **Time since exposure:** It is widely assumed that excess risk of lung cancer will not occur within 10 years of initial exposure to asbestos. In fact little attention has been paid to the minimum latency period for asbestos-related lung cancer. In one of the pioneering studies of asbestos-related lung cancers, Selikoff observed no lung cancer deaths within 10 years of first exposure, although an excess risk appeared immediately beyond 10 years.¹⁷ In their 1985 review of the health effects of asbestos, Doll and Peto stated that while such cases do not generally occur within 10 years of exposure, some cases may appear as soon as five to nine years from initial exposure.¹⁸ Therefore attribution to asbestos of lung cancer should not be ruled out solely on the grounds that it occurred within 10 years of initial exposure.*
- **Smoking history:** Most studies on the interrelationship between asbestos and smoking have concluded that the relationship is multiplicative, that is, the relative risk from asbestos exposure is the same irrespective of smoking history. As shown in the example given in the previous chapter (page 39), it follows that the effect of smoking is the same irrespective of asbestos exposure. It is unlikely that this relationship is so simple, in view of the dose-related effects of both smoking and asbestos exposure. Indeed a recent review has concluded that the relative risk of asbestos exposure is about twice as high in non-smokers as in smokers.²⁰ However, taking such factors into account would require a degree of mathematical modelling which available data would not justify for compensation purposes. Accordingly it is recommended that the RR be determined on the basis of fibre exposure as in Table 5, except that in borderline cases, where the estimated cumulative asbestos exposure is close to the doubling dose, variation with smoking could be taken into account. In such cases, for those who have never smoked the doubling dose of asbestos would be less than that shown in Table 5, so that for a given exposure the corresponding RR will be higher. Conversely for heavy smokers the doubling dose would be higher than in Table 5 and for a given exposure the corresponding RR will be lower.

Table 5. Recommended estimates of risk and doubling dose according to type of asbestos exposure

Fibre type	% increase in RR per (fibre/mL).year	Doubling dose in (fibre/mL).years
Amphibole asbestos (includes crocidolite and amosite)	4.8	21
Mixed fibres	4.8	21
Chrysotile mining	0.06	1667
Pure chrysotile other than mining	2.3	43

Box 3. What is the doubling dose of asbestos?

The risk of lung cancer increases with increasing asbestos exposure. A number of studies have allowed the plotting of risk against exposure, so that a level of exposure at which the RR is equal to 2, can be calculated. This level of exposure is called the doubling dose (see Chapter 4).

A report from the UK Health and Safety Executive (HSE) has reviewed the risk estimates for asbestos-related lung cancer.¹⁹ For pure amphibole exposure (eg crocidolite and amosite) the additional risk per fibre/mL.yr has been estimated at 4.8%, giving a doubling dose of 21 fibre/mL.yr.

For other exposures the risk estimate has proved difficult to summarise. This is largely due to a particular study of chrysotile exposure in Carolina which showed a much higher level of risk than all other chrysotile studies. Whereas all other studies show a summary additional risk of only 0.06% per fibre/mL.yr, the Carolina study shows a risk similar to that of amphibole asbestos. It is possible that the higher risk estimate in the Carolina cohort may be due to the presence of some amphiboles, that is an exposure to mixed fibres. The Carolina estimates are even higher than other cohorts exposed to mixed fibres.

The mixed fibre cohort studies themselves also show a wide range of risk estimates (from 0 to as high as 6.2% per fibre/mL.yr).

The multiple anomalies may be related to uncertainties in the exposure estimates in these cohort studies. In earlier decades asbestos exposure was measured not in fibre counts but in particle counts, and the conversion scale of particles to fibres is itself an uncertain procedure. A further anomaly may lie in the possibility that matters other than total asbestos exposure, such as rate of exposure, may affect risk. For example a heavy exposure over a short period may confer a greater risk than the same total exposure over a longer time period.

These uncertainties make the estimation of doubling dose for compensation purposes very difficult. Since there is evidence that mixed fibre exposure can confer a risk similar to that of pure amphiboles, it is therefore reasonable that the doubling dose be taken as the same as for pure amphiboles, that is 21 fibre/mL.yr, unless it is certain that the exposure was to pure chrysotile. The HSE report summarises the risk from chrysotile as 0.06% per fibre/mL.yr for chrysotile mining (doubling dose 1667 fibre/mL.yr) and 2.3% per fibre/mL.yr for chrysotile other than mining (doubling dose 43 fibre/mL.yr).

These issues are important if the jurisdiction concludes that the presence of asbestosis is not an essential condition for asbestos-caused lung cancer, a question that is not settled at present.

Assessment of probability of causation: mesothelioma

Assessment of mesotheliomas is usually simpler because, unlike lung cancer, nearly all cases are asbestos related.

As with lung cancer, the risk increases with exposure. Unlike lung cancer, however, there is no need to consider whether asbestosis is present, since mesothelioma has been reported at exposures well below levels likely to cause asbestosis, and in most cases asbestosis is not present.

Risk of mesothelioma is related to exposure, and most mesotheliomas in the past have been concentrated in industries with high exposure, such as shipbuilding, railways, insulation, asbestos mining and textile production.^{21,22} These heaviest exposures were brought under control several decades ago, so that the proportion of mesothelioma cases from these industries is declining.

An increasing number of cases are now coming from industries such as construction, where exposures were less intense but were brought under control at a later time than the heavy users of asbestos. Although the risk to individuals is lower, the number of people exposed is much greater.²³ Therefore in these industries with a history of asbestos exposure, mesothelioma can be confidently attributed to the exposure even if exposure has been light or transient.

Where no occupational exposure history of asbestos use is found, the exposure may have been residential or para-occupational. In some cases mining town residents who were not employed in the industry have been exposed from asbestos miners or other users bringing asbestos home on their clothing, or from residential renovations involving asbestos products.

One area of difficulty is with individuals who have had no known exposure but who have worked in a building where asbestos insulation has been sprayed. Exposure studies in public buildings have shown that exposures in office buildings and schools with asbestos-containing materials are no different from those where asbestos-containing materials are not present, because asbestos fibres do not spontaneously become airborne.²⁴ Occupants of these buildings may therefore be expected to have no greater risk of mesothelioma than people in an asbestos-free environment. The evidence that this is so would be found from a relative lack of mesotheliomas in women, who make up a high proportion of office-building occupants. In fact the low and almost static incidence of mesotheliomas in women has led to the view that background levels of asbestos are unlikely to cause mesothelioma.²⁵ However since the early 1990s the rate of mesotheliomas in women has risen from its previous level of 4 to 11 per million person-years.²⁶ This rise has only been observed in Australia and may be the result of high use of crocidolite, which is the most potent of asbestos species in causation of mesothelioma. The implication is that mesothelioma can arise from asbestos levels close to background levels (ie the low levels in the general environment to which all urban dwellers are exposed).

An Australian study of asbestos fibre counts in the lungs of mesothelioma cases and controls has found that the risk of mesothelioma does not increase until levels of amphibole fibres <10 microns (μ) in length exceed 3 million fibres/g of dried lung. On the other hand when the analysis was restricted to fibres >10 μ in length the risk increased at much lower fibre concentration, that is 250,000 fibres/g.²⁷ A possible explanation is that extremely low level amphibole exposure can cause mesothelioma in individuals whose lungs are unable to clear long amphibole fibres. In practical terms this means that mesothelioma cases, whose only possible asbestos exposure could have been as occupants of buildings containing asbestos, may have had such a susceptibility to mesothelioma, in which case their exposure may have been quite minor. It is therefore important to probe for a history of even minor transient exposure, such as being in a building during maintenance or asbestos removal.*

There is no need to consider smoking history as smoking has no role in causing mesothelioma.

The latency period from first exposure is long - up to 40 years or even more being quite common. Mesothelioma is unlikely to be related to asbestos if it is diagnosed within 10 years of initial exposure.

If a person has had more than one source of exposure, allocation of causation may be helped by consideration of the latency period. One review of the epidemiological literature²⁹ has estimated that the probability of occurrence of mesothelioma (p) is estimated from the function:

$$p = k.c.t^{3.5}$$

where k is a constant

c is cumulative asbestos exposure

t = years since initial exposure.

This equation can be applied to estimate the relative probability of causation of exposures at different times of the person's working life. (Of course there is a probability that the tumour is a result of cumulative exposure from more than one source, in which case allocation of liability is moot.)

Another consideration in allocation of liability is the species of asbestos. The risk of mesothelioma from chrysotile is estimated to be 1/50th of comparable exposure to crocidolite.¹⁶ This consideration may be important where a person with mesothelioma has been exposed to different asbestos types in different jobs.

A recent review stated that chrysotile does not cause peritoneal mesothelioma.³⁰ However an Australian study based on analysis of lung tissue found two cases of peritoneal mesothelioma where only chrysotile was found in the lungs.³¹

* There is some evidence to suggest that other co-factors (including genetic factors) can increase the likelihood of mesothelioma in certain individuals. This may explain the fact that only a fraction of those with asbestos exposure develop mesothelioma, and that mesothelioma occurs in some individuals with minimal asbestos exposure.²⁸ This does not mean that asbestos exposure, however small, is not a necessary causal factor in a particular case. In compensatio jurisdictions, the possibility of other co-factors does not diminish liability from asbestos exposure.

Prevention of asbestos-related cancer

The recent observation of a steep increase in the incidence of mesothelioma in Australian women highlights the risk of mesothelioma in the absence of known exposure, suggesting that very low exposures, comparable to environmental (“background”) levels can cause the disease. Great caution is therefore still required to avoid exposure to any airborne asbestos.

Such exposures are possible from asbestos removal operations, particularly removal of sprayed asbestos insulation in buildings. Although such operations are usually undertaken under strictly controlled conditions, achieving zero exposure to removal workers or bystanders may be an unrealistic expectation. Consideration should be given to alternatives to removal, such as sealing or encapsulation, which are much less likely than removal operations to cause asbestos to become airborne. Some Australian jurisdictions favour removal as the control method of choice. A more appropriate regulation might simply be to require a risk assessment to determine which method of control will cause the least harm to the fewest people.

The New Zealand Guidelines for the Removal and Management of Asbestos include a useful table which notes when each of the control methods (removal, sealing or encapsulation, enclosure, deferral) is or is not appropriate.

Another residual concern is the continuing use of asbestos-containing materials: brake linings, clutch linings, gaskets and non-sag adhesive putties used in the building industry. Although importation of these items is scheduled to cease, their use is likely to continue for some time. These items contain chrysotile asbestos, which carries a comparatively low risk of mesothelioma. Nevertheless where they are being installed or replaced protective measures should be observed as set out in Chapter 2. Australian governments have agreed to enact a prohibition on the use of asbestos, to take effect by the end of 2003.

6 CANCER CLUSTERS IN THE WORKPLACE

An issue for occupational medicine is the occurrence of clusters of cases of cancer in the workplace or in the nearby community. A prominent example of recent years has been the cluster of cases of leukaemia in Port Kembla near the BHP plant.¹

Clusters of disease may arouse considerable concern in the workplace and even industrial disputation or media investigation. For occupational physicians they seem to hold out the promise of interesting investigations and new knowledge about some exposure. But cluster investigations are usually beset with difficulties.

The nature of clusters

In some ways clusters are quite like epidemics but there are some important differences. Last² has defined a cluster as “(an) aggregation of relatively uncommon events or diseases in space and/or time in amounts that are believed or perceived to be greater than could be expected by chance”.

Although similar, clusters are not the same as epidemics. Usually, epidemics are of diseases where the natural history and pathogenesis of the condition is well known - often (although not always) infectious disease with a short time course. The epidemic is almost always identified by clinicians or routine surveillance and there is little doubt that the number of cases is excessive. Clusters on the other hand are usually of non-infectious diseases, such as cancer or birth defects, or perhaps of lung disease or renal failure. For these conditions, the pathogenesis may not be clear. Rather than being found by doctors, clusters are commonly identified by cases or their colleagues. In such situations it is not easy to confirm that the particular excess of cases is real. As well as identifying the cluster, the community or workgroup often identifies what they think is the cause, perhaps some chemical or exotic exposure.

The possible situation in a workplace is the occurrence of a number of cases of cancer. The cancers may be of a particular type (eg bladder cancer) or may be a range of different ones. For many people the term cluster is reserved for cancers of a single type because such cancers are more likely to have a single cause. The community or workforce may not recognise that cancer is a common disease, affecting more than one third of people at least once in their lifetime and causing nearly 25% of deaths. Nevertheless a collection of different cancers should not be dismissed out of hand.

Box 4. A cluster report

You are the occupational physician for a medium sized foundry. The human resources manager reports that a fitter who works in the mould area has just been diagnosed with leukaemia. The HR manager goes on to tell you that the union is concerned that one other person in the mould area has cancer and two people who have retired from the area in the last two years have cancer. You agree to look into the matter. It is found that the second person mentioned is being investigated for possible bladder cancer.

The two reports on retirees are difficult to confirm (you cannot just phone the person and ask) but it appears likely that of the two, one has lung cancer and the other cannot be confirmed. There is no more than one case of any individual cancer type. It is likely that the different cancers have different causes.

Clusters can occur by chance

Random distribution of disease throughout the population is quite compatible with clustering. Therefore the appearance of a cluster of diseases in a workplace at a particular time does not necessarily mean that it results from a workplace exposure. In fact it is quite common for investigators to calculate a low “p-value”, that is, a low probability that such a cluster could occur by chance. Interpretation of a p-value depends on whether there was a prior hypothesis. With a prior hypothesis it may be appropriate to accept a p-value of <0.05 as significant. Without a hypothesis such a p-value is less likely to reflect a meaningful variation.

Considerations such as this have led some authorities to state that there is nothing to be gained by investigating a cluster and that any such investigations rarely lead to new knowledge.³⁻⁷ It is true that investigation of a cluster will never enable chance to be excluded, only independent studies on different populations can do that.

Box 5. Is a finding due to chance?

Compare two scenarios:

An investigation is being made of whether exposure to benz[a]pyrene in the aluminium industry causes bladder cancer. A case-control study comparing benz[a]pyrene exposure in 85 bladder cases with exposure in 255 controls showed an odds ratio of 2.70, indicating an association between benzo[a]pyrene exposure and bladder cancer. The p-value was <0.05 , indicating that the probability of such a finding occurring by chance was less than 1 in 20.

In the second scenario, the statisticians in the Cancer Registry do a study of cancer rates in people whose occupational histories suggest past exposure to benz[a]pyrene. The study is a surveillance exercise, with no hypothesis on whether benz[a]pyrene causes any particular type of cancer. Of 25 cancer types studied, only one, brain cancer, occurs at a rate higher than expected with a p-value < 0.05 . While this may, like the first case, indicate that the probability of such a finding occurring by chance was less than 1 in 20, in fact a chance occurrence is quite likely. Since 25 cancers are studied, it is to be expected that at least one cancer type will occur in excess, with $p < 0.05$, by chance alone. The more tests we do the greater the chance that at least one of them is positive even if no specific cause is operating.

There is an important difference in interpretation of these two findings. In the first case, provided that the study was free of bias, there is an inference that benz[a]pyrene exposure causes bladder cancer. In the second example, because of the simultaneous estimation of several cancer associations at once, in the absence of a hypothesis, no such inference may be made without supporting evidence.

Now consider a third scenario.

An observant company physician notes that three cases of chronic lymphatic leukaemia have occurred in a single workplace in the last five years. After comparing the cancer rate with that of the general population over the same period (adjusting for age differences), it is found that the rate in the workforce is three times higher than expected, with a p-value < 0.05 . Clusters of excess cancers occur in particular places and particular windows of time by chance. This situation here is in fact similar to the second case. The occupational physician (or the workforce) did not start out with the idea that there was excess leukaemia in the workforce. Rather they can be said to have tested every known cancer for excesses. This of course is a very long list and some of them will have an increased rate of occurrence by chance alone. Even though the cluster happened to be noticed by a company physician and had a low p-value, no causal inference can be made. However, certain lines of investigation can and should be followed.

There are, however, good reasons to investigate clusters:

- Investigations can determine whether there is an excess of a particular cancer compared with the expected number.
- They can examine whether the excess is associated with any known carcinogenic agent present in the workplace. If there is no identifiable cause, the distribution of cases by location, time and job description can be examined.
- This may lead to formulation of a hypothesis which can be tested in future studies.

There is a further reason to investigate clusters - concern in the workforce and the community.

Expectations of the community

Clusters arouse people's concerns. Unexplained collections of cases of cancer or other potentially serious disease upset people because they may be worried that they or their family could be hapless victims of an insidious exposure in the local environment or workplace. It is this concern that may bring the presence of the cluster to the attention of health workers but it may also hamper any investigation.

Sandman⁸ has called the sociocultural or emotional component involved in risk assessment issues "outrage" and he has described many of the features of it. This concept of "outrage" applies equally well to clusters and the community response.

Clusters need to be investigated, and not only to gain new knowledge. The social and political reasons to investigate clusters should not be ignored.^{9,10} Communities are understandably concerned about clusters and need some explanation. An off-hand dismissal of a cluster and a decision not to investigate it tends to fuel anxiety, industrial action, media debates and government inquiries.

A suggested approach

A number of authors have suggested ways to investigate clusters.^{11,12,13} The following represents a practical approach in the workplace.

General aspects

Be receptive to the existence of a cluster.

There are no grounds for disregarding clusters.

It is important to remember that many carcinogens have been identified because of an alert observer detecting a cluster. There are some classic papers such as Creech and Johnson's initial report of a cluster of cases of angiosarcoma of the liver in men who had worked with vinyl chloride.¹⁴ Had these been disregarded the identification of some carcinogenic substances would have been delayed and more lives lost.

The nature of clusters is that their cause may not be immediately obvious. Occupational physicians who become aware of a cluster of diseases in the workplace should not dismiss it initially. It may be simply a chance finding and no cause for concern, but dismissing a cluster out of hand is likely to be poor industrial relations and possibly negligence. This is also true if it is immediately clear that the reported "cluster" consists of a number of different types of cancer or even other unrelated diseases. The industrial relations results of not doing some investigation can be very grave.

Be open and involve the interested parties in the workplace.

If investigating a cluster is not likely to find new knowledge, then a major objective would be to allay community and workplace concern. Openness is the key to this. Any form of investigation that even looks clandestine will be counter-productive. Management and workers should be involved in the investigation from the outset. This could be through an existing structure such as a occupational health and safety committee or a special committee convened to deal with the cluster. This is often a good idea if the investigation proceeds to a formal study and involves many outside people.

Communicate the results.

Part of being open and involving people is good communication of the results and progress of the investigation. All the interested parties should get an opportunity to be given all the results and an explanation of what they mean. Often people assume that complex scientific details and figures will confuse or scare workers. This is a mistake and rather patronising. When results are presented in a logical format and people given a chance to ask questions which are in turn answered frankly, most people can understand quite complex concepts if they feel they need to. People are usually more worried if they believe that they are not being given all the facts than whatever the facts are.

Specific steps

Decide whether to investigate.

Our first response sets the tone for the whole investigation. Respond with a mind open to the possibility of clustering. Discuss the issues with the parties concerned and make a joint decision on whether to proceed with an investigation. Some factors that might prompt further investigation would be an uncommon cancer, a number of cases or a plausible exposure.

Box 6. Even a cluster of small size needs to be taken seriously

Cluster investigations in very small organisations are rarely satisfactory because of the small numbers involved even though two or three cases can appear so spectacular. Both management and the workforce will be concerned about any apparent cancer cluster, and the initial response should be to discuss the situation with both management and unions and decide what to do. Cancer is a common disease and its incidence is age-related so retirees might be getting to the higher risk age groups. It may well be that occurrence of a number of cancers is purely a coincidence but we should not jump to this conclusion. The occupational health and safety committee would be a good venue for initial discussion.

Confirm the diagnosis of the initial cases.

The obvious starting point in any investigation is the index cases - the cases that have drawn attention to the cluster in the first place. Identify these cases and confirm the diagnosis. Without this no further serious investigation is possible. If all the cases have the same diagnosis we can easily proceed to the next step. If there are many different diagnoses then, as discussed above, the likelihood of a single cause is low. Of course, it is quite possible that any one of the cases may be work related, and if a particular chemical exposure is suspected each case should be evaluated for any association with work (as in Chapter 4).

Exercise great caution in approaching individual workers who are reported to have cancer. The information may not be correct or the worker may not have been told of or come to terms with the diagnosis. However, if it is clear that the worker is aware and able to discuss the matter, obtain consent to confirm the diagnosis with the attending physicians and the pathologist. This should confirm if the current employees do have a particular cancer. Finding employees who have left can be difficult even in the context of a formal epidemiological study. The employee "grapevine" may help but it may not be possible to get good information. This can be a problem also when finding other cases. It is unlikely (although possible) that there are other current employees with cancer that are not known.

Establish whether there is a suspected cause.

Occasionally an acknowledged cause may be identifiable for a cancer cluster in a workplace. If a known carcinogen is in use, then each individual cancer case should be evaluated for possible association with that exposure, as described in Chapter 4.

In most cases no cause will be obvious, in which case it is a matter of deciding whether the cluster is likely to be a chance occurrence or whether there is a causal factor, and in particular a work-related causal factor, responsible. If no carcinogen is in use but the number of cancer cases observed seems extreme relative to the number expected, a thorough search should be made of the workplace by an experienced occupational hygienist for possible exposures. The occurrence of cases of cancer of various types is most unlikely to be caused by a single specific chemical exposure as specific carcinogens usually have specific target organs.

Identify all cases in current and former employees.

These days, the existence of accurate cancer registries and sophisticated computer matching techniques makes identifying all cases relatively easy. Search the Cancer Registry to identify all current and past employees (going back as far as possible) who have a registered cancer over a defined time period. This requires compiling a list of all employees over a defined time period, including those who have resigned or died. The time period should not just be for the period over which the cluster of cancers has been observed. Extending the time period backwards may enable the existence of a cluster to be disproven. If, say, a cluster of three cancers of a particular type occurred in the period 2001 to 2003, this may appear excessive. But if it is then found that no cases occurred in the period 1990-2000, the cancer rate (cumulative incidence rate) over the whole period will be seen to be unremarkable.

Submit the complete list of present and past employees, back to the agreed starting date, to the Cancer Registry of the relevant State. It is also possible to search the combined cancer registries of all states and territories in the National Cancer Statistics Clearing House, maintained by the Australian Institute of Health and Welfare (AIHW). Data are similarly accessible in New Zealand. This will enable identification of cancers in people who have moved interstate after leaving the workplace.

When all the cases of cancer have been identified, describe them in terms of demography and occupational history including occupational hygiene assessment. This may reveal common patterns such as a particular workplace, common job type or common exposures. Examine the time relationships to see that exposure has preceded the condition and sufficient time has elapsed from exposure to illness.

Identify whether there is an excess of cancers.

One way to identify whether there is an excess of cancers is to calculate the rate of cancer occurrence in the workforce and compare it to the number expected based on the general population. The cancer rate is the number of cancer cases identified in the previous section divided by the number of person-years at risk, computed from the list of past and present employees. The comparison with the general population should take into account the age distribution of the workplace population. Commonly indirect age standardisation is used to compute a standardised incidence ratio (SIR), which is an estimate of the ratio of the number of cases of the particular cancer in the workforce to the number expected in an unexposed population of the same size and age/sex distribution.¹⁵

The validity of the SIR estimate may be enhanced if instead of the entire state population, the local community where the workplace is located is used as a comparison. Cancer registries compile data for different regions within each state. However, this may not be desirable in a small town (eg a mining town) if the workgroup makes up a significant proportion of the population.

To enable this to be done the Human Resources section needs to provide the date of birth, date of hire and date of termination of each employee over the study period. The list of employees also needs to be submitted to the National Death Index (NDI) to identify any ex-employees who have died. The NDI is also maintained by the AIHW.

These estimates have a number of ethical considerations, particularly confidentiality. Moreover they require the assistance of an epidemiologist. It may therefore be expedient for the calculations to be carried out by Cancer Registry personnel.

Box 7. Is there an excess cancer rate?

Employees at a metal manufacturing plant become aware of 3 cases of laryngeal cancer that occurred over a 3-year period from 1999 to 2001.

A list is drawn up of all workers employed since 1960 and all names, with dates of birth, submitted to the State Cancer Registry. The names are matched against all cancer registrations going back to the commencement date of the registry, and 120 are identified with cancer, of whom 5 were laryngeal cancers. Applying the Cancer Registry data incidence rates for the whole population to the group of workers the expected number of cases in this population is calculated as 1.8.

The Standardised Incidence Ratio (SIR) is therefore $5/1.8 = 2.8$, that is the ratio is elevated.

In some situations it may be possible to identify all the cancers but sufficient information to allow calculation of an SIR may be lacking. In such cases a proportional incidence ratio can be measured.¹⁵ This involves calculating the proportion of cases of the cancer of interest to all cancers in this workforce, and comparing it with the proportion in the general population.

Establish whether the excess is work related.

Although we cannot prove the association of an excess with work, we can investigate possibilities. A useful method is an internal case-control study.

The simplest study would be to match each case of the cancer of interest with a number of controls, that is employees or ex-employees without that cancer (up to five controls per case), and to compare the duration of employment in cases and controls. A work-related cause would be suggested if cases overall had had longer employment periods than controls.

It is important to examine the timing of the cancer diagnosis in relation to employment. Cancers occurring within five years of hire are unlikely to be related to any exposure at that workplace. The data should be examined to determine whether the cancer rate varies according to the number of years since hire.

Assess obvious exposure control.

Perhaps the most important aspect of investigating a cluster is obvious exposure control. Possible exposure in the workplace should be assessed in an attempt to explain the cluster. Look for known causes of cancer in the workplace.

If exposures to a known carcinogen are found they should be promptly controlled (as described in Chapter 2), even if they do not seem likely to have caused the illnesses in the cluster. Do not underestimate the industrial relations value of a thorough assessment of the workplace in the context of concern over a perceived cluster.

Investigate for previously unknown causes.

Even if there is no known carcinogen present in the workplace, investigations should be made for a previously unknown cause. If there is a suspected cause, such as a particular chemical in use or a particular process, a case-control study could be undertaken, with comparison of cases and controls according to whether or not they had been exposed to the agent or process.

Document the investigation.

At this stage we may not be able to go further in this workplace. All the information found so far should be explained in detail to the employees. The cluster then should be written up, perhaps as a letter to the editor of an Occupational Health and Safety journal as a reference for people who observe similar clusters in the future. Beyond that, further investigation can only be on a completely different study population.

Conduct a formal epidemiological study.

If the investigation suggests a possible carcinogenic exposure that has not been previously recognised, further epidemiological investigation would involve a separate population. Although a more formal study of the same population might find more cases and arrive at a more precise risk estimate, the statistical and interpretation difficulties remain. Indeed, an epidemiological study may be invalid if it includes any of the cancer cases identified in the original cluster. The only way to determine if a particular new exposure causes a particular cancer is to test this hypothesis in a new population. A formal epidemiological study will require additional resources and expertise which will often mean liaison with epidemiologists in a university department or public health unit. A decision on undertaking further epidemiological studies will depend on several factors: the magnitude of the original cancer excess, the findings of the internal case-control study, the plausibility of the excess being occupation-related, as well as extrinsic factors such as the degree of employer and union support. The type of study undertaken will depend on the condition and the availability of data. Cohort studies¹⁶ and case control studies¹⁷ have each been used to investigate clusters.

What if the "cluster" consists of more than one type of cancer?

Although we may recognise the distinction between different sites and types of cancer are different, the community rarely does so and lumps all cancer together. Thus in practice alleged clusters often include a variety of different cancers. It is then important to explain that if the cases include more than one type of cancer, it is doubtful that they are attributable to a single cause. However, some carcinogens, such as tobacco smoke, asbestos and arsenic are known to cause cancer of different types and at different sites, so that it is possible that more than one cancer type will require investigation. This will be a matter of judgement, and it is possibly better to be inclusive initially. Attempt to confirm the diagnosis of all cancers in the alleged cluster, and then to make a decision on which, if any, require investigation.

One particular concern is whether different species of leukaemia can be included in the same cluster. Some exposures have been associated with particular benzene types, for example benzene with acute myeloid leukaemia. Some researchers nevertheless believe that the effect of benzene is not specific and that it can cause any type of leukaemia.^{18,19} While this question is not settled, most haematologists consider the leukaemias to be different diseases. If a cluster of leukaemia cases occurs, investigate it regardless of differences in leukaemia type. However, the significance is much greater if they are all the same type.

If a decision is made to investigate multiple types of cancer or all cancers combined, the total number of cancers that have occurred in the workforce can be compared to the number expected based on the general population (obtained from the State Cancer Registry or the AIHW). Indirect age standardisation can be used to compute an SIR.

Outcome of cluster investigations

The fact that many cluster investigations do not lead to new associations between exposure and disease should not daunt us. There are other benefits to a cluster investigation. People who are concerned about a possible threat to their health deserve to have it addressed. The investigation may provide an impetus for assessing and improving workplace conditions, facilitate better rapport between management and workforce, and help resolve concern by both parties.

Conclusion

Clusters of cases of disease do occur in workplaces and may generate considerable concern. Rather than dismissing them, occupational physicians should be actively involved in the management of workplace clusters. Systematic investigation provides an important way of dealing with the concern surrounding a cluster, provides a focus for the improvement of workplace conditions and just may lead to the recognition of new hazards.

APPENDIX 1

How the IARC Classifies Evidence of Carcinogenicity

The orderly evaluation of available data is exemplified by procedures which the International Agency for Research on Cancer (IARC - an arm of the World Health Organization) have developed. The agency publishes a series entitled 'IARC Monographs on the Evaluation of Carcinogenic Risks to Humans' and the preamble of each volume describes how carcinogenicity data are organised and evaluated.

Evidence of carcinogenic activity is primarily established on the basis of studies on relevant human populations or groups (epidemiological data) or chronic toxicological testing using animals (experimental data). In addition, a range of other relevant evidence is considered, such as the reactivity of the chemical in validated *in vitro* tests for mutagenicity, DNA damage and ability to cause malignant transformation, and the distribution, metabolism and excretion of the chemical following human or animal exposure.

A conclusion in relation to epidemiological evidence is most conveniently expressed by reference to IARC terminology (shown in italics) as follows:

Sufficient or definitive evidence of carcinogenicity is indicative that a causal relationship is established between exposure to the chemical in question and development of cancer. *Limited* or equivocal evidence of carcinogenicity is indicative of evidence consistent with causation, but chance, bias or confounding as contributing to the result recorded cannot be excluded with reasonable confidence. *Inadequate* evidence refers to evidence which falls short of demonstrating associations already described.

Definitive evidence that a chemical may cause cancer in humans must arise as a consequence of epidemiological investigations. Nonetheless, an indication that a specific substance poses a carcinogenic hazard may be obtained from experimental studies using animals, which are almost invariably rodents.

Individual chemicals may be subject to one or more tests by chronic toxicity in experimental animals. Such findings may provide clear or *sufficient* evidence of carcinogenicity which is indicated by an increased incidence of tumours (relative to controls) consequent upon administration of the agent in question, particularly if more than one such study has been reported and/or the yield of tumours is dose-related and/or tumours occur in more than one species and/or the tumours produced are of a type that are particularly rare in the species used for test purposes. The IARC has adopted the principle that a chemical exhibiting *sufficient* evidence of carcinogenicity in experimental animals should be regarded as if it presents a carcinogenic hazard to humans.

It is critical that certain standards must be met in testing chemicals for carcinogenic activity using experimental animals. Minimal standards include proper specification of the species and strain of animals employed, the source and composition of their diet, the source, purity and mode of administration of the test compound, the allocation and appropriate treatment of controls, procedures for pathological assessment of organs and tissue from control and test animals and adequate reporting and statistical analysis of any occurrence of tumours or other pathological findings.

Evidence suggestive of carcinogenicity in experimental animals, but whose interpretation is complicated by shortcomings in the relevant experimental design (including the availability of only one study) or the growth of certain adenomas in mice, may be classified as equivocal or *limited*. Experimental findings which fall short of those required to indicate *limited* evidence may be classified as *inadequate* evidence of carcinogenicity in experimental animals.

Classification

When available epidemiological and experimental evidence has been evaluated (as *sufficient*, *limited*, etc) classification of carcinogenicity is made in accordance with IARC criteria. Chemicals (or other exposures) shown on available evidence to cause cancer in humans are categorised "Group 1 (causes cancer in humans) Carcinogens". This category includes agents immediately recognised as carcinogens such as cigarette smoke, radon daughters and asbestos. Implicit in the discussion above is that Group 1 carcinogens exhibit *sufficient* epidemiological evidence of carcinogenicity; evidence in experimental animals for most of these agents is also *sufficient*, although *limited* evidence in experimental animals may be recorded for Group 1 Carcinogens.

Chemicals categorised “Group 2A (probably causes cancer in humans) Carcinogens” are typically substances for which there is *limited* epidemiological evidence, and *sufficient* experimental evidence. One consideration for many industrial chemicals is that although increased risk of cancer may be demonstrated in the relevant occupationally exposed workforce, this population may be exposed to multiple agents and attributing cancer causation to one chemical in particular is difficult. Hence *limited* epidemiological evidence. Chemicals categorised Group 2A include acrylamide and trichloroethylene.

Chemicals categorised Group 2B (possibly causes cancer in humans) Carcinogens are typically substances for which scant or no epidemiological data (*inadequate* evidence) are available, although carcinogenicity in experimental animals may be clearly established. The consideration that such agents are deemed to present some carcinogenic hazard to humans is implicit in the category Group 2B Carcinogens. Examples include DDT, propylene oxide and vinyl acetate.

Chemicals unable to be categorised in the terms just summarised are allocated to either Group 3 (not classifiable as to carcinogenicity for humans) or Group 4 (probably not carcinogenic to humans).

The classification system is summarised in Table A1.

Table A1. IARC classification (default) of agents on the basis of the strength of evidence of carcinogenicity to humans and to experimental animals

	Human data	Sufficient evidence	Limited evidence	Inadequate or lack of data
Animal data	Sufficient evidence	1	2A	2B
	Limited evidence	1	2B	3
	Inadequate or lack of data	1	2B	3

In a small number of cases the overall evaluations have been varied (in either direction) on the basis of mechanistic data, that is, information on the mechanism of development of cancer. For example, a chemical might be classified as Category 1 despite insufficient epidemiological evidence, on the basis of evidence of genotoxic carcinogenicity. Conversely, a chemical could be classified as Category 2B despite sufficient experimental evidence, if the mechanism is assessed as not occurring in humans. No fixed rules are established for this process and, where evaluations are altered in the light of mechanistic data, this is specified in the evaluation.

As well as evaluating individual chemicals, an evaluation may be made of the carcinogenic hazard posed by a particular occupation or work environment. Such data are often complementary to evaluation of the carcinogenicity of specific substances. Thus the carcinogenic hazard posed by work as a painter or insecticide applicator may be related to (but can be distinguished from) the carcinogenicity of particular paint solvents or insecticides respectively. The criteria for evaluation of epidemiological data (*sufficient, limited, etc.*) are the same as those outlined above in relation to single substances. With very rare exceptions, experimental data are not immediately relevant to evaluation of the carcinogenic hazard associated with particular work environments.

The schedule of substances categorised in Groups 1, 2A and 2B is set out on the IARC website at www.iarc.fr.

In the absence of an IARC evaluation, ancillary information, of the type just summarised, may be recorded in the context of an evaluation of carcinogenicity.

In the light of all available data, specifically including epidemiological and experimental evidence of cancer causation, a final evaluation of the carcinogenic hazard posed by a specific chemical may be made. Again, IARC procedures are indicative of principles commonly adopted in this regard. The following summation of evidence and presentation of examples is intended for illustrative purposes. Certain of the examples given, in terms of the relationship of strength of evidence to final categorisation, are not the only scenarios which give rise to the category illustrated. In all cases, referral to relevant IARC documentation is appropriate for comprehensive and definitive information.

IARC evaluations may be perceived as being primarily concerned with meeting the need for appropriate preventive action in relation to carcinogens; such evaluations are not concerned primarily with attributing individual instances of cancer. A principal consideration in this regard is that the evaluation system provides no specific reference to “target” organ. That is, a chemical is usually categorised as presenting a carcinogenic hazard without any immediate reference to a particular anatomical site or tumour type.

However, in some instances IARC working groups have specified a target organ in relation to sufficient or other levels of evidence, as in the following examples:

- There is sufficient evidence in humans that tobacco smoke causes cancer of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, oesophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia).
- There is sufficient evidence in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and nonmelanocytic skin cancer.
- There is sufficient evidence for the carcinogenicity of Epstein-Barr virus in the causation of Burkitt lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppression-related lymphoma, Hodgkin disease and nasopharyngeal carcinoma.
- There is compelling but as yet limited evidence for a role of Kaposi sarcoma herpesvirus in the causation of Kaposi sarcoma.
- There is limited evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukaemia.
- There is inadequate evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to all other cancers.
- There is inadequate evidence in humans for the carcinogenicity of implanted prostheses made of silicone for neoplasms other than female breast carcinoma.
- There is evidence suggesting lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast and endometrium.

As yet, the IARC Preamble does not provide for such statements. The statements, nonetheless, provide insight, and reference to “target” organs in this context may become standard practice.

Virtually all known chemical carcinogens cause tumours of one type/one site or cause tumours at a limited number of sites and of limited type. Accordingly, the outcome of any assessment of carcinogenicity must include reference to the strength of evidence (as already described) and an indication of the tumour type(s) caused by the agent in question. The latter information is generally implicit in the relevant epidemiological data. If only experimental data are available, the site of possible tumorigenesis may be subject to speculation on the basis of the behaviour of chemically related carcinogens and/or other biological data particularly including criteria determining absorption, metabolism and excretion in experimental animals and, where possible, in humans.

On the basis of data summarised in this section, an evaluation of the carcinogenicity of particular substance(s) and/or work in a particular context may be made. Confidence in any such evaluation(s) is greatly increased if appropriate reference can be made to authoritative sources such as IARC. However, an IARC determination should not necessarily be regarded as the ultimate authority on whether an agent is carcinogenic. IARC classifications are made on the basis of scientific evidence available at the time. Quite often there is only limited information. Moreover not all the information may come to the attention of the evaluating group: a particular concern is publication bias, which leads to significant studies remaining unpublished. This can particularly apply to negative studies, where the researcher may feel that the absence of any demonstrated association between an exposure and cancer is not of sufficient interest to submit for publication. Alternatively, editors may believe that such “negative studies” may be of no interest to their readership. Negative studies are particularly prone to rejection because they lack statistical power; that is, the study population may be too small to ensure that a statistically significant effect has not been detected (Type II statistical error.) Such criticisms cannot be made of studies of comparable size where the findings are “positive”.

APPENDIX 2.

Identification of Chemicals as Carcinogens

Sources of information

The following sources provide information that helps determine whether a substance is carcinogenic:

- Schedule 2 of the NOHSC National Model Regulations for the Control of Scheduled Carcinogenic Substances. [NOHSC: 1011 (1995)]. www.nohsc.gov.au/publications/
- Carcinogenic category listed against a chemical in the NOHSC Exposure Standards for Atmospheric Contaminants in the Occupational Environment. [NOHSC: 3008 (1995)] www.nohsc.gov.au/databases/exp/toc/expsearch.asp
- NOHSC Approved Criteria for Classifying Hazardous Substances. Appendix 1, Carcinogenic effect. [NOHSC: 1008 (1999)] www.nohsc.gov.au/publications/fulltext/standards/
- International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans. www.iarc.fr
- American Conference of Governmental Industrial Hygienists (ACGIH) list: Identification and classification of carcinogens.
- National Institute of Environmental Health Sciences (US): ongoing program of carcinogen evaluation and classification. ntp-server.niehs.nih.gov/NewHomeRoc/AboutRoC.html
- Labels and material safety data sheets (MSDS).

Appendix 2a. NOHSC Schedule 1 and Schedule 2 Carcinogens

Schedule 1: Prohibited Carcinogenic Substances

Substance name [Chemical Abstract Number]

2-Acetylaminofluorene [53-96-3]

Aflatoxins

4-Aminodiphenyl [92-67-1]

Amosite [12172-73-5] (brown asbestos)

- except for removal and disposal purposes and situations where amosite occurs naturally and is not used for any new application.

Benzidine [92-87-5] and its salts (including benzidine dihydrochloride [531-85-1])

bis(Chloromethyl) ether [542-88-1]

Chloromethyl methyl ether [107-30-2] (technical grade which contains bis(chloromethyl) ether)

Chrysotile [12001-29-5] (white asbestos)

Crocidolite [12001-28-4] (blue asbestos)

- except for removal and disposal purposes and situations where crocidolite occurs naturally and is not used for any new application.

4-Dimethylaminoazobenzene [60-11-7]

2-Naphthylamine [91-59-8] and its salts

4-Nitrodiphenyl [92-93-3].

Schedule 2: Notifiable Carcinogenic Substances

Substance Name [Chemical Abstract Number]

Acrylonitrile [107-13-1]

Benzene [71-43-2]

- when used as a feedstock containing more than 50% of benzene by volume

Cyclophosphamide [50-18-0] (cytotoxic drug)

- when used in preparation for therapeutic use in hospitals and oncological treatment facilities, and in manufacturing operations

3,3'-Dichlorobenzidine [91-94-1] and its salts (including 3,3'-Dichlorobenzidine dihydrochloride [612-83-9])

Diethyl sulfate [64-67-5]

Dimethyl sulfate [77-78-1]

Ethylene dibromide [106-93-4]

- when used as a fumigant

4,4'-Methylene bis(2-chloroaniline) [101-14-4] - MOCA

2-Propiolactone [57-57-8]

o-Toluidine [95-53-4] and o-Toluidine hydrochloride [636-21-5]

Vinyl chloride monomer [75-01-4]

Appendix 2b. Category A1 and A2 Carcinogens in New Zealand

Category A1: Confirmed Human Carcinogens

4-Aminodiphenyl
Benzidine
 β -naphthylamine
4-Nitrodiphenyl
Arsenic and soluble compounds
Asbestos
Benzene
Beryllium and compounds
Bis(Chloromethyl) ether
Chromite ore processing
Chromium (VI) compounds (certain water insoluble)
Coal tar pitch volatiles as benzene solubles
Nickel sulphide roasting, fume and dust
Vinyl chloride
Zinc chromates

Category A2: Suspected Human Carcinogens

1,3-Butadiene
Antimony trioxide
Benzo(a)pyrene
Benzo(b)fluoranthrene
Cadmium and compounds
Calcium chromate
Carbon tetrachloride
Chloromethyl ether
Chrysene
Diazomethane
1,4-dichloro-2-butene
Dimethyl carbamoyl chloride
Ethylene oxide
Formaldehyde
Lead chromate
4,4-methylene bis(2-chloroaniline)
4,4-methylene dianiline
n-phenyl- β -naphthylamine
2-nitropropane
Strontium chromate
Sulphuric acid
Triethanolamine
Vinyl bromide
Vinyl fluoride

APPENDIX 3.

Occupational Health Related Professional Bodies in Australia and New Zealand

Toxicology

Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
Secretariat Office: 145 Macquarie Street, Sydney NSW 2000 Australia.
Phone: +61 2 9256 5456. Fax: +61 2 9252 0294. Email: rguss@mail.usyd.edu.au;
Webpage: accept.facbacs.uq.edu.au/ASCEPT.html

Mutagenesis and Experimental Pathology Society of Australasia
Hon. Secretary, Jack Dempsey
PO Box 100, Woden ACT 2606 Australia
Phone: +61 2 6270 4357 (w); Fax: +61 2 6270 4353; Email: secretary@mepso.org

Occupational Medicine

The Australasian Faculty of Occupational Medicine
145 Macquarie Street, Sydney, 2000.
Website: www.racp.edu.au/afom/
For New Zealand:
c/o Surgeon Commander Alison Drewry
RNZ Naval Hospital, Devonport New Zealand

Australian and New Zealand Society of Occupational Medicine
PO Box 304, Collins Street West Melbourne Victoria 8007
For New Zealand
c/o Dr C Walls
Occupational Medicine Specialists Ltd
Private Bag 28911, Remuera Auckland New Zealand

Occupational Hygiene

Australian Institute of Occupational Hygienists
82 Carrick Drive, Tullamarine Victoria 3043
PO Box 1205, Tullamarine Victoria 3043
Phone: +61 3 9335 2577; Fax: +61 3 9335 3454; Email: aiohcc@ozemail.com.au

New Zealand Occupational Hygiene Society Inc
PO Box 11-303, Ellerslie Auckland New Zealand

REFERENCES

Chapter 1: Introduction

1. Case RAM, Hosker ME, McDonald DB, Pearson JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. *Br J Ind Med*, 1954; 11: 75-104.
2. MacMahon B. The epidemiological evidence on the carcinogenicity of beryllium in humans. *JOM*, 1994; 36: 15-24.
3. Kotin P. re: The epidemiological evidence on the carcinogenicity of beryllium, by MacMahon. Editorial, *JOM*, 1994; 36: 25-26.
4. Vainio H, Kleihues P. IARC Working Group on Carcinogenicity of Beryllium (letter). *JOM*, 1994; 36: 1068-1069.
5. Kotin P. IARC Working Group on Carcinogenicity of Beryllium (letter in reply to Vainio). *JOM*, 1994; 36: 1069-1070.
6. British Industry Scientific Advisory Committee. Is beryllium carcinogenic to humans? *JOEM*, 1997; 39: 205-208.
7. Vainio H, Rice JM. Beryllium revisited. *JOEM*, 1997; 39: 203-204.
8. Kazantzis G, Blanks RG, Sullivan KR. Is cadmium a human carcinogen? In: *Cadmium in the human environment: Toxicity and carcinogenicity*, pp 435-446. IARC Scientific Publications No 118, Lyon France. 1992.
9. Sorahan T, Lancashire R. Lung cancer findings from the NIOSH study of United States cadmium recovery workers: a cautionary note. *Occup Environ Med*, 1994; 51: 139-140.
10. Sorahan T, Lister A, Gilthorpe MS, Harrington JM. Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. *Occup Environ Med*, 1995; 52: 804-812.
11. Soutar CA, Robertson A, Miller BG et al. Epidemiological evidence of silica: factors in scientific judgement. *Ann Occup Hyg*, 2000; 44: 3-14
12. Hessel PA, Gamble JF, Gee JBL, Gibbs G, Green FHY, Morgan WKC, Mossman BT. Silica, silicosis, and lung cancer: a response to a recent working group report. *J Occup Env Med*, 2000; 42: 704-720.
13. McDonald JC. Silica and lung cancer: hazard or risk (editorial). *Ann Occup Hyg*, 2000; 44: 1-2.
14. Checkoway H, Franzblau A. Is silicosis required for silica-associated lung cancer? *Am J Ind Med*, 2000; 37: 252-259
15. Wong O. The epidemiology of silica, silicosis and lung cancer: some recent findings and future challenges. *Ann Epidemiol*, 2002; 12: 288-294.
16. Department of Health and Human Services (US). Health effects of occupational exposure to respirable crystalline silica. NIOSH Hazard Review. DHHS (NIOSH) Publication No. 2002-129, Cincinnati. 2002.
17. Burton A. Is industry influencing IARC to downgrade carcinogens? *Lancet Oncology*, 2003; 4: 4.
18. Baker ES, Connor TH. Monitoring occupational exposure to cancer chemotherapy drugs. *Am J Health Syst Pharm*, 1996; 53: 2713-2723.
19. Hessel H, Radon K, Pethran A, et al. The genotoxic risk of hospital, pharmacy and medical personnel occupationally exposed to cytostatic drugs - evaluation by the micronucleus assay. *Mutation Res*, 2001; 497: 101-109.

20. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States. *JNCI*, 1981; 66: 1193-1308.
21. Winder C, Lewis S. A thousand a year: an estimate of deaths in Australia from cancer associated with occupation. *Cancer Forum*, 1991; 15: 70-76.
22. Kerr C, Morrell S, Taylor R et al. Best estimate of the magnitude of health effects of occupational exposure to chemicals: Stage One. Volume 1. Final unpublished report to NOHSC.
23. Leigh J, Davidson P, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945-2000. *Am J Ind Med*, 2002; 41: 188-201.
24. Gun RT, Langley AJ, Dundas SJ, McCaul K. The human cost of work. Analysis of 10 leading causes of occupational morbidity and mortality in South Australia. Second edition. SA Health Commission, Adelaide. 1996.
25. Staples M, Marks R, Giles G. Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985-1995: are primary prevention programs starting to have an effect? *Int J Cancer*, 1998; 78: 144-148.
26. Armstrong BK, Kricger A, English DR. Aetiology and pathogenesis of skin cancer: sun exposure and skin cancer. *Australasian J Dermatology*, 1997; 38 (supp): S1-S6
27. Ministry of Health (NZ). Cancer Control Strategy, September 2002.
28. Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. *Scan J Work Environ Health*, 2001; 27: 161-213.
29. Peto J. Cancer epidemiology in the last century and the next decade. *Nature*, 2001; 411: 390-395.

Chapter 2: Primary prevention of occupational cancer

1. National Occupational Health and Safety Commission. National Model Regulations for the Control of Scheduled Carcinogenic Substances. Schedule 1. NOHSC:1011(1995)]. NOHSC, Canberra. 1995. www.nohsc.gov.au/publications/
2. National Occupational Health and Safety Commission. Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(1999)] Appendix 1, Carcinogenic effect. NOHSC, Canberra. 1999. www.nohsc.gov.au/publications/fulltext/standards/
3. Peto R, Darby S, Deo H et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ*, 2000; 321: 323-329.
4. Vainio H. Biomarkers in the identification of risks, especially with regard to susceptible persons and subgroups. *Scand J Work Environ Health*, 1999; 25:1-3.
5. Bonn D. How DNA-repair pathways may affect cancer risk *The Lancet* 1998; 351: 42.
6. Vogelstein B, Kinzler KW. *The genetic basis of human cancer*. McGraw-Hill, New York. 1998.
7. Australian Law Reform Commission. Protection of genetic information. ALRC Discussion Paper 66, August 2002.
8. Green J, Banks E, Berrington A, et al. N-acetyltransferase 2 and bladder cancer: an overview and consideration of the evidence for gene-environment interaction. *Br J Cancer*, 2000; 83: 412-417.
9. Bennett WP, Alavanja MC, Blomeke B et al. Environmental tobacco smoke, genetic susceptibility, and risk of cancer in never-smoking women. *J Nat Cancer Inst*, 1999; 91: 2009-2014.
10. South Australian Cancer Registry. Epidemiology of cancer in South Australia. Incidence, mortality and survival 1977 to 1999. Cancer series number 22. SA Cancer Registry, Adelaide. 2000.
11. Potter JD. Cancer prevention: epidemiology and experiment. *Cancer Lett*, 1997; 114: 7-9.
12. Omenn GS. Chemoprevention of lung cancer: the rise and demise of beta-carotene. *Ann Rev Public Health* 1998; 19: 73-99.
13. Patterson RE, White E, Kristal AR, et al. Vitamin supplements and cancer risk: the epidemiologic evidence. *Cancer Causes Control*, 1997; 8: 786-802.
14. Vainio H. Modification of lung cancer prevention by gene-nutrient interaction. *Scand J Work Environ Health*, 2000; 26: 459-460.
15. deKlerk NH, Musk AW, Ambrosini GL et al. Vitamin A and cancer prevention II: comparison of the effects of retinol and beta-carotene. *Int J Cancer*, 1998; 75: 362-367.

Chapter 3: Surveillance of workers exposed to carcinogens

1. National Occupational Health and Safety Commission. Exposure standards for atmospheric contaminants in the occupational environment [NOHSC:1003(1991)]. Australian Government Publishing Service, Canberra. 1991.
2. Hatjian BA, Edwards JW, Harrison J et al. Risk assessment of occupational exposure to bitumen fumes in the road paving and roofing industries. *JOHSANZ*, 1997; 13: 65-78.
3. Mielzynska D, Braszczyńska Z, Siwińska E et al. Exposure of coke-oven workers to polycyclic aromatic hydrocarbons based on biological monitoring results. *AIHA Journal*, 1997; 58: 661-666.
4. Kang HK, Watanabe KK, Breen J et al. Dioxins and dibenzofurans in adipose tissue of Vietnam veterans and controls. *AJPH*, 1991; 81: 344-349.
5. American Conference of Governmental Industrial Hygienists. 2003 TLVs® and BEIs® Book. ACGIH®, Cincinnati, Ohio. 2003.
6. Health and Safety Executive. Occupational Exposure Limits EH40/2002. HSE Books, Sudbury, UK. 2002.
7. McDonagh AJ, Gawkrödger DJ, Walker AE. Chloracne - study of an outbreak with new clinical observations. *Clin Exp Dermatol*, 1993 Nov; 18(6): 523-525.
8. Jansing PJ, Korff R. Blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin and gamma-globulins in a follow-up investigation of employees with chloracne. *J Dermatol Sci*, 1994; 8: 91-95.
9. Bianchi C, Brollo A, Ramani L, Zuch C. Pleural plaques as risk indicators for malignant pleural mesothelioma: a necropsy-based study. *Am J Ind Med*, 1997; 32: 445-449.
10. Singh NP, McCoy MT, Tice RR, Schneider EL. A simple technique for quantitation of low levels of DNA damage in individual cells. *Exp Cell Res*, 1988; 175: 184-191.
11. Collins AR, Dobson VL, Dusinska M, Kennedy G, Stetina R. The comet assay: what can it really tell us? *Mutat Res*, 1997; 375: 183-193.
12. Waksvik H, Klepp O, Brogger A. Chromosome analyses of nurses handling cytostatic agents. *Cancer Treatment Reports*, 1981; 65: 607-610.
13. Bonassi S, Hagmar L, Stromberg U et al (European Study Group on Cytogenetic Biomarkers and Health). Chromosomal aberrations in lymphocytes predict human cancer independently of exposure to carcinogens. *Cancer Res*, 2000; 60: 1619-1625.13.
14. Hulka BS. Screening for cancer: lessons learned. *JOM*, 1986; 28: 687-691
15. Strauss G, Gleason R, Sugarbaker D. Chest x-ray screening improves outcome in lung cancer: a reappraisal of randomized trials on lung cancer screening. *Chest*, 1995: 107 supp: 270-279.
16. Strauss G, Gleason R, Sugarbaker D. Screening for lung cancer: another look: a different view. *Chest*, 1997; 111: 754-768.
17. Manser RL, Irving LB, Stone C et al. Screening for lung cancer. *Cochrane Database of Systematic Reviews*. 2001.
18. Henschke CI, Yankelevitz DF, Libby DM et al. Early lung cancer action project: annual screening using single-slice helical CT. *Ann NY Acad Sci* 2001, 952: 124-134.

Chapter 4: Evaluating whether an occupational exposure has caused cancer in an individual case

1. Kang HK, Watanabe KK, Breen J et al. Dioxins and dibenzofurans in adipose tissue of Vietnam veterans and controls. *Am J Public Health*, 1991; 81: 344-349.
2. National Center for Environmental Health (NCEH) Centers for Disease Control and Prevention (CDC). Exposure of Air Force veterans to Agent Orange in Vietnam. NCEH fact sheet. www.cdc.gov/nceh/dls/factsheets/agent/orange.htm
3. Davison AG, Fayers PM, Taylor AJ et al. Cadmium fume inhalation and emphysema. *Lancet*, 1988; 1(8587): 663-667.
4. Ferreccio C, Gonzalez C, Milosavljevic V, Marshall G, Sancha AM, Smith AH. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology*, 2000; 11: 673-679.
5. Byrd DM, Roegner ML, Griffiths JC et al. Carcinogenic risks of inorganic arsenic in perspective. *Int Arch Occup Environ Health*, 1996; 68: 484-494.
6. Hayes RB, Yin S-N, Dosemeci M et al. Benzene and the dose-related incidence of hematologic neoplasms in China. *JNCI*, 1997; 89: 1065-1071.
7. Yin S-N, Li Q, Liu Y et al. Occupational exposure to benzene in China. *Br J Ind Med*, 1987; 44: 192-195.
8. Yin S-N, Li G-L, Tain F-D et al. A retrospective cohort study of leukemia and other cancers in benzene workers. *Environ Health Perspect*, 1989; 82: 207-213.
9. Vigliani EC. Leukemia associated with benzene exposure. *Ann N Y Acad Sci*, 1976: 143-151.
10. Monash University and Deakin University Report. Lympho-haematopoietic cancer and exposure to benzene in the Australian petroleum industry. Technical report and appendices. www.inchem.org/documents/cicads/cicads/cicad24.htm
11. Armstrong B, Theriault G. Compensating lung cancer patients occupationally exposed to coal tar pitches. *Occ Environ Med* 1996; 53: 160-167.
12. Wakeford R, Antell BA, Leigh WJ. A review of probability of causation and its use in a compensation scheme for nuclear industry workers in the United Kingdom. *Health Physics*, 1998; 74: 1-9.
13. Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. *Lancet* 2001; 357: 709-712.

Chapter 5: Asbestos-related cancers

1. Weiss W The lack of causality between asbestos and colorectal cancer. *J Occ Env Med*, 1995; 37: 1364-1373.
2. Berry G, Newhouse M, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933-80. *OEM*, 2000; 57: 782-785.
3. Browne K, Gee JB. Asbestos exposure and laryngeal cancer. *Ann Occup Hyg*, 2000; 44: 239-250.
4. Davis JM. Other diseases in animals. *Ann Occ Hyg*, 1994; 38: 581-587, 420.
5. Pepelko WE. Effect of exposure route on potency of carcinogens. *Regul Toxicol Pharmacol*, 1991; 13: 3-17.
6. Lemen R, Meinhardt T, Becking GC et al. Report on cancer risks associated with the ingestion of asbestos. *Env Health Perspectives*, 1987; 72: 253-265.
7. Sluis-Cremer GK, Bezuidenhout BN. Relation between asbestosis and bronchial cancer in amphibole asbestos miners. *Br J Ind Med*, 1989; 46: 537-540.
8. Hughes JM, Weill H. Asbestosis as a precursor of asbestos related lung cancer. *Br J Ind Med*, 1991; 48: 229-233.
9. Kipen HM, Liolis R, Suzuki Y, Valciukas JA, Selikoff IJ. Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histological evaluation. *Br J Ind Med*, 1987; 44: 96-100.
10. Churg A, Green FHY. Occupational lung disease. In: WM Thurlbeck, A Churg (Eds) *Pathology of the lung* (2nd edition). Thieme, New York. 1995.
11. Weiss W. Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos. *Chest*, 1999; 115: 536-549.
12. Henderson DW, deKlerk NH, Hammar SP et al. Asbestos and lung cancer; is it attributable to asbestosis or to asbestos fiber burden. In: B Corrin (Ed) *Pathology of lung tumors*. Churchill-Livingstone, New York. 1997.
13. Karjalainen A, Anttila S, Vanhala E, Vainio H. Asbestos exposure and the risk of lung cancer in a general urban population. *Scand J Work Environ Health*, 1994; 20:243-250.
14. Hillerdal G. Pleural plaques and risk for bronchial carcinoma and mesothelioma - a prospective study. *Chest*, 1994; 105: 145-150.
15. Jones RN, Hughes JM, Weill H. Asbestos exposure, asbestosis, and asbestos-related lung cancer. *Thorax*, 1996; 51 Suppl 2: S9-15.
16. Meldrum M. Review of fibre toxicology. HSE Books, Sudbury, UK. 1996.
17. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann NY Acad Sci*, 1979; 330: 91-116.
18. Doll R, Peto J. *Asbestos: effects on health of exposure to asbestos*. HMSO, London. 1985.
19. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*, 2000; 44: 565-601.
20. Liddell FDK. The interaction of asbestos and smoking in lung cancer. *Ann Occup Hyg*, 2001; 45: 341-356.
21. McDonald AD, McDonald JC. Malignant mesothelioma in North America. *Cancer*, 1980; 46: 1650-1656.
22. Ferguson DA, Berry G, Jelihovsky T et al. The Australian Mesothelioma Surveillance Program 1979-1985. *Med J Aust*. 1987; 147: 166-172.
23. Rogers AJ, Yeung P, Johnson A et al. Trends in occupational groups and industries associated with Australian mesothelioma cases 1979-1995. *Ann Occup Hyg*, 1997; 41 Suppl1: 123-128.
24. Harvard University Energy and Environment Policy Center. Summary of symposium on health aspects of exposure to asbestos in buildings. John Kennedy School of Government, Cambridge, MA. 1989.

25. McDonald JC. Health implications of environmental exposure to asbestos. *Environ Health Persp* 1985; 62: 319-328
26. Leigh J, Davidson P, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945-2000. *Am J Ind Med*, 2002; 41: 188-201.
27. Rogers AJ, Leigh J, Berry G et al. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma; a case-control study. *Cancer*, 1991; 67: 1912-1920.
28. Carbone M, Kratzke, RA, Testa, JR. The pathogenesis of mesothelioma. *Seminars in Oncology*, 2002; 29: 2-17.
29. Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. *Br J Cancer*, 1982; 45: 124-135.
30. Liddell D. Asbestos and cancer (letter). *Ann Occup Hyg*, 2001; 45: 327-338.
31. Rogers AJ, Leigh J, Berry G et al. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma: a case-control study. *Cancer*, 1991; 67: 1912-1920.

Chapter 6: Cancer clusters in the workplace

1. Westley-Wise VJ, Stewart BW, Kries I et al. Investigation of a cluster of leukaemia in the Illawarra region of New South Wales, 1989-1996. *Med J Aust*, 1999; 171: 178-183.
2. Last J M (ed). *A dictionary of epidemiology* (3rd edition). Oxford University Press, New York. 1995.
3. Rothman K. A sobering start to the cluster busters' conference. *Am J Epidemiol*, 1990; 132(1 Suppl): S6-13.
4. Caldwell GG. Twenty-two years of cancer cluster investigations at the Centers for Disease Control. *Am J Epidemiol*, 1990; 132: S43-47.
5. Devier JR, Brownson RC, Bagby JR, Carlson GM, Crellin JR. A public health response to cancer clusters in Missouri. *Am J Epidemiol*, 1990; 132: S23-31.
6. Maskarinec G. Investigating increased incidence of events in the islands: a Hawaii Department of Health perspective. *Statistics in Medicine*, 1996; 15: 699-705.
7. Cartwright RA. Cluster investigations: are they worth it? *Med J Aust*, 1999; 171: 172.
8. Sandman PM. Risk = hazard + outrage: a formula for effective risk communication [videorecording]. American Industrial Hygiene Association, Akron, Ohio. 1991.
9. Neutra RA. Counterpoint from a cluster buster. *Am J Epidemiol*, 1990; 132: 1-8.
10. Bender AP, Williams AN, Johnson, RA, Jagger HG. Appropriate public health responses to clusters: the art of being responsibly responsive. *Am J Epidemiol*, 1990; 132: S48-52.
11. Frumkin H, Kantrowitz W. Cancer clusters in the workplace: an approach to investigation. *J Occup Med*, 1987; 29: 949-952.
12. Fleming LE, Ducatman AM, Shalat SL. Disease clusters in occupational medicine: a protocol for their investigation in the workplace. *Am J Ind Med*, 1992; 22: 33-47.
13. Centers for Disease Control and Prevention. Guidelines for investigating clusters of health events. *MMWR*, 1990; 39: 1-16.
14. Creech JL, Johnson MN. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *J Occup Med*, 1974; 16: 150-151.
15. Checkoway H, Pearce NE, Crawford-Brown DJ. *Research methods in occupational epidemiology*. Oxford University Press, New York. 1989.
16. Brown AM, Christie D, Devey P, Nie VM, Hicks MN. A cluster of brain tumours in a New South Wales colliery: a problem in interpretation. *Aust J Public Health*, 1993; 17: 302-305.
17. Marshall EG, Melius JM, London MA, Nasca PC, Burnett WS. Investigation of a testicular cancer cluster using a case-control approach. *Int J Epidemiol*, 1990; 19: 269-273.
18. Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. *Am J Ind Med*, 1997; 31: 287-295.
19. Infante PF, White MC. Benzene: epidemiologic observations of leukemia by cell type and adverse health effects associated with low-level exposure. *Environ Health Perspect*, 1983; 52: 75-82.