THE UNIVERSITY OF WESTERN AUSTRALIA

A REVIEW OF THE AUSTRALIAN OCCUPATIONAL EXPOSURE STANDARD FOR CRYSTALLINE SILICA

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EXECUTIVE SUMMARY

Background

In May 1998, the Occupational and Respiratory Epidemiology Group at the Department of Public Health (University of Western Australia) was commissioned by the National Occupational Health and Safety Commission of Australia (NOHSC) to review the Australian occupational exposure standard for crystalline silica.

The conclusions of the review are based as transparently as possible on the available information. It is recognised that occupational health policy, including standard setting, is the outcome of political debate aimed at developing consensus about the ways in which occupational health is valued in society. It is recognised by the authors that this exposure standard therefore has only a basis in science.

Methods

As a means of directly addressing the basis for determining a reasonable exposure standard based on observed effect levels, the emphasis of this review is to examine the dose-response relationships for each of the silica-related diseases separately. In addition, this review describes the current (to the end of 2001) scientific literature on the biological effects of crystalline silica, including quartz and cristobalite forms. Coal has not been reviewed in this document because of its different physico-chemical characteristics and associated pathologies, and therefore requires separate assessment for its own exposure standard. The specific health effects of tridymite have not been reviewed because of the limited research on its effects and its negligible use in Australia.

Two new quantitative studies of West Australian gold miners were commissioned as part of this review in order to add to the body of dose-response data on the health effects from crystalline silica, and to utilise locally relevant data (de Klerk et al., 2002a, de Klerk et al., 2002b). In quantitatively summarising all of the suitable dose-response data, including the West Australian studies, recommendations are made for an Australian exposure standard which aims to prevent adverse health effects acquired through occupational exposures to crystalline silica.

Results

Diseases caused by or associated with inhalation of free crystalline silica include silicosis, pulmonary tuberculosis, bronchogenic carcinoma, industrial bronchitis with airflow limitation, and auto-immune diseases, including end-stage renal disease.

Epidemiological research has established crystalline silica as being fibrogenic to humans and this is supported by toxicology studies in laboratory animals. Significant dose-response relationships have been identified between crystalline silica exposure and silicosis, and deficit in lung function (forced expiratory volume in one second, or FEV_1). Based on the available evidence, it is also likely that the risk of auto-immune disease and tuberculosis is increased in workers who develop silicosis. It is currently not possible to determine if silicosis is a necessary precursor for these diseases.

The classification of crystalline silica as a human carcinogen is based upon substantial epidemiological evidence that is supported by strong toxicological evidence. The International Agency for Research on Cancer classified crystalline silica (quartz and cristobalite) as a human carcinogen in 1997 (IARC, 1997b), and crystalline silica was given a provisional A2 'Suspected human carcinogen' rating by the American Conference of Government Industrial Hygienists in 1998 (ACGIH, 2000).

We originally found a small but significant dose-response relationship between crystalline silica and lung cancer after combining results from several epidemiological studies. However, a more recent study funded by NIOSH and OSHA and carried out at IARC, was able to pool data from ten cohorts of workers, and produced similar but more reliable results (Steenland et al., 2001a).

There is evidence that the risk of lung cancer in silica exposed people resides mainly in those who have established silicosis, however the current evidence does not support with any certainty a determination of whether or not silicosis is a necessary precursor to silica-induced lung cancer. We have therefore treated silicosis and lung cancer as separate and distinct responses to silica exposure, for the purpose of this review.

Lung cancer is the least acceptable adverse health effect from exposure to crystalline silica, as it is very likely to be fatal. The dose-response relationship between crystalline silica and lung cancer is the most consistent quantitative relationship to be observed in the available epidemiological data on the health effects of crystalline silica exposure. We have therefore based the setting of an exposure standard for crystalline silica on the dose-response relationship between exposures to crystalline silica and lung cancer found by the international study of ten cohorts (Steenland et al., 2001a). We interpret the quantitative evidence as indicating that protection against lung cancer will also protect against of other silica-related diseases.

Conclusions

As there is no generally accepted 'acceptable' increased risk of mortality from lung cancer, we have followed the risk assessment guidelines set out by the UK Royal Society (Warner, 1983), where it is stated that an annual risk of 1 per 100,000 is considered low, such that 'very few would consider action necessary', and an annual risk of 1 per 10,000 person-years is considered moderate, such that 'few would commit their own resources to reduce risk', and therefore recommend an exposure standard that will ensure that the excess risk of lung cancer lies between these 2 values.

Our quantitative overview of the dose-response data indicates that by implementing an occupational exposure standard of 0.13 mg/m^3 of quartz or cristobalite, excess annual incidence of lung cancer will be kept below 1 per 10,000 after 40 years of exposure and is likely to be around 1 per 100,000 or less. It must be emphasised that this standard is based on current (2001) Australian protocols for dust sampling and measurement, so that this level would be equivalent to a NIOSH or ACGIH (US) standard of 0.067 mg/m^3 (see Appendices 4,5).

Given this recommended level for protection against lung cancer we are confident, based on the data from Western Australian gold miners, that this standard should, after a 40 year working lifetime, restrict the lifetime risk of silicosis to less than 1%. The standard should

also result in any excess deficit in FEV_1 being kept below a total of 200 mL, provided levels of other dusts are also controlled. It is unlikely that there would be any excess incidence of tuberculosis or auto-immune disease mortality. Other possible scenarios are also described in this document. We also strongly recommend that a separate standard for coal dust containing quartz be derived.

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1.0 OBJECTIVES AND OUTCOMES

This review of the crystalline silica exposure standard for Australia was proposed and directed by the National Occupational Health and Safety Commission (NOHSC) .

1.1 Project Objectives

a. review the Australian and international epidemiological studies providing data for estimating a dose response relationship between silica exposure, silicosis and lung cancer;
b. review the Australian and international studies of the toxicological relationship between silica exposure, silicosis and lung cancer;
c. review the Australian and international epidemiological and toxicological studies of the relationship between silica exposure and adverse human health conditions other than silicosis and lung cancer; and,
d. in response to these reviews, make transparent and reasoned recommendations for suitable exposure standards for crystalline silica in Australia providing supporting argument and documentation.

1.2 Project Outcomes

a. provide a current review of available studies (both toxicological and epidemiological) on the relationship between crystalline silica exposure and silicosis, lung cancer and other adverse human health conditions
b. make recommendations for suitable exposure standards for crystalline silica in Australia
c. provide argument and documentation to support the recommended exposure standard options.

1.3 Project Rationale

Silicosis has long been a major occupational disease worldwide, and lung cancer is the most common fatal cancer to occur among Australian males. Both of these diseases are associated with crystalline silica exposure, are therefore those most crucial to epidemiological research that may assist in understanding dose-response relationships, in order to estimate acceptable levels of exposure in the workplace.

There is evidence that the risk of lung cancer in silica-exposed people resides mainly in those who have established silicosis. This observation raises important and interesting issues concerning the biological mechanisms of carcinogenesis, along with practical issues relating to protection of people against silicosis in order to protect them against subsequent lung cancer development. However, examination of the silicosis-lung cancer association is not a defined objective of this review. Furthermore, studies demonstrating increased lung cancer risk in people with silicosis have been criticised because of possible confounding resulting from silicosis simply being another indicator of heavy exposure to silica. The majority of these studies are also limited by selection bias because their lung cancer cases have been selected solely from among compensated silicotics, whose disability is often also related to

smoking and other factors (McDonald, 1989). Existing studies have experienced difficulty in separating those with and without silicosis in the analysis. We have therefore not utilised studies of lung cancer in cohorts of silicotics.

This review is concerned only with exposures to crystalline silica, and the epidemiological and toxicological data concerning exposures to coal dust have not been reviewed for the reasons given below. Given the large number of workers (10%) potentially exposed to crystalline silica through coal mining in Australia (Nurminen et al., 1992), it is strongly recommended that the exposure standard for quartz-containing coal dust be reviewed separately.

a. *The physico-chemistry of coal is different to that of crystalline silica*

Coal "is a generic term for a heterogeneous, carbonaceous rock" valued for its carbon content (IARC, 1997a). Coal dust is a complex and variable mixture of coal, quartz and other minerals, and may contain up to 20% crystalline silica-quartz (Greskovich et al., 1992). However, coal dust is capable of inhibiting the fibrogenic effect of crystalline silica and therefore, possibly its carcinogenicity, due to protective impurities associated with coal dust modifying the reactivity of the crystalline silica surface (IARC, 1997a, Le Bouffant et al., 1982). The decreased carcinogenicity of coal dust versus crystalline silica has been shown in studies of lung cancer among coal miners. Coal miners in Lancashire, north-west England, had a prevalence of lung cancer at necropsy no greater than that of the general male population of the same area (Rooke et al., 1979). Mortality from lung cancer was less than that expected in a cohort of West Australian coal miners followed up for 14 years (Armstrong et al., 1979), and no relationship between duration of underground coal mining and lung cancer incidence was found in a hospital based case-control study of Dutch coal miners (Meijers et al., 1988).

b. *Pathologies associated with coal are distinguished from those associated with crystalline silica*

Coal worker's pneumoconiosis (CWP), mixed dust pneumoconiosis, or radiological findings of nodular pneumoconiosis, are associated with the inhalation of dust containing a mixture of minerals usually containing quartz. The radiographic appearances are of a simple multi-nodular pneumoconiosis which appear similar to silicosis on a plain chest radiograph however, silicosis is a pathologically different disease. The basic histological abnormality in silicosis is the silicotic nodule (see *4.2.4.1 Inflammation and Fibrosis*) (Gibbs, 1995). With CWP, the basic histological abnormality is the development of the characteristic coal macule with focal emphysema (Gibbs, 1995).

Studies of workers exposed to coal dust containing little crystalline silica have clearly related the risk of CWP to the total exposure of respirable coal dust, independent of the quartz content (Seaton et al., 1981, Tourmann et al., 1993). However, as the content of quartz in inhaled mixed dust increases (as often occurs when drilling occurs outside the coal seam and into hard rock), the radiological appearances approximate those of silicosis more, and typical silicosis may occur in workers in industries normally associated with mixed dust pneumoconiosis (Miller et al., 1998, Seaton et al., 1981).

Given this, and the large number of workers exposed to coal or mixed dust in Australia, we recommend that the exposure standard for quartz found in coal dust be reviewed separately.

c. *Separate exposure standards for coal dust and crystalline silica*

Owing to the differences in their potential for adverse health effects, silica and coal dust were examined in separate International Agency for Research on Cancer IARC Monographs for the Evaluation of the Carcinogenic Risk of Chemicals to Humans in 1997 (IARC, 1997a). In the Coal Dust Monograph it was concluded that there was *inadequate evidence* in humans for the carcinogenicity of coal dust, *inadequate evidence* in experimental animals for the carcinogenicity of coal dust, and that coal dust *cannot be classified as to its carcinogenicity to humans* (IARC, 1997a). Further highlighting their differences, separate Occupational Exposure Limits (OELs) have been set for quartz and for coal dust in the US by the Occupational Safety and Health Administration (OSHA) (OSHA,) and the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH, 1985) (refer *Table 1*), and a separate occupational exposure standard for respirable coal dust containing < 5% quartz (3 mg/m^3) has been enforced in Australia since 1990 (NOHSC, 1995).

The extrapolation of experimental animal studies to the human situation has been considered inappropriate, and therefore has not been undertaken in this review (IARC, 1997b). The available animal models on the health effects from crystalline silica exposure are currently not suited for improving estimates of human equivalent concentrations extrapolated from laboratory animal studies (IARC, 1997b). However, they add to the toxicological weight of evidence supporting the epidemiological findings in humans.

In reviewing the Australian exposure standard for crystalline silica, only those data considered relevant to developing an exposure standard for crystalline silica have been included; poorly designed, confounded studies, and those not presenting quantitative exposure estimates have been disregarded. Epidemiological research on the health effects of crystalline silica has been dominated by studies on mining industries but it has been estimated that 70% of workers at risk of exposure to crystalline silica in Australian workplaces are in the construction and quarrying industries (Nurminen et al., 1992). There remains a lack of exposure and follow up data from these industries.

By conducting reviews of appropriately conducted human studies presenting health effects according to quantitative exposure data, we have presented exposure-response summaries for each of the adverse health effects, where possible.

1.4 Advisory Committee

An Advisory Committee was established by NOHSC to oversee this review, comprising of representatives from the NOHSC Office (Epidemiology), Unions (extractive and construction industries), Academia (occupational health and safety, silica research/practice), State/Territory Occupational Hygienists and/or Physicians with silica experience, Industry (extractive and construction), and a NOHSC Office Convenor. We are unclear as to the

present status of this committee, as two of the three NOHSC representatives are no longer incumbent with NOHSC (as of July 2001).

The Advisory Committee has had the following roles in relation to the consultants:

a. provide advice to the consultants
b. facilitate consultation during the project with concerned groups
c. ensure adequate coverage of all relevant literature
d. ensure scientific rigour and transparency in decision making
e. review the report in preliminary and final draft formats

Statistical analyses performed for this review are by the consultants and will be submitted for publication in peer reviewed scientific journals at their discretion. Ownership of the Report will reside with NOHSC. NOHSC will retain the right to use any or all of the produced report as documentation to be provided to the public as part of a public comment phase to develop national exposure standards for crystalline silica.

1.5 Original Members of the Advisory Committee

Union Representatives

Mr Yossi Berger	Director, National OHS Unit, Australian Worker's Union
Mr Lindsay Fraser	Asst. National Secretary, Construction, Forestry, Mining and Energy Union (CFMEU)
Mr Ron Stothard	District Check Inspector, Northern Districts, CFMEU

Industry Representatives

Mr Patrick Gilroy	CEO, Mining and Resource Contractors Safety Training Association (MARCSTA)
Dr Maggie Goldie	Boral Industries
Mr John Winters	James Hardie Industries Ltd

Academic Representatives

Dr David Grantham	Senior Principal Advisor, Hygiene Division of Workplace Health and Safety, Dept of Employment, Training, and Industrial Relations, Queensland Gov't.
Dr Richie Gunn	Senior Lecturer in Environmental and Occupational Health, Department of Public Health, University of Adelaide
Dr Malcolm Sim	Assoc Professor, Dept of Epidemiology and Preventive Medicine, Monash University

NOHSC Office

Dr Jim Leigh	Research Unit Head, Prevention Strategies and Facilitation Branch, NOHSC
Dr Max McEwan	Senior Professional Officer, Hazardous Substances Unit, NOHSC

NOHSC Office Convenor

Mr Stephen Holland Manager, Hazardous Substances Unit, NOHSC

2.0 BACKGROUND

2.1 Occupational Exposure Standards

Occupational exposure standards are established to provide protection, by neither impairing the health of, nor causing undue discomfort, to nearly all workers who are exposed for twelve hours per day and five days per week for their working life.

NOHSC Guidance Notes (NOHSC, 1995) state:

" ...Exposure standards do not represent 'no effect' levels which guarantee protection to every worker. Given the nature of biological variation and the range of individual susceptibility, it is inevitable that a small proportion of workers...may suffer mild and transitory discomfort. An even smaller number may exhibit signs of illness..."

"...It follows from the foregoing that the exposure standards are not fine dividing lines between satisfactory and unsatisfactory working conditions, but rather that they are best used to assess the quality of the working environment and indicate where appropriate measures are required..."

While the latter statement is chiefly addressed to such diseases as occupational asthma or rhinitis etc, there is an analogy to occupational cancer, in that some subjects may be biologically more susceptible than others to developing cancer on exposure to a carcinogen (Anderson, 1982, Economou et al., 1994).

According to Vincent (Vincent, 1998), the OEL reflects the maximum level of exposure than can be accepted (according to a decision on what 'acceptable' is at the time), and is a component of an occupational exposure standard. The other important components are exposure measurement and exposure control. The ideal health-based standard should contain (Vincent, 1998):

a. Criteria for exposure which identify the agent and its specific physical, chemical and/or biological properties, relevant to a specific adverse health outcome.
b. Reference to monitoring instruments and analytical methods with performance characteristics matching the defined exposure criteria.
c. Reference to a monitoring strategy that aims to assess exposure in a manner representative of the temporal histories and variability of workers' exposures.
d. A health based OEL based on considerations of the effects of exposure at various levels, known occurrence of the health outcome in question, and what might be determined to be an 'acceptable' level of risk.

2.2 The Australian Exposure Standard for Crystalline Silica

In 1983-84 the National Health and Medical Research Council (NHMRC) recommended exposure standards specifically for quartz (0.2mg/m^3), cristobalite (0.1 mg/m^3) and tridymite (0.1mg/m^3).

In 1988, exposure standards for silica in the occupational environment were reconsidered by the Exposure Standards Expert Working Group (ESEWG), working under the Standards Development Standing Committee (SDSC). Following the recommendations of the American Conference of Governmental Industrial Hygienists (ACGIH, 1985), the Working Group recommended a reduction of the standard to 0.1 mg/m^3 respirable fraction for quartz, silica (fused), and tripoli (as quartz). For cristobalite and tridymite, the proposed exposure standards were set at one half of these values, at 0.05 mg/m^3 respirable fraction. This standard was released for a public comment period in late 1988. Considerable adverse comment was received on the proposed reduction to 0.1 mg/m^3 for respirable quartz.

The following reasons were cited:

a. the NHMRC standard of 0.2mg/m^3 respirable quartz had been in force in Australia for a decade. The incidence of silico-pneumoconiosis in most areas of Australia (WA, SA, NSW and Queensland) was very low and current incidence probably related to those ageing workers who had been exposed to significantly higher levels of respirable silica in the past;

b. The proposed standard of 0.1mg/m^3 for respirable quartz adopted from ACGIH was based a conversion of mppcf to mg/m^3 which was believed to be inaccurate;

c. The ACGIH's definition of *respirable dust* corresponded to a median aerodynamic diameter of 3.5micrometers, which was different from the Johannesburg Curve adopted in the draft document.

d. It was argued that the Australian sampling technique would give a higher dust reading than the ACGIH recommended method; and

e. The proposed exposure standard for respirable quartz was not adequately justified.

In view of strong opposition to the proposed standard, in particular from the mining industry, the Expert Working Group believed a more thorough examination of the issue was warranted. The SDSC regarded the issue of an exposure standard for crystalline silica sufficiently important to establish an Expert Working Group on Crystalline Silica (EWGCS) and a Reference Group (*Appendix 1*). A Draft Technical Report on Crystalline Silica was prepared by the EWGCS in consultation with the Reference Group and other NOHSC staff (NOHSC, 1996). The Draft Technical Report examined toxicity, health outcomes in exposed populations, exposure data, exposure estimates and measurement, put forward a risk assessment model to predict the incidence of silicosis and cancer from different exposure

levels, and made recommendations to reduce the incidence of adverse health outcomes associated with silica exposure. A summary of the findings can be found in Appendix 1.

Between 1988 and 1996, no formal national exposure standard for crystalline silica existed in Australia, although some mining and occupational health and safety authorities assumed their own standards. After the Draft Technical Report of 1996, NOHSC reinstated the original 1983-84 NHMRC atmospheric exposure standard of 0.2 mg/m^3. A review of the interim exposure standard for crystalline silica was referred to the Hazardous Substances Sub Committee (HSSC) by NOHSC. In April 1998, the HSSC agreed to recommend the current independent review of the crystalline silica exposure standard.

2.3 Overseas Occupational Exposure Standards

2.3.1 U.S.A.- The Vermont Granite Workers

The ACGIH Threshold Limit Value (TLV) and Current OSHA Standard or Permissable Exposure Level (PEL), both 0.1 mg/m^3, rely heavily upon research conducted on the Vermont granite workers originating in the 1920's (Graham, 1999). Using follow up data over the 20's and 30's with optical particle counts, results from the early studies of these workers led to the adoption of a national standard for quartz dust of 10 mppcf, which has remained in effect to this day.

Surveillance of the Vermont granite sheds and quarries between 1940 and 1970 included dust level compliance inspections and annual chest radiographs of workers. No cases of silicosis were found after dust control measures were fully in place, during which time dust exposures were reduced to less than half of the first TLV to be based on measuring the percentage of crystalline silica in airborne dust (Graham, 1999). It was agreed that further follow up was necessary to evaluate lifetime exposures to the current TLV.

The methods of analysis of quartz changed to gravimetric methods in the late 1960's and an equivalent of 10mppcf = 0.1mg/m^3 has been generally accepted, although with some debate.

The 1974 National Institute for Occupational Safety and Health (NIOSH) Criteria Document for Crystalline Silica utilised a refinement of exposures using gravimetric methods and re-analysis of the Vermont granite workers' experiences (NIOSH, 1974). It was found that a particle count of10 mppcf was closer to a respirable mass concentration of 0.2 mg/m^3. The 1974 NIOSH Criteria Document recommended a new exposure limit for quartz of 0.05 mg/m^3, effectively half of the previous exposure standard that was considered protective of worker's health (NIOSH, 1974). However, it was later proposed that the study reporting significant losses in lung function among the Vermont workers at the current TLV, upon which the new Recommended Exposure Limit (REL) was based, included some measurement errors. These data were reviewed and re-analysed twenty years later in 1994, and found no such impact on lung function at the current TLV, creating much debate about the need for the NIOSH REL and the adequacy of the current TLV of 0.1 mg/^{3} (and PEL), which continues today (Graham, 1999). This debate has been overtaken somewhat by subsequent events,

particularly the classification of silica as a carcinogen, and the need to protect workers against lung cancer.

In 1998 the ACGIH added 'A2 Carcinogenicity' to the Notation for Crystalline Silica and Quartz and presented a proposal to reduce the TLV for respirable quartz from 0.1 mg/m^3 to 0.05 mg/m^3 (Silica Coalition, 1999). This recommendation was ratified in 2000 (ACGIH, 2000).

2.3.2 Other Overseas Occupational Exposure Standards

The collection and analytical methods used by the various standard-setting bodies internationally have resulted in differences in measured exposures which have in turn, influenced the results of comparisons made between exposure standards. Any consideration of overseas exposure standards should therefore also include an account of the collection and analytical methods prescribed. The current overseas occupational standards for crystalline silica are listed in *Table 1*.

The defined respirable fraction of collected dust used in the majority of jurisdictions including Australia is detailed in the First International Conference on Pneumoconiosis, Johannesburg, 1958 (NOHSC, 1996). A different definition has been, and continues to be used, in the United States of America. There are much overdue moves at an international level to standardise the dust collection fractions and adopt universal definitions for the inhalable and respirable fractions of airborne dust. Definitions endorsed by the International Standards Organisation (ISO) are to be adopted by the ACGIH in 2001, and Australia is expected to follow.

2.4 Workplace Monitoring

An important component of control strategies involves monitoring respirable dust exposure. The current Australian collection method is based on the British Medical Research Council (BMRC) method which differs slightly in size selection, and hence the measurement of mass concentration, from the ACGIH criteria used in the USA.

Airborne concentrations of contaminants in most occupational settings vary markedly with respect to time and space. Air currents within the area, individual work practices, and variation in the emission rate of the contaminant are some of the factors contributing to this variation. In the measurement of personal exposures to crystalline silica for particular jobs or tasks, several considerations are important:

a. Which employees' personal exposures to sample
b. Where sampling devices should be located
c. The number of samples needed to define a representative sample for a worker or job category
d. The sampling interval
e. The number of workdays during a year to be sampled
f. The level of mobility associated with each job

These considerations provide the foundation for decisions on the type of instrumentation to be used and the method of application. More information on workplace monitoring, exposure sampling and analytical methods can be found in Appendix 4.

Table 1. Overseas Occupational Exposure Limits for Crystalline Silica.

Country	Substance	Interpretation	Nature of Dust	Concentration mg/m^3	Measure Duration	Date of Publication or Implementation
ARGENTINA	quartz	MPC	RD	0.1	8 hr TWA	1991
	tridymite		RD	0.05	8 hr TWA	1991
	cristobalite		RD	0.05	8 hr TWA	1991
AUSTRALIA						
NHMRC	quartz	TWA	RF	0.2	8hr TWA	1983
	cristobalite, tridymite		RF	0.1		
NOHSC	< 5% quartz in coal dust	TWA	RD	3		1990
AUSTRIA	quartz, cristobalite and tridymite	MAK	FD	0.15	8 hr daily and	1992
	quartz containing dust		FD	4	40 hr weekly	
BELGIUM	quartz		RD	0.1	Average values over	1995
	cristobalite, tridymite		RD	0.05	15min, 8 hr daily	1996
CANADA	quartz, fused silica, tripoli	TWA	RD	0.1	8 hr	1996
Quebec	tridymite		RD	0.05	8 hr	1996
	cristobalite		RD	0.05	8 hr	1996
Ontario	crystalline silica, respirable		RD	0.1	8 hr	1993
DENMARK	quartz	TLV	RD	0.1	8 hr	1988
			TD	0.3		
	cristobalite, tridymite		RD	0.05		
			TD	0.15		
FINLAND	quartz	OES	FD	0.2	8 hr TWA	1993
	cristobalite, tridymite		FD	0.1		
FRANCE	quartz	VME	RD	0.1	8 hr	1996
	cristobalite, tridymite		RD	0.05		
GERMANY	quartz, cristobalite, tridymite	MAK	RF	0.15	8 hr, 40 hr week	1996
ITALY	quartz	TLV-TWA	RD	0.1	8 hr TWA, 40 hr weekly	1991
	cristobalite, tridymite	TLV	RD	0.05		
NETHERLANDS	quartz, cristobalite, tridymite	MAK	RD	0.075	8 hr TWA	1996
NORWAY	quartz	TLV	RD	0.1	8 hr	1994
			TD	0.3		
	cristobalite, tridymite	TLV	RD	0.05		
			TD	0.15		

Taken from the IARC Monographs Volume 68 (IARC, 1997b).

RD, respirable dust; RF, respirable fraction; TD, total dust; OEL, occupational exposure limit; OES, occupational exposure standard; PEL, permissible exposure limit; TLV, threshold limit value; TWA, time weighted average; FD, fine dust; VME, mean exposure value (valeur moyenne d'exposition); REL, recommended exposure limit; Q/C/T, quartz/cristobalite/tridymite; MAK, maximal workplace concentration; MAC, maximal allowed concentration; MEL, maximum exposure limit; MSHA, Mine Safety and Health Administration;

Table 1 (cont'd). Overseas Occupational Exposure Limits for Crystalline Silica.

Country	Substance	Interpretation	Nature of Dust	Concentration mg/m^3	Measure Duration	Date of Publication or Implementation
PORTUGAL	quartz	Recommended norms	RD	0.1	8 hr TWA	1988
			TD	0.3		
	cristobalite, tridymite		RD	0.05		
RUSSIA	quartz		Aerosol (silica > 70%)	1		1990
			Aerosol (silica 10-70%)	2		
			Aerosol (silica < 10%)	4		
	Cristobalite		Aerosol	1		
SOUTH AFRICA	quartz	TWA	RD	0.1	8 hr TWA	1996
SPAIN	< 5 % free silica quartz	Limit value	RD	6	8 hr	1991
SWEDEN	quartz		RD	0.1	8 hr	1993
	cristobalite, tridymite		RD	0.05		
SWITZERLAND	dust containing quartz, cristobalite or tridymite	VME	FD (1-5% Q/C/T)	4		
	quartz, cristobalite, tridymite		FD	0.15		
UNITED KINGDOM	quartz, cristobalite, tridymite	MEL	RD	0.3	8 hr TWA	1999
USA						
OSHA	quartz	PEL	RD	10mg/m^3/(% Sio_2+ 2)	8 hr TWA	OSHA 1989
	quartz		TD	30mg/m^3/(% Sio_2+ 2)		MSHA 1978
	quartz in coal mines		RD	2.4		MSHA 1978
	>5% quartz in coal mines		RD	10mg/m^3/(% Sio_2+ 2)		OSHA 1971
	cristobalite, tridymite			half of quartz value		MSHA 1978
ACGIH	quartz	TWA	RF	0.05		ACGIH 2000[§]
	Cristobalite			0.0025		ACGIH 2000[§]
	Tridymite			0.025		ACGIH 2000[§]
	tripoli			0.1 of contained respirable quartz		ACGIH 2000[§]
	Coal dust		RD	2		ACGIH 1985
NIOSH	fused silica, cristobalite, quartz, tridymite, tripoli	REL	RD	0.05	10 hr/day, 40 hr/wk TWA	NIOSH 1974 [#]

Taken from the IARC Monographs Volume 68 (IARC, 1997b). [#] (NIOSH, 1974) [§] (ACGIH, 2000)

RD, respirable dust; RF, respirable fraction; TD, total dust; OEL, occupational exposure limit; OES, occupational exposure standard; PEL, permissible exposure limit; TLV, threshold limit value; TWA, time weighted average; FD, fine dust; VME, mean exposure value (valeur moyenne d'exposition); REL, recommended exposure limit; Q/C/T, quartz/cristobalite/tridymite; MAK, maximal workplace concentration; MAC, maximal allowed concentration; MEL, maximum exposure limit; MSHA, Mine Safety and Health Administration;

3.0 PHYSICO-CHEMISTRY OF SILICA

Silica (silicon dioxide, SiO_2) constitutes a major part of the earth's crust and is associated with many types of igneous, metamorphic and sedimentary rocks, and soils derived from these rock types. There are several types of silica, although crystalline silica is most important for its biological effects.

3.1 Types of Silica

Silica occurs as crystalline, cryptocrystalline and amorphous (non-crystalline) forms. Silica in its free form is distinguished as either crystalline or amorphous (eg. silica gel).

The main forms of crystalline silica include quartz, cristobalite and tridymite. The arrangement of their silicon and oxygen atoms is in a definite regular tetrahedral pattern throughout the crystal. Silica may be combined with other elements to form silicates, however these forms of silica differ markedly in terms of their biological effects.

In amorphous silica there is no definite regular pattern between molecules, but a non-periodic random molecular arrangement. The amorphous variety includes diatomaceous earth and opal, although the latter is sometimes included in the cryptocrystalline group.

Cryptocrystalline (microcrystalline) silica is an intermediate form between crystalline and amorphous silica, in that it consists of minute crystals or crystallites of silica which are themselves arranged in no regular orientation to one another. Flint, chert, chalcedony, tripoli and silica flour are important members of the cryptocrystalline group.

This review is concerned only with exposure standards for crystalline silica ie. quartz, cristobalite and tridymite.

3.2 Chemical Properties

Silica is insoluble in water, organic solvents, and most mineral acids. It is attacked by alkaline aqueous solutions and by hydrofluoric acid (to create silicon tetrafluoride gas) (IARC, 1997b).

Cristobalite may be formed as a consequence of the calcining of diatomaceous earth (earth containing fossilised algae or diatoms), the amount depending on calcination temperature and duration. Temperatures greater than 1500°C (as is occasionally found in industry) may convert amorphous silica and quartz to tridymite and cristobalite.

The physical form of silica determines its fibrogenicity. The order of fibrogenicity of different forms of crystalline silica is thought to be (Gibbs, 1995):

quartz < cristobalite < tridymite

However, a recent report from the UK Health and Safety Executive (HSE) was unable to find any evidence that quartz and cristobalite should be treated differently when assessing human exposure (Meldrum et al., 2001).

3.3 Distribution

Quartz is the most important and widespread form of crystalline silica. It is a major constituent of igneous rocks (granite and pegmatite), sedimentary rocks (sandstone and shales) and metamorphic rocks (quartzites and slates), as well as being the major component of sand in locations such as stream beds, beaches, deserts and gardens. The occurrence of crystalline silica in rock types is widespread, and the crystalline silica content in rock is highly variable. Cristobalite and tridymite are often associated with metamorphosis in volcanic areas.

3.4 Structure

The SiO_4 tetrahedron is the primary structural basis of silica minerals. Slight variations in the orientation of the tetrahedra give rise to different polymorphs of silica. When units are oriented randomly, amorphous varieties will result. Differences in symmetry and cell parameters are designated by the prefixes α- and ß-. The structure of quartz is more compact than either cristobalite or tridymite and hence its density is greater.

Quartz, cristobalite and tridymite are chemically identical but may be differentiated on the basis of their crystalline form, through the application of techniques such as microscopic examination, x-ray diffractometry and infrared spectrophotometry. The three forms of crystalline silica are also interrelated in that they may change their form under different conditions of temperature and pressure. The α-, or low temperature forms are the most common.

3.5 Exposure Sources

Processes which may give rise to airborne concentrations of crystalline silica dust include hard rock mining, excavation tunnelling and earthworks, construction, foundry operations, ceramics production, stone works, refractory brick production, abrasive blasting, agricultural ploughing and harvesting, and the production of asphalt, agricultural chemicals, abrasives, glass, and paint.

Quartz is the most widespread form of crystalline silica in the Australian context, mainly due to the magnitude of mining and construction industries. Cristobalite exposure appears to be restricted to the ceramic, diatomaceous earth and hot metal industries. Tridymite exposures are negligible in Australia.

The nature of health effects arising from exposure to crystalline silica depend on its source, as the physical properties of different forms of silica induce different health effects. For example, the effects of exposure to coal dust containing crystalline silica are less than would be expected for exposure to the same amount of crystalline silica alone. It is thought that surface modification by extraneous material on the crystalline silica particles provides some protective effect. The physical and chemical properties of crystalline silica that influence biological effects are discussed in the next chapter.

4.0 TOXICOLOGY

This chapter summarises the currently hypothesised mechanisms for the biological effects of crystalline silica by reviewing the literature on animal and human evidence of its toxicological effects. Extensive reviews of the toxicology of silica (both malignant and non-malignant effects) in humans and animals were published in IARC's 1997 Monograph on the Evaluation of Carcinogenic Risks to Humans (IARC, 1997b). We present a summary of the pertinent literature with a focus on the more recent studies published since 1996.

4.1 Health Effects

Many health effects have been associated with exposure to crystalline silica in humans. Those reported in the scientific literature include:

a. Silicosis ie. nodular fibrosis of the lung with a typical microscopic appearance, diagnosed clinically and epidemiologically by small rounded opacities on plain chest x-ray with profusions according to the ILO classification ≥ 1/0 with or without large opacities, indicating complicated pneumoconiosis or progressive massive fibrosis (PMF), silicotic nodules at autopsy, compensated silicosis, or mortality from pneumoconiosis

b. Bronchogenic lung cancer

c. Bronchitis, ie. the presence of cough or sputum

d. Chronic obstructive pulmonary disease (COPD) or an abnormal decline in pulmonary function, ie. a lower than expected forced expiratory volume in 1 second (FEV_1) or excessive rate of annual decline in FEV_1 with a reduced ratio of FEV_1 to forced vital capacity (FVC) ie. FEV_1/FVC when compared to levels in a normal population, emphysema at autopsy, or mortality from COPD

e. Tuberculosis (or silico-tuberculosis) ie. pulmonary infection with *Mycobacterium tuberculosis*

f. Coal worker's pneumoconiosis, mixed dust pneumoconiosis, or radiological findings of nodular pneumoconiosis, are associated with the inhalation of dust containing a mixture of minerals usually containing quartz. Coal workers' pneumoconiosis (CWP), in which inhaled carbon and silicates play an important role in the aetiology; foundry man's pneumoconiosis, related in part to the inhalation of oxides of iron; and oil shale pneumoconiosis, again caused by organic and silicate minerals, may all be regarded as forms of mixed dust pneumoconiosis (Gibbs, 1995). The radiographic appearances are of a simple multi-nodular pneumoconiosis which appear similar to silicosis on a plain chest radiograph however, silicosis is a pathologically different disease. As this review is concerned only with exposures to crystalline silica, epidemiological and toxicological data concerning exposures to mixed dust have not been reviewed here (see *1.3 Project Rationale*).

g. Auto-immune disease, ie. systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, end-stage renal disease or glomerulonephritis.

In 1997, IARC deemed crystalline silica to be carcinogenic to humans, based on sufficient human and animal evidence (IARC, 1997b). Data on the carcinogenicity of silica in humans have been derived mostly from studies of lung cancer incidence in the following industries: metal ore mining, quarrying and granite production, pottery and other ceramics production, refractory brick production, diatomaceous earth processing and foundry work (Armstrong, 1998). The epidemiological evidence of malignant and non-malignant health effects from crystalline silica exposure is reviewed in the next chapter.

4.2 Currently Hypothesised Mechanisms of Toxicity

Hypothesised mechanisms for the biological effects of crystalline silica are continually evolving. The evidence indicates that toxicological processes associated with crystalline silica exposure depend upon the form of crystalline silica and its surface chemistry, the internal dose of crystalline silica (which is determined by the balance between deposition and clearance), and the cellular and tissue responses.

4.2.1 Surface Chemistry

The nature of the surface chemistry of crystalline silica is partly responsible for its toxicity, and alterations in this chemistry are associated with differing biological effects.

Animal studies show that the inhalation of freshly cleaved quartz results in increased inflammatory and cytotoxic responses in the lungs, compared to these effects produced by aged quartz dust (Shoemaker et al., 1995). Freshly ground silicas have a higher degree of toxicity due to the reactivity of their newly created surfaces. Grinding silica cleaves the silicon-oxygen bonds, resulting in reactive $Si^{\cdot}$ and $SiO^{\cdot}$ radicals. These either reform as unstable 'bridges' or react with atmospheric components, creating reactive oxygen species (ROS) at the surface and subsurface layers of the silica molecule (Fubini et al., 1995). If ground while wet, crystalline silica produces fewer radicals than when ground dry, even if previously heated (Fubini et al., 1995).

The effect of surface area and particle size on the inflammatory and cytotoxic potency of crystalline silica has been examined in human cells. Human epithelial lung cells (A549) were exposed to different sized fractions of quartz (aerodynamic diameter 0.5, 2 and 10 um), and all particle sizes induced an increased release of proinflammatory cytokines (Interleukin –6 and –8) (Hetland et al., 2001). When cells were exposed to equal masses of quartz, the smallest size fraction produced the most marked effect. However, when cells were exposed to equal total surface areas of quartz, there were no differences in cytokine production, between fraction sizes. The surface area of the crystalline silica dose may therefore be more important than the particle size (Hetland et al., 2001).

Silica particles are often contaminated with minerals such as iron or aluminium. Often the silica particle takes on the properties of the contaminant, and its toxicity either increases or decreases. Both aluminium and iron decrease membranolysis (Begin et al., 1987, Fubini et al., 1995).

However, iron may be a potential source of ROS that cause DNA damage, and can therefore increase the carcinogenic potential of the associated silica particle (Fubini et al., 1995).

The heating of crystalline silica can diminish the presence of surface radicals, and converts the normally hydrophilic silica surface into a hydrophobic one (Fubini, 1997). This lowers the membranolytic potential, however it does not decrease the overall fibrogenic potential of the dust, and has been shown to enhance the transport of silica particles to lymph nodes in rats (Fubini et al., 1995).

Fubini and colleagues exposed cell lines to cristobalite and heat treated cristobalite (CRIS-1300) dusts (Fubini et al., 1999). Heating of the cristobalite dust to 1300 °C annealed surface radicals and resulted in a completely hydrophobic surface. Cytotoxicity was apparent after treatment with cristobalite but not CRIS-1300 in murine macrophage cell lines (J774), shown by the colony forming efficiency of proliferating cells. Cytotoxicity indicated by lactate dehydrogenase (LDH) release from rat alveolar macrophages was apparent after cristobalite exposure, but this release was inactivated for CRIS-1300. These results indicate that hydrophobicity may be one of the surface properties governing the cytotoxic potential of silica dust (Fubini et al., 1999).

4.2.2 Deposition

Airborne crystalline silica dust from occupational sources usually consists of particles of many different sizes, which can be measured as the total dust. Deposition in the respiratory airways is determined by the shape, size, density, surface area, penetrability, electrostatic charge, hygroscopicity, alkalinity and acidity of the particles, as well as other host factors (Morgan, 1995). The aerodynamic diameter is commonly used to describe the shape, size and density of inhaled particles, and is defined as the diameter (in micrometres or um) of a spherical particle of unit density (1 g/mL) that settles at the same speed as the particle in question (ACGIH, 1989). The respiratory tract airspace can be divided into three compartments:

a. the upper respiratory tract, ie. nose and extra-thoracic airways, extending to the glottis (nose, pharynx, sinuses)
b. the conducting airways, ie. trachea and bronchi, extending to the terminal bronchioles
c. the lung parenchyma, ie. where gas exchange occurs (alveoli)

The act of breathing involves air being drawn through the nose into the nasopharynx and trachea and through the conducting airways of the lungs. Air reaches the alveoli via the various bronchi, terminal bronchioles, respiratory bronchioles, and alveolar ducts. The flow rate of inspired air decreases as it enters the trachea, and is further reduced in the main segmental bronchi, and so on (Morgan, 1995). By the time inspired air reaches the terminal bronchioles, the flow rate is no more than 2 to 3 cm per second (Morgan, 1995).

Only particles of a certain size range can enter and be deposited into the various compartments of respiratory system (*Figure 1*). Particles up to 100 micrometers in diameter can enter the upper respiratory tract through the nose or mouth, and are termed the *inhalable fraction*. The nose is capable of efficiently filtering most large particles, however smaller particles will reach the conducting airways and parenchyma.

Particles able to continue through the respiratory tract to the intra-thoracic conducting airways (bronchi and bronchioles) have a median aerodynamic diameter of 10 micrometres. These are termed the *thoracic fraction*. Deposition in these airways is heterogeneous, and bifurcations may receive particularly high particle deposits (Brody et al., 1985, Brody et al., 1982, Morgan, 1995).

Only particles with a median diameter of around four micrometres can enter the lung parenchyma (respiratory bronchioles and alveoli). These are termed the *respirable fraction* and are most likely to cause lung injury, as they deposit beyond the muco-ciliary clearance mechanism, can only be removed via macrophage phagocytosis, and are slow to be cleared (IARC, 1997b). For the purposes of workplace monitoring, a size-selection sampling strategy may measure only the respirable fraction while ignoring other fractions.

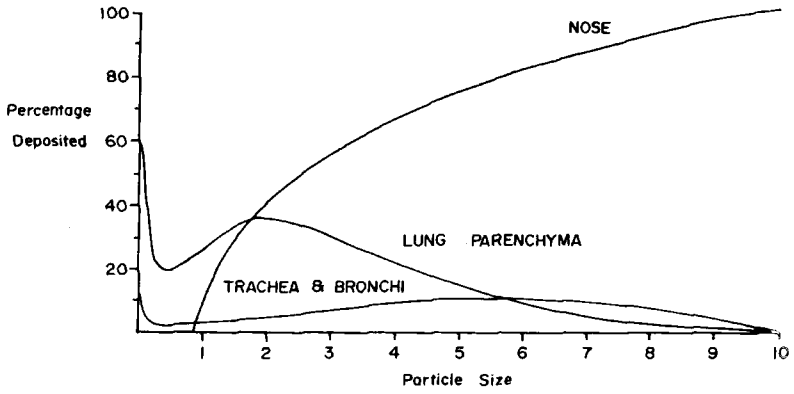


Figure 1. Regional deposition of particles as a function of their size in microns.
Taken from (Morgan, 1995) p 116

4.2.3 Clearance

The retained dose of silica is determined by the rate of material deposited versus the rate of clearance. The compartments within the respiratory system have differing clearing mechanisms, and these mechanisms can themselves be effected by the amount deposited. Overload situations develop when the clearance mechanism does not keep up with deposition, and particles then accumulate at these sites. Ideally, health based exposure standards should be developed to prevent the overload of clearance mechanisms.

4.2.3.1 Upper respiratory tract

Particles deposited in the anterior of the nose are removed by mechanical means such as blowing or sneezing, whereas soluble particles may be quickly absorbed (Morgan, 1995). Clearance from the posterior portion of the nose including the turbinates is by muco-ciliary mechanisms which propels particles towards the nasopharynx for removal (Morgan, 1995).

4.2.3.2 Thoracic fraction

The broncho-ciliary escalator extends from the trachea to the terminal bronchioles. Cilia motion continually propels the bronchial mucous upwards (Morgan, 1995). The larynx is covered by mucus-secreting squamous epithelium, whereas the trachea and bronchi are lined with columnar cells interspersed with submucosal glands and goblet cells that produce respiratory mucus (Morgan, 1995). Not all columnar cells are ciliated, and the relative number of ciliated columnar cells progressively decreases from the trachea to the terminal bronchioles (Morgan, 1995).

Particles depositing in the conducting airways are usually cleared relatively rapidly by the upward motion of the muco-ciliary escalator, however some particulate material can be retained in the bronchial mucosa (IARC, 1997b). Animal models show retained particles near the basement membrane of conducting airways following either inhalation or instillation of crystalline silica, with some of the retained material found within macrophages (Gore et al., 1982, Snipes, 1989). Post-mortem studies in lifetime non-smokers have revealed that silica can not only be retained, but appears to be concentrated in the airways, when compared to silicates such as asbestos (Churg et al., 1990). The retention of particles may be important with respect to cancers of the airways. Studies of lung cancer patients reveal that airways with tumours often retain the highest concentration of retained particles (Churg et al., 1988).

4.2.3.3 Lung parenchyma

Respirable particles entering the lung parenchyma are initially deposited on the hydrophobic pulmonary surfactant fluid. Their removal is only possible through phagocytic transport via the alveolar macrophage, to either the terminal bronchioles for removal via the muco-ciliary escalator, or to the interstitium of the lung (Steenland et al., 1995c).

Even though particles deposited in the gas-exchanging regions of the lung can be removed by alveolar macrophage phagocytosis, they may be toxic to the macrophages and thereby initiate inflammatory, fibrotic and/or neoplastic processes. Some phagocytosed silica is transported to regional lymph nodes where it may initiate granulomatous inflammation and the production of typical silicotic nodules. Radiographically, this is seen as hilar and mediastinal adenopathy and later, eggshell calcification.

The inhalation of particles less than 10 micrometres in aerodynamic diameter (*respirable* and *thoracic* fractions) is therefore most likely to cause adverse health effects (IARC, 1997b).

4.2.4 Cellular and Tissue Responses

Although not fully understood, it is fairly well accepted that chronic inflammation in the lower respiratory tract is an intrinsic part of the patho-physiological mechanisms that cause dust-related diseases (Begin et al., 1989, Huaux et al., 1998).

4.2.4.1 Inflammation and fibrosis

Most respirable particles depositing in the gas-exchanging parts of the lung are ingested by macrophages (Begin et al., 1989). Alveolar macrophages containing silica particles are capable of releasing large quantities of inflammatory cytokines such as fibronectin and other fibroblast growth factors, which are chemo-attractants and stimulants for fibroblasts (Begin et al., 1989). Fibrotic disease due to crystalline silica exposure, or silicosis of the lung, is characterised by persistent pulmonary inflammation that leads to the proliferation of fibroblasts and production of collagen (Huaux et al., 1998).

Silica is insoluble in the human body. Some engulfed silica particles accumulate as silicotic nodules in the interstitial and alveolar spaces (Begin et al., 1989). A silicotic nodule develops when fibroblasts and collagen tissue infiltrate and surround the macrophage enclosed particles. At its most advanced stage, the nodule is almost spherical, consisting of a hyalinised substance within a collagenous capsule. Nodules tend to gather in clusters and may conglomerate into larger structures (as in progressive massive fibrosis or PMF) which can be easily seen on a chest x-ray, and are capable of cavitating due to the ischaemic necrosis of their centres.

4.2.4.2 Particle migration

Inhaled silica particles have been shown to migrate via macrophages through the circulatory system, to the liver, spleen, kidneys, bone marrow and extra-thoracic lymph nodes. The presence of particles in the lymphatic system activates the immune system and stimulates T-helper and B-cell production, etc (Steenland et al., 1995c). This activation has been associated with humoral responses including hyper-gammaglobulinaemia and the production of rheumatoid factor, various auto-antibodies and other immune complexes (Steenland et al., 1995c). This immuno-stimulation may lead to conditions such as rheumatoid arthritis and connective tissue disorders including systemic lupus, scleroderma and glomerulonephritis, with which silica exposure has been associated (Haustein et al., 1990).

4.2.4.3 Oxidative stress

Particle-stimulated alveolar macrophages can release large amounts of ROS, including superoxide and hydrogen peroxide (Begin et al., 1989). The production of ROS by alveolar macrophages is thought to stimulate cytokine and chemokine production, which stimulate a range of inflammatory responses. The current research on oxidative stress in the inflammatory response suggests a possible role for antioxidants in the prevention of fibrosis initiation (Zhang et al., 2000).

4.2.4.4 Cytokines and chemo-attractants

In addition to ingesting particles, alveolar macrophages play several other important roles through their generation of cytokines, including: Tumour Necrosis Factor (TNF), a promoter of fibroblast recruitment and replication; Fibronectin, a chemo-attractant for fibroblasts and primer of fibroblast proliferation; and Transforming Growth Factor (TGF), which is involved in cell growth and differentiation, inflammation and tissue repair (Rom et al., 1987, Williams et al., 1995).

4.2.4.5 Neutrophils

Macrophages releasing various chemotactic factors are likely to be responsible for the influx of neutrophils to the site of dust deposition immediately following silica exposure (Begin et al., 1989). Excess neutrophils can chronically persist in the alveolar space, and are capable of secreting collagenase, elastase, and ROS which may attack the extracellular connective tissue matrix, causing cell and tissue damage. Such damage is well documented in acute silicosis (associated with short term, heavy quartz exposures) where air spaces are filled with neutrophils and epithelial cells (Begin et al., 1989). By-products of arachidonic acid metabolism involved in the inflammation response can also activate neutrophil recruitment (Vanhee et al., 1995).

4.2.4.6 Lymphocytes

Expansion of the lymphocyte population has been observed in the lung lavages of humans with silicosis and animals with experimentally induced silicosis (Begin et al., 1989, Davis et al., 2001). The alveolar macrophage may influence the activation of lymphocytes in the pathogenesis of silicosis through its release of cytokines such as interleukin (IL)-1, which is known to stimulate receptive helper/inducer T-cells to secrete IL-2, and induce the proliferation of active helper T-cells (Begin et al., 1989, Davis et al., 2001). It is thought that silica-induced increases in lymphocyte populations may contribute to the development of auto-immune disease associated with silicosis (Haustein et al., 1994).

4.2.4.7 Macrophage injury

Injured alveolar macrophages may rupture soon after the phagocytosis of silica particles, and are capable of releasing toxins, proteolytic enzymes, and lysosomal hydrolases. This is thought more marked *in-vitro* than *in-vivo*, as the coating of inhaled minerals with pulmonary surfactant liquids and other alveolar lining fluids may mitigate this process (Begin et al., 1989).

Continued deposition of silica dust leads to the necrosis of macrophages and the release of the phagocytosed silica particles onto the alveolar surface. The cycle of capture and release of particles leads to the ongoing recruitment of alveolar macrophages and neutrophils, producing chronic inflammation and ultimately, fibrosis (Tran et al., 1995).

4.2.4.8 Carcinogenicity and genotoxicity

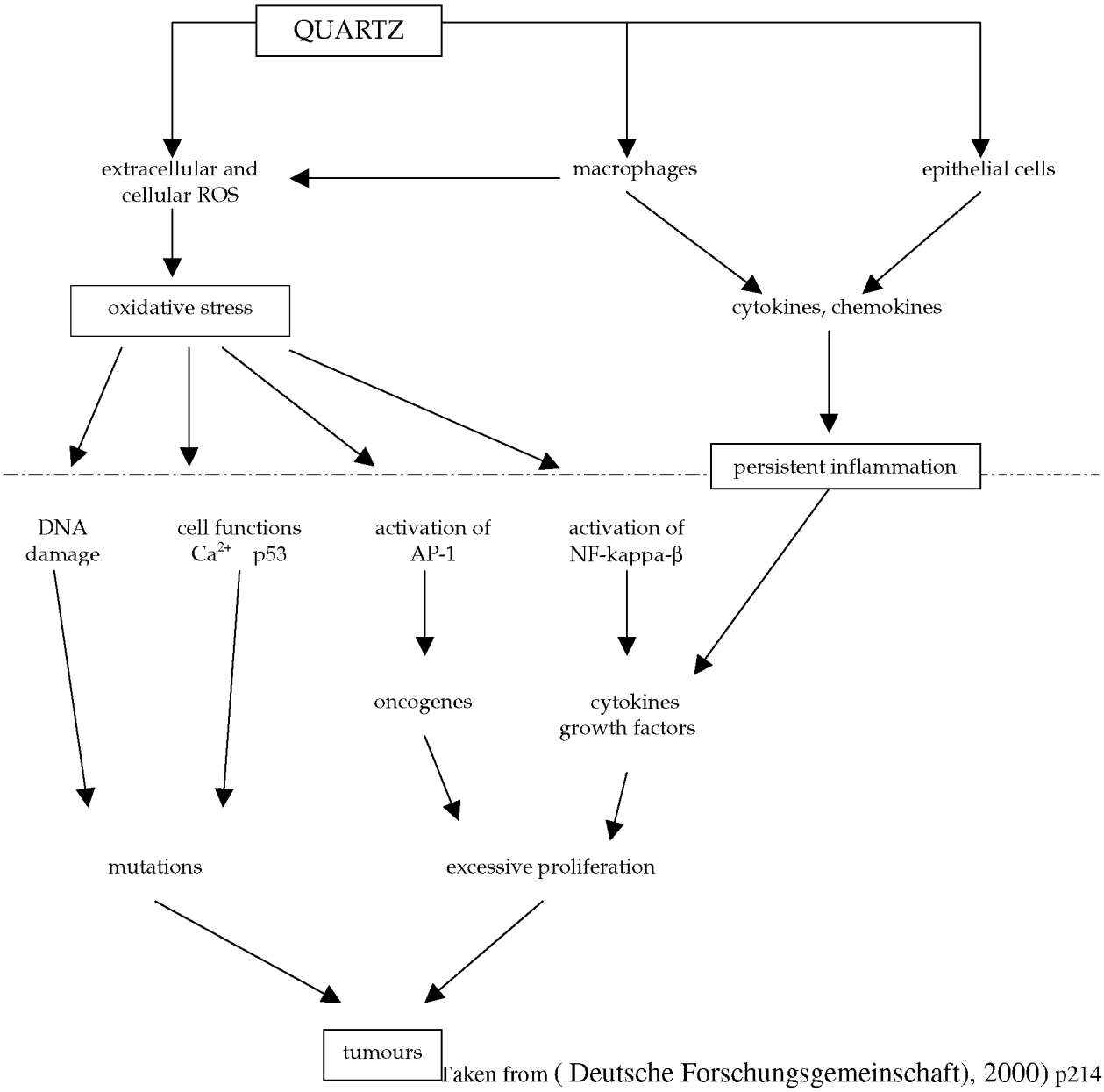
Alveolar type II cells synthesise and secrete pulmonary surfactant, and function as progenitor cells for maintaining the alveolar epithelium (Miller et al., 1990). Damage to alveolar type I cells stimulates Type II cells to proliferate and differentiate to replace injured type I cells (Miller et al., 1990). Quartz induces hypertrophic and hyperplastic changes in alveolar type II cells, which can lead to persistent proliferative changes that may eventually result in alveolar cell tumours appearing adjacent to granulomatous lesions (Williams et al., 1995).

In-vitro studies of animal cells indicate that crystalline silica is capable of inducing DNA strand breakage and chromosomal damage; ROS have been implicated in these processes (IARC, 1997b). If damage to DNA is sufficient to affect oncogenes or cause other genetic changes that

may result in unregulated cell proliferation, then carcinogenesis will result (IARC, 1997b). However, these effects on isolated cells *in-vitro* have only been associated with large doses.

There is limited evidence of a direct genotoxic effect from crystalline silica (IARC, 1997b). However, chronic inflammation, oxidative stress and epithelial hyperplasia induced by crystalline silica exposures are thought responsible for increasing the risk of genetic alterations associated with neoplastic transformation (*Figure 2*) (IARC, 1997b). The relationship between chronic inflammation with hyperplasia and neoplasia is well described in many biological systems, such as scar cancers in the lung and squamous cell cancers in chronic skin ulcers. It is well established that crystalline silica is capable of activating inflammatory and genotoxic responses in the lung through inflammatory and growth stimulatory factors, ROS, reactive nitrogen species and activated neutrophils and monocytes.

Figure 2. A proposed inflammation-based mechanism for quartz-induced carcinogenesis in the rat.



Taken from (Deutsche Forschungsgemeinschaft), 2000) p214

4.3 Toxic Effects in Animals

Acute and most subchronic (≤ 3 months) and chronic quartz inhalation studies have induced non-malignant health effects in rats and mice including fibrosis, increased collagen and elastin content of the lungs, or impaired phagocytic ability of alveolar macrophages (Gift et al., 1997). Carcinogenic and genotoxic effects have been noted *in-vivo* and *in-vitro*, after single and repeated doses of crystalline silica.

4.3.1 Inflammation and Fibrosis

Significant inflammatory responses have been noted in rats exposed to crystalline silica (IARC, 1997b). Warheit and colleagues showed that the inhalation of aerosolised quartz particles in rats (Min-U-Sil, mass median aerodynamic diameter 3.7 micrometres) for 6 hours daily over 3 days resulted in a persistent pulmonary inflammatory response (Warheit et al., 1997). This was characterised by neutrophil recruitment, consistently elevated biomarkers of cytotoxicity in broncho-alveolar lavage (BAL) fluid, and impairment of alveolar macrophage clearance. One month after exposure, progressive histopathologic lesions were observed. Hyperplasia in type II alveolar epithelial cells and the mobilisation of macrophages and neutrophils into alveoli and interstitial compartments was shown by light and electron microscopy. Lesions developed into a multifocal, granulomatous-type pneumonitis within 2 months after exposure. These features were in contrast to no response seen after 3 day exposures to carbonyl iron particles. This short term, high dose inhalation study showed similar outcomes to those previously observed using intratracheal instillation and chronic inhalation models (Warheit et al., 1997).

The instillation and inhalation of quartz causes a fibrogenic response in rats, guinea pigs and mice, however strain- and species-specific differences in response mechanisms have been shown to exist (IARC, 1997b). Experimental silicosis is dependent on TNF-alpha in quartz-instilled mice, whereas fibronectin release from alveolar macrophages is associated with the attraction of fibroblasts and mesenchymal cell growth in rats after quartz inhalation (IARC, 1997b). In a recent comparison of species-specific inflammatory responses to quartz exposure, rats and hamsters were intratracheally instilled with saline or 0.2, 2.0 or 20mg of alpha-quartz (Carter et al., 2001). BAL seven days later showed dose-related increases in neutrophil numbers and LDH in both species, with significantly greater increases in the rat. Rats showed a greater expression of several pro-inflammatory mediators and lower levels of anti-inflammatory mediators, indicating that the rat may be the more sensitive species.

It has been questioned as to whether the effects of a single dose of quartz exposure are comparable to those from multiple doses. Reasor and Antonini compared BAL fluid markers of inflammation and damage to the capillary-epithelium barrier in male F344 rats after multiple and single doses of quartz (Reasor et al., 2001). Doses of either 0.2, 1 or 5 mg/crystalline silica/100g body weight were given for 5 consecutive days, or as a single dose. BAL markers were increased at higher doses, with less severe responses at lower doses. There were no significant differences in outcomes between rats treated with multiple doses and those treated with a single dose.

4.3.2 Air Flow Obstruction

Quartz may produce morphologic and functional changes of air-flow obstruction in rats. Female Sprague-Dawley rats were intratracheally injected with either saline, iron oxide, or silica (10mg or 30mg of Min-U-Sil in 0.5 mL of saline) (Wright et al., 1988). Pulmonary function tests conducted one month later indicated significant air flow obstruction in the quartz treated groups, with the high dose group most severely impeded. Lung tissue morphology in silica treated groups was consistent with emphysema and thickened airway walls, and was most severe in the high dose group. This group also developed silicotic nodules. No changes were seen in the iron oxide or saline treated groups.

The same researchers compared lung tissue morphology in the same rat species after treatment with 30mg silica (Min-U-Sil 5), 50 units of porcine pancreatic elastase/100 gm body weight, or saline as a control (Churg et al., 1989). Elastase instillation is a standard model for producing emphysema. Increases in residual volume and forced residual volume were seen in both treatment groups, but were most marked in the silica group. After one month, both treatments produced similar amounts of airspace enlargement in the alveoli and alveolar ducts. Elastic fibre length per unit volume was also decreased in both groups. Additionally, small airway walls were significantly thicker in the silica treated group. The marked air-flow reduction in silica treated animals appeared to be related to the changes in small airway structure (Churg et al., 1989).

4.3.3 Particle Migration

Fibrosis has occurred in the lymph nodes of rats following inhalation exposure to quartz and intratracheal instillation with amorphous silica (IARC, 1997b).

Enlargement of the thoracic lymph nodes has been reported in F433 rats that developed experimental silicosis via aerosol inhalation of α-cristobalite (Friedetzky et al., 1998). There were profound increases in the weight of the lymph nodes with increases of 3.5-fold at 2 weeks, and 35-fold one year after the 8 day exposure period. There was an early proliferation of T-cell and B-cell leukocytes. Lymph node weight increases were due to increases in cell numbers (leukocytes, macrophages) and the development of granulomas, but not fibrosis. *In-vitro* examination of the early cytokines suggested that Interferon (IFN)-gamma was primarily responsible for the recruitment of T-cells within the thoracic lymph nodes (Garn et al., 2000).

The specific nephrotoxicity of silica was demonstrated in a study of renal cell lines from the proximal convoluted tubule and inner medullary collecting tubule of transgenic mice (Cha et al., 1999). Silica caused a bi-phasic increase in cytosolic free Ca^{++}, and dose-dependent cell injury that was evident via a vital dye exclusion procedure. Cellular adenosine triphosphate (ATP) decreased with increasing silica concentrations. It was concluded that ATP depletion contributed to the increase in free Ca^{++} and its passage through the plasma membrane via the calcium channel and non-specific membrane damage (Cha et al., 1999).

4.3.4 Concomitant Infections

Simultaneous infection during silica exposure has been shown to result in more substantial pulmonary effects after silica exposure (Chiappino et al., 1982). Rats instilled with tridymite

were kept either under normal laboratory conditions or quarantined from endemic bacterial flora. Those kept under normal conditions developed silicosis more rapidly and severely than quarantined rats. This suggests that bronchopulmonary infections endemic to animal houses acted as a co-stimulus for silica-induced fibrosis (Chiappino et al., 1982).

Alternatively, pneumotoxic substances such as silica may increase the susceptibility to pulmonary infection (Antonini et al., 2000). Antonini and colleagues investigated the effect of silica exposure on pulmonary defence mechanisms after pulmonary infection (Antonini et al., 2000). Male F344 rats were exposed to 15 mg/m^3 of crystalline Min-u-Sil 5 silica by inhalation, for six hours per day, 5 days per week for either 21 or 59 days. Controls received filtered air. After the exposure periods, both treatment and control rats were inoculated intratracheally with *Listeria monocytogenes*, a bacterial agent commonly used to assess pulmonary host defense mechanisms. Inflammation and pulmonary injury indicated by neutrophils and LDH activity respectively, was significantly increased in animals exposed to silica for 59 days compared to controls (who also showed increases), indicating a synergistic toxic effect between silica and the bacteria. At 3 and 7 days after inoculation, the left lung was removed and cultured for *Listeria monocytogenes* colonies. Surprisingly, both groups of animals pre-treated with silica showed significantly increased clearance of the *Listeria monocytogenes* bacteria from the lungs, compared to controls. This may have been due to the activation of lung neutrophils and alveolar macrophages. Chemiluminescence of the extracted lungs showed significantly elevated levels of lung phagocytes, indicating that silica exposed animals produced greater ROS, possibly to facilitate the destruction of bacteria.

4.3.5 Oxidative Stress

Lim and colleagues showed dose-dependent free radical production by alveolar macrophages from male Sprague-Dawley rats after *in-vitro* treatment with silica (Lim et al., 1997). Silica increased intracellular calcium, and extracellular calcium depletion, calcium channel blockers and calcium release blockers decreased silica-induced free radical production. Protein kinase, phospholipase C and protein tyrosine kinase also suppressed silica-induced free radical production by alveolar macrophages. These results suggest that signal transduction pathways are involved in the generation of ROS by silica-stimulated macrophages (Lim et al., 1997).

Fubini and colleagues investigated the effect of exposure to cristobalite and modified quartz on ROS and morphological reactions in Syrian hamster embryo (SHE) cell transformation assays (Fubini et al., 2001). The crystalline surface of quartz was modified either by etching with hydrofluoric acid, by depriving the surface of trace iron, or by enriching it with iron. Cristobalite was formed after the heating of quartz above the phase transition temperature. Treatment of SHE cells with the original forms of quartz and cristobalite resulted in free radical (hydrogen peroxide) release, were cytotoxic, and induced morphological transformations. Hydrogen peroxide release, cytotoxicity and transforming potency were reduced after exposure to surface-etched quartz, but was lowest after treatment with iron-deprived or iron-enriched quartz. The amount of hydrogen peroxide released was linearly related to cell transformation frequency, and the number of transformed cells could be reduced by the presence of antioxidant enzymes.

4.3.6 Cytokines and Chemokines

Acute experimental silicosis in mice has demonstrated that increases in cytokine expression contribute to the complex pathways of lung injury, inflammation and eventual fibrosis. Orfila and colleagues showed that after a single intratracheal instillation of silica, the number of macrophages recovered from murine BAL fluid confirmed an acute inflammatory reaction that was followed by interstitial granulomas (Orfila et al., 1998). The immuno-histochemical analyses of lung tissue sections showed increased alveolar and interstitial expression of the TNF-alpha and IL-1-beta cytokines.

IFN-gamma is a lymphocyte cytokine responsible mostly for activating macrophages. In a short term heavy inhalation study, mice exposed to an aerosol of cristobalite silica for 5 hours daily ($70mg/m^3$ for 12 days) produced significantly more IFN-gamma mRNA in the lung than controls (Davis et al., 1999). Treated mice developed diffuse pulmonary pathologic changes with macrophage, lymphocyte and neutrophil recruitment and increased lung collagen. Similar cytokine patterns were seen in mediastinal lymph node and spleen tissues, suggesting that silicosis in mice after cristobalite exposure involves a lymphocyte-mediated immune inflammatory response in both the lung and lymph tissue (Davis et al., 1999).

Interleukin-10 (IL-10) is thought to be an anti-inflammatory cytokine (Huaux et al., 1998). To provide a model of pulmonary inflammation, female NMRI mice were treated with intratracheal instillation of silica (0.5 mg or 5mg of DQ12 silica/mouse) or saline (Huaux et al., 1998). Twenty four hours after instillation, IL-10 levels in lung tissue homogenate and BAL cells were found to be dependent on silica dose. Inflammatory and fibrotic effects were also examined in IL-10 deficient mice after instillation with 5mg DQ12 silica (Huaux et al., 1998). After 24 hours, LDH, total protein content and total cells were most elevated in IL-10 deficient mice, compared to wild type breeds. However 30 days later, lung hydroxyproline content and histopathologic analyses showed that the fibrotic response was reduced in the IL-10 deficient mice. This study suggests that although silica acts to increase the synthesis of IL-10 which limits the inflammatory response, IL-10 also contributes to the fibrotic process (Huaux et al., 1998).

Inbred strains of mice were exposed to a respirable aerosol of cristobalite (70mg/m3, 5 hours a day, for 12 days) and developed silicosis some months later (Davis et al., 2001). They exhibited accumulated lymphocytes in alveolar spaces, lung parenchymal lesions and nodules, and in enlarged bronchial-associated lymphoid tissues and thoracic lymph nodes. Lung lymphocytes were mostly made up of T-helper cells (CD4+ type). An increase in IFN-gamma production was observed, and was thought to be T-helper cell activated. In the silicotic lung tissue, mRNA transcripts for macrophage derived cytokines IL-12 and -18 were increased. Mice without the IFN-gamma gene developed less extensive silicosis and less lung collagen accumulation than the wild type after exposure to the same dose of respirable cristobalite. The authors propose a reiterative process of cytokine production, whereby macrophages containing silica particles induce cytokine synthesis (namely IL-12 and -18), which attract and activate lymphocytes (Davis et al., 2001). These in turn produce additional mediators that attract and activate a secondary population of macrophages, and so cytokine production continues.

Silica-induced pulmonary inflammation is associated with Nuclear Factor (NF)-kappa B, which is a multiprotein complex believed to regulate inflammatory cytokines involved in the initiation and progression of silicosis (Sacks et al., 1998). Male F344 rats were intratracheally instilled with

100mg/kg silica in 1mL/kg of saline or 1mL/kg of saline only (Sacks et al., 1998). Increased chemiluminescence indicated significant ROS production in BAL cells from silica-treated animals, one day after instillation. After 3 days, NF-kappa B production was detected in silica-treated animals. Treatment with anti-inflammatory steroid (5mg/kg dexamethasone) resulted in a 70% reduction of NF-kappa B expression after 3 hours, and chemiluminescence , BAL neutrophils and BAL cell counts were also reduced.

Transforming growth factor-β1 (TGF-β1) plays a major role in metabolic activities, cell growth and differentiation, and inflammation and tissue repair (Williams et al., 1995). It can stimulate human and rodent fibroblasts to promote the formation of collagen and connective tissues, and is present in many human and animal tissues, both benign and malignant. Williams and Saffioti suggested roles for TGF-β1 in the production of silica-induced lesions in the lung after a single intratracheal dose of 12 mg of Min-U-Sil 5 in male and female F344/NCr rats (Williams et al., 1996). TGF-β1 was localised intra-cellularly in fibroblasts and macrophages at the periphery of silicotic granulomas, indicating a requirement for TGF-β1 for their progressive repair and healing. Extra-cellular TGF-β1 was localised in the connective tissue matrix adjacent to hyperplastic alveolar type II cells and probably assisted in the deposition of collagen and extracellular matrix, as a substrate for repeated cycles of epithelial proliferation. Many of the rats examined after 60 days had developed malignancies in alveolar type II cells, which were thought to be caused by clonal outgrowth during the active epithelial proliferation, or the escape of cells from the regulatory effects of TGF-β1.

The importance of oxidative stress in the generation of cytokine and chemokines by alveolar macrophages during the development of silicosis was examined in mouse peritoneal macrophage cell lines (RAW 264.7) exposed to cristobalite (Barrett et al., 1999). Macrophage responses to 35 micrograms/cm^2 of cristobalite were mediated by the presence of antioxidants and various modifiers of cell antioxidant status. Treatment with dimethyl sulfoxide (DMSO), extracellular glutathione (GSH) or N-acetyl-L-cysteine (NAC) antioxidants decreased cristobalite-induced TNF mRNA levels by 40%, 20% and 42% respectively. Cristobalite-induced macrophage inflammatory protein mRNA levels were reduced by 52%, 38% and 57% with DMSO, GSH and NAC treatment respectively. These results suggest that oxidative stress increases cytokine and chemokine expression in alveolar macrophages exposed to cristobalite (Barrett et al., 1999).

The involvement of reactive oxygen species in silica-induced inflammation and NF-kappa B production was demonstrated by Kang and colleagues, using the same murine model (Kang et al., 2000). Using RAW264.7 cells *in-vitro,* exposure to 100micrograms/mL of silica resulted in a doubling of ROS production and caused the activation of NF-kappa B. The addition of hydrogen peroxide enhanced NF-kappa B binding with DNA. NF-kappa B activation was inhibited by the addition of antioxidants including superoxide dismutase, alpha-tocopherol and N-acetylcysteine.

4.3.7 Nitric Oxide

Nitric oxide (NO) and its more reactive product per-oxynitrite may be important mediators of inflammation, including granuloma formation in the lung. NO has been associated with lung inflammation following exposure to silica (Blackford et al., 1997). Rats were intratracheally instilled with 5 mg/100 g body weight of silica, coal, carbonyl iron, or titanium dioxide, with dust particles averaging less than 5 micrometers in diameter (Blackford et al., 1997). Broncho-alveolar lavage was performed 24 h later. When exposure was adjusted for an equal

number of particles, the pneumotoxic dusts, silica and coal, caused more inflammation and NO production than the nuisance dusts, carbonyl iron and titanium dioxide.

The amino acid, L-arginine may be involved in the production of NO during the pulmonary inflammatory response. Twenty-four hours after instillation of silica into the lungs of rats, lung inflammatory cells were shown to increase L-arginine uptake compared to saline controls (Schapira et al., 1998). Isolated cells showed that greater L-arginine uptake was associated with greater NO and urea production. The addition of L-arginine to isolated cells from silica-treated animals resulted in a dose-dependent increase in the production of NO and urea.

Increased NO production in rat BAL fluid after silica exposure *in-vivo* was confirmed by Huffman and colleagues (Huffman et al., 1998). However, they also conducted *in-vitro* tests on normal rat BAL cells and found that after silica treatment (0.1-100 micrograms/mL) there were no changes in basal NO levels. *In-vitro* NO generation could not be increased by interferon gamma or other cytokines before, after or during silica treatment. As alveolar macrophages in BAL fluid increased NO production after silica treatment *in-vivo* and the *in-vitro* experiments did not, it appears that cell-cell communication factors are necessary for the induction of NO by alveolar macrophages (Huffman et al., 1998).

4.3.8 Cell-cell Communication

The Intercellular Adhesion Molecule (ICAM-1) is expressed on several cells, including endothelial cells, alveolar epithelial cells and alveolar macrophages. Endothelial and epithelial cell ICAM-1 acts in the migration of leukocytes out of the blood, in response to pulmonary inflammation. Nario and colleagues showed that in mice intratracheally injected with silica, ICAM-1 significantly increased after 24 hours and aggregated with pulmonary macrophages and type II epithelial cells (Nario et al., 1997). Areas of the lung with increased ICAM-1 exhibited increased TNF-alpha expression. Immuno-cytochemical staining of BAL cells showed increased ICAM-1 expression in alveolar macrophages at days 3, 5 and 7, after exposure to silica.

4.3.9 Apoptosis

Apoptosis or programmed cell death has been induced with intratracheally distilled doses of Min-U-Sil 5 silica in male Wistar rats (Leigh et al., 1997b). The number of apoptotic cells identified in BAL fluid ten days after instillation were clearly related to increasing silica dosage. Apoptotic cells were identified in granulomatous cells from lung tissues fifty-six days after instillation. The authors concluded that apoptosis is likely to be involved in the silica-induced inflammatory response after both acute and long term exposures (Leigh et al., 1997b). BAL apoptotic cells were also shown to be significantly greater in Sprague-Dawley rats treated with 10, 20 or 40 mg silica/kg, one week after intratracheal installation (Lim et al., 1999).

4.3.10 Carcinogenicity and Genotoxicity

Crystalline silica was first classified as a carcinogen in experimental animals by IARC in 1987 (IARC, 1987). This was confirmed in their review of all available animal data again in 1996, with the conclusion that there was sufficient evidence in experimental animals for the carcinogenicity of the quartz and cristobalite forms of crystalline silica (IARC, 1997b).

Acute, subchronic and chronic exposure studies have shown significant increases in the incidence of adenocarcinomas and squamous cell carcinomas of the lung accompanied by pulmonary fibrosis, in rats exposed to silica by inhalation or intratracheal instillation (IARC, 1997b). Thoracic and abdominal malignant lymphomas have been found in studies of rats undergoing single intrapleural or intraperitoneal injections with quartz (IARC, 1997b). One study using a relatively low silica dose exposed SPF F344 rats by inhalation to DQ12 quartz at 1mg/m^3, 6 hours/day, 5 days/week, for 24 months (Muhle et al., 1995). Six weeks after exposure finished, there was a significant increase in the incidence of primary lung cancers in quartz-treated animals compared with those exposed to 5 mg/m^3 of titanium dioxide or air only (Muhle et al., 1995).

Differences in tumour incidences after silica exposure have been noted between some species. Quartz has been established as carcinogenic to rats, but few or no malignant tumours have been associated with silica exposure in studies involving mice and hamsters (Donaldson et al., 1998). Differences between rats and hamsters in their molecular responses to quartz exposure were recently demonstrated in a study that examined molecular mechanisms of induction and protection against tumorigenesis after silica exposure (Seiler et al., 2001b). Female Wistar rats and female Chinese hamsters were exposed to either 0.3 or 1.2 mg/100g body weight of D12 quartz, via intratracheal installation. Pulmonary inflammation (neutrophil recruitment, TNF), toxicity (8-oxoguanine, p53) and cell proliferation was examined in BAL fluid and lung tissue, 90 days later. Rats exhibited significantly higher responses that hamsters after quartz exposure, for all of these parameters.

The rat model is thought the best available for studying the potential carcinogenicity of silica in humans, as it displays some of the carcinogenic responses seen in human studies (Donaldson et al., 1998). Several mechanisms have been proposed for silica induced carcinogenesis, making the classification of silica as a carcinogen eminently biologically plausible.

Gene mutations were reportedly first experimentally observed after a crystalline silica dose in female F344 rats by Driscoll and colleagues (Driscoll et al., 1995). Seven months after intratracheal instillation with 100 mg/kg body weight of α-quartz, a significant increase in the hypoxanthine-guanine phosphoribosyl transferase (hprt) gene was observed in the alveolar type II cells. Leigh and colleagues intratracheally instilled male Wistar rats with relatively low doses crystalline silica (0.025mg, 0.25mg and 2.5mg Min-U-Sil 5) and observed dose-dependent elevations in micronuclei numbers in the alveolar macrophages, five days later (Leigh et al., 2000). Liu and colleagues treated Chinese hamster lung fibroblasts (V79 cells) with respirable silica particles *in-vitro,* which also induced micronuclei formation in a dose-dependant manner (Liu et al., 1996).

Zhang and colleagues subjected rat alveolar macrophages to silica *in-vitro* and noted cytotoxic and genotoxic effects via LDH leakage and DNA migration, respectively (Zhang et al., 2000). A dose- and time-dependent relationship between silica and LDH and DNA migration was noted in addition to increases in hydrogen peroxide and ROS production by macrophages. Superoxide dismutase and catalase antioxidants were able to reduce all of these effects.

DNA damage detected by single cell/comet assay was demonstrated in cultured Chinese hamster lung fibroblasts and human embryonic lung fibroblasts (Zhong et al., 1997). Both cell types were exposed to crystalline silica (Min-U-Sil 5), amorphous silica (Spherisorb), carbon black or glass fibres (AAA-10) for 3 hours, at various concentrations. In both cell types, almost all concentrations of crystalline silica and glass fibres resulted in significant increases in DNA

migration measured by tail length. Increases in DNA migration were greatest after crystalline silica treatment of hamster lung fibroblasts. Amorphous silica treatment also caused increases in tail lengths, but not to the same degree as crystalline silica. These results show that crystalline silica, glass fibres and amorphous silica may induce DNA damaging activity in mammalian cells, and that crystalline silica has greater DNA damaging potential than amorphous silica or glass fibres (Zhong et al., 1997).

Electron-microscopy studies of fetal rat lung alveolar type II cells treated with Min-U-Sil 5 or Chinese standard α-quartz have lead to the theory that silica particles are capable of binding to DNA through hydrogen bonding between surface silanol groups and the phosphate-sugar backbone of DNA (Daniel et al., 1995, Saffiotti et al., 1994). Silica-induced DNA strand breakage may occur through the formation of ROS on the silica surface. The anchorage of DNA to crystalline silica allows short-lived free radicals to reach DNA bases and cause damage crucial for mutagenesis, neoplastic cell transformation, and carcinogenesis. It is thought that this union may also lead to DNA damage through interference with the replication, repair or expression of DNA, or by altering normal mitotic processes (Daniel et al., 1995).

Seiler and colleagues recently examined ROS production as a marker of inflammation, and cellular levels of p53 mutant protein as a marker of DNA damage in rat BAL fluid (Seiler et al., 2001c). Rats were treated via intratracheal instillation with either 0.3, 1.5, or 7.5 mg/rat of quartz, or the same amount of corundum as a control dose. BAL fluid was assessed at 7, 21 and 90 days after exposure. Corundum had no adverse effects, except a slightly increased level of 8-oxoguanine (induced by ROS production associated with inflammation) at the 7.5 mg/rat dose. Quartz exposure lead to a linear dose-response in inflammation, but not in oxidative DNA damage and mutagenicity. In quartz-treated rats, the level of 8-oxoguanine was significantly elevated at 1.5 and 7.5 mg/rat doses. Increased p53 mutant protein (indicating DNA damage) were observed at all time points after the instillation of quartz at the highest dose (7.5mg/rat) only.

In another of their studies, Seiler and colleagues examined the effect of different doses of D12 quartz (0.15, 0.3, 0.6, 1.2, 2.4 mg/rat) via intratracheal instillation, and examined BAL fluid 21 and 90 days after exposure (Seiler et al., 2001a). Surfactant phospholipids in BAL were measured as indicators of fibrotic processes in the lung, and 8-oxoguanine was measured as an indicator of DNA oxidation in rat lung cells. Levels of phospholipids increased in a dose-dependent fashion, and 8-oxoguanine was significantly increased after 1.2 and 2.4 mg/quartz/rat. Indicators of DNA mutagenicity were increased at 1.2 and 2.4 mg/quartz/rat (p53 protein) and 2.4 mg/quartz/rat (p53 mutant protein). The authors concluded that there was a no-effect level for mutagenicity at a low, but fibrogenic level of quartz exposure.

Shukla and colleagues suggested that "silica may act mechanistically as a mitogen or tumor promotor, rather than a genotoxic carcinogen in the development of lung cancer" (Shukla et al., 2001). After treating murine alveolar epithelial type II cell lines (C10) with alpha-quartz concentrations of either 10 or 20 ug/cm^2, dose-related increases in phosphorylated c-Jun-NH_2-terminal amino kinases (JNK's) were observed using Western blot assays. Phosphorylation of JNK proteins may cause the activation of transcription factors that interact with regulatory domains in the promoter regions of genes integral to proliferation, apoptosis or inflammation responses.

4.4 Toxic Effects in Humans

Evidence of non-malignant and malignant biological effects from crystalline silica in humans has mostly been provided by epidemiological studies, which are reviewed in the next chapter.

4.4.1 Fibrosis

Silica may modify extracellular matrix (ECM) synthesis by acting directly on lung fibroblasts. Human lung fibroblast cell lines (WI-1003) were exposed to 50ug/mL of crystalline silica (1-5 um in diameter) for 24 hours, and ECM synthesis and cytokine production was examined (Baroni et al., 2001). Silica exposure stimulated collagen synthesis, but down regulated fibroblasts production of TGF-β (a modulator of fibroblast replication), thus reversing TGF-β induced cell proliferation.

Alveolar macrophages from non-smoking individuals with silicosis have been shown to spontaneously release significantly large amounts of superoxide and hydrogen peroxide in comparison to healthy controls (Rom et al., 1987). In addition to these oxidants, there was spontaneous release of increased amounts of fibronectin and macrophage-derived growth factors, which act to stimulate fibroblast replication and contribute to the fibrogenic process (Rom et al., 1987).

The metabolism of arachidonic acid modulates the inflammatory process and is increased in alveolar macrophages after silica exposure. Macrophages from healthy volunteers were incubated for 3 or 24 hours with 60 or 100 microgram/mL of silica (Koren et al., 1992). There was an increased release of arachidonic acid metabolites including leukotriene B4, leukotrienes C4/D4/E4 and 5-hydroxy-eicosatetraenoic acid (which act as pro-inflammatory agents) after 3 hours, and decreases in the production of prostaglandin E2 and thromboxane B2 after 24 hours of exposure to 100 microgram/mL (Koren et al., 1992).

The apoptosis of alveolar macrophages is believed to be an important event in particle-induced inflammation and consequent fibrosis, and the fibrogenicity of dust may depend on its ability to induce apoptosis (Iyer et al., 1996). Iyer and colleagues demonstrated the apoptotic potential of silica by treating human alveolar macrophages with silica (133microgram/mL), amorphous silica (80microgram/mL) and titanium dioxide (60 micrograms/mL) for either 6 or 24 hours (Iyer et al., 1996). Treatment with silica resulted in enhanced DNA fragmentation (characteristic of programmed cell death) as well as significant cell death. Apoptosis was not demonstrated in cells treated with amorphous silica or titanium dioxide. Lim and colleagues also induced apoptosis in human alveolar epithelial cell lines (A549) treated with silica (10 and 50 micrograms per cm2) (Lim et al., 1999).

Cytokine production by human alveolar macrophages was examined after exposure to crystalline silica (Hamilton et al., 2001). After exposure for 24 hours, silica exposure upregulated IFN-gamma and IL-4 production. The authors concluded that, because silica demonstrated selective toxicity to suppressor macrophages, activator macrophages were free to enhance antigen-presenting cell activity and increase lymphocyte-derived proinflammatory cytokine production (Hamilton et al., 2001).

4.4.2 Carcinogenesis

Human alveolar type II cells are known to proliferate in response to silica-induced lung injury. Melloni and colleagues incubated human alveolar macrophages collected from the BAL fluid of non-smokers without histories of dust exposure in increasing concentrations of Min-U-Sil 5 for 24 hours (10, 25, 50, 100, 500 and 1000 micrograms/mL) (Melloni et al., 1996). Cytotoxicity was evident at high doses, with LDH release significantly higher in cells treated with 100, 500 and 1000 microgram/mL of silica compared to lower doses and controls. A linear relationship was found between dust concentration and the percentage of adherent macrophages containing silica particles at 25, 50 and 100 micrograms/mL silica.

Silica-stimulated human alveolar macrophages are capable of releasing mitogens that induce the proliferation of type II epithelial cells (Melloni et al., 1996). This was demonstrated using fetal rat lung type II cells treated with supernatant from silica-stimulated (50 microgram/mL Min-U-Sil 5, for 24 hours) human alveolar macrophages. Type II cell DNA synthesis and cell number was significantly increased. Molecules similar to IGF, fibroblast-derived growth factor, and platelet-derived growth factor were released by the silica-stimulated human alveolar macrophages, and these are thought to be involved in epithelial repair and type II cell hyperplasia (Melloni et al., 1996).

4.4.3 Genotoxicity

Few *in-vitro* studies using human cells have conclusively demonstrated direct genotoxic effects from crystalline silica (IARC, 1997b). Nagalakshmi and colleagues treated human embryonic lung (Hel 299) cells and hamster lung fibroblasts (V79) with Min-U-Sil 5 and Min-U-Sil 10 for 24 hours, at concentrations of 40, 80,160 and 320 micrograms/cm^2 (Nagalakshmi et al., 1995). In human cells, micronucleus formation was induced by 160 and 320 microgram/cm^2 concentrations of both Min-U-Sils. In hamster cells, induced micronuclei formation was evident at all doses. This showed that *in-vitro*, differing crystalline silica particle sizes are capable of inducing micronuclei, although cultured animal cells appear more sensitive to silica than cultured human cells (Nagalakshmi et al., 1995).

DNA damage was detected in human embryonic lung fibroblasts after exposure to crystalline silica (Min-U-Sil 5) and amorphous silica (Spherisorb) at various concentrations (Zhong et al., 1997). Significant increases in DNA migration measured by comet assay (single-cell gel electrophoresis) were noted at almost all concentrations of crystalline silica exposure however, crystalline silica caused greater increases in tail lengths compared with amorphous silica.

The production of ROS by human polymorphonuclear leukocytes was demonstrated *in-vitro*, by Koskela and colleagues, using different density fractions of grey, red and black granite (Koskela et al., 1994). The strongest ROS production was seen for red granite (70% quartz; 64-74% of particles < 10 micrometers in diameter) and grey granite (>75% quartz; 59-76% of particles < 10 micrometers in diameter). They estimated that the effects from 100 microgram/mL of granite-dust fractions corresponded to ROS production induced by 25-50ug/ml of purified DQ-quartz (Koskela et al., 1994).

4.4.4 Auto-immune Disease

Haustein and colleagues treated human dermal microvascular endothelial cells (HDME cells), peripheral mononuclear cells (pre-cursors of macrophages), and dermal fibroblasts, with DQ12 silica (aerodynamic diameter < 5 micrometres) *in-vitro* (Haustein et al., 1998). Silica induced an increase in expression of ICAM-1 by HDME cells, which is thought to enhance adhesion of mononuclear blood cells to the microvascular wall, an important site for the development of connective tissue disease. In turn, mononuclear cells phagocytosed the silica particles. Collagenase activity appeared to be increased in treated HDME and dermal fibroblasts, which may have caused the escape of monocytes into surrounding tissue. A combination of these observed effects in the three cell types may be responsible for the inflammatory infiltration of mononuclear cells around microvessels that has been shown to occur in idiopathic and silica-induced systemic sclerosis (Haustein et al., 1998).

5.0 EPIDEMIOLOGY

Of the hundreds of epidemiological studies on the health effects of crystalline silica, very few support quantifiable risk assessments or the determination of dose-response relationships. Nevertheless, epidemiological studies provide the most important information for standard setting. The majority of studies have been conducted using occupational cohorts and their historical exposure estimates. Here we describe the current body of evidence and review the quantitative studies critical for the development of an occupational exposure standard in Australia, ie. those that appear the least confounded, and report quantitative crystalline silica exposures and risk estimates. All epidemiological studies (included and excluded) considered for this review are tabulated at the end of this chapter.

5.1 Chronic Obstructive Pulmonary Disease

Occupational exposure to dust containing respirable crystalline silica is associated with bronchitis, emphysema and other obstructive airway diseases ((IPCS), 1999). Although these health effects are most often associated with tobacco smoking, they may be present to a significant extent in non-smokers with occupational exposure to quartz. Evidence for this has been derived from studies of workers exposed to crystalline silica who do not have silicosis. Impaired pulmonary function in granite workers (Malmberg et al., 1993, Theriault et al., 1974), hard rock miners (Kreiss et al., 1989), gold miners (Cowie et al., 1991, Holman et al., 1987, Irwig et al., 1978), construction workers (Ulvestad et al., 2001), brick refractory workers (Myers et al., 1989) and foundry workers (Wang et al., 1997) has been associated with occupational crystalline silica exposures, as has emphysema and chronic bronchitis in gold miners (Becklake et al., 1987, Hnizdo et al., 1991b, Reid et al., 1996, Sluis-Cremer et al., 1967). A synergistic effect between tobacco smoking and crystalline silica exposure on mortality from COPD has been demonstrated in studies of South African gold miners (Hnizdo, 1990).

There is good evidence that exposure to any occupational dust can cause chronic bronchitis and clinically important losses of lung function in both smokers and non smokers, and that dust exposure can exacerbate COPD in smokers (Oxman et al., 1993). The impairment of respiratory function in workers may therefore be a more important cause of disability for prevention than the development of fibrosis (Cowie et al., 1991, Wang et al., 1997). However, existing studies may underestimate the effect of occupational dust exposure on lung function, because of exposure sampling errors and biases (Oxman et al., 1993). It may also be that the measurement of the respirable fraction of dust is inappropriate for examining airway responses, since *dust* deposition in the conducting airways is probably responsible for the airway effects measured by FEV_1.

It has been argued that there is inconsistent evidence of a dose-response relationship between crystalline silica exposure and COPD, and that the impact of silica exposure is likely to be less than that of smoking, therefore COPD is unlikely in the absence of either smoking or asthma (Hendrick, 1996, Tsai et al., 1996). The American Thoracic Society takes this view, stating that chronic bronchitis resulting from silica (or other dust exposure) is difficult to clinically distinguish from that caused by tobacco smoking (ATS, 1997). However, they support the possibility that in the absence of radiological evidence of silicosis, chronic airflow limitation and/or mucus hyper-secretion (ie. bronchitis), and/or pathological emphysema may still manifest

at low doses of exposure. In the German MAK Document, there is no consideration of COPD resulting from crystalline silica exposure (Deutsche Forschungsgemeinschaft), 2000).

In a recent review for the Silica Coalition (a group of scientists representing trade associations and individual companies), Gibbs and colleagues claimed that decrements in pulmonary function are not associated with silica exposure in persons with radiological changes of category 1/1 or less (Gibbs et al., 1999). Although they acknowledge that silica-workers do not die because of opacities on the radiograph but because of the associated reduction in ventilatory capacity, they assert that clinically important (obstructive airways) disease is absent in persons with radiological changes below ILO classification 1/1 with small round opacities, and that disabling lung disease due to silica exposure is only that which progresses beyond this level. Based upon evidence from the British Coal Industry, they believe there is no risk of premature death in persons with radiological changes below this category. While ignoring the majority of silica-exposed workers who receive greater crystalline silica exposures than those in the coal industry, this also ignores the pathological differences between coal worker's pneumoconiosis and silicosis. They continued that it may not be possible to determine if observed lung function changes are due to silica exposure, associated total dust exposure, or tobacco smoking. In conclusion, they state that the monitoring of pulmonary function over time is inappropriate for studying the health effects of silica or for defining acceptable airborne silica levels, and that the level of silica exposure which prevents radiographic silicosis (ie. category 1/1 round opacities) is likely to be acceptable for the prevention of obstructive airways disease due to airborne silica dust (Gibbs et al., 1999). This argument is similar to that put forward in this review concerning setting a standard for protection against lung cancer. However, the arguments presented here do not invalidate an association between silica (or any dust) exposure and decline in lung function. It could also be argued that the effects of silica or total dust exposure are proportionately and biologically greater in workers whose lung function is already impaired by other exposures, eg. cigarette smoke.

5.2 Quantitative Studies of Chronic Obstructive Pulmonary Disease

5.2.1 Granite Workers

The effects of chronic exposure to granite dust on FEV_1 were assessed in 618 white male granite workers in Vermont aged 25-65 years, who participated in a medical monitoring survey in 1970 and were then followed for 5 years (Eisen et al., 1995). Subjects who had previously worked in other dusty trades and those who had worked in the industry prior to dust controls were excluded. Cumulative cigarette smoking was calculated as pack-years however, only for those who were smokers at the time of the survey.

The quartz levels of Vermont granite are believed to be approximately 11%. Personal size-selective air monitors were worn for a full shift by a sample of workers representing each job in the industry during several industrial hygiene surveys conducted between 1970 and 1976. A healthy worker effect was demonstrated in the 315 subjects (mean age 39 years) followed up for the entire 5 years, where no association was found between the rate of FEV_1 decline and lifetime silica exposure. However, the remaining 265 workers (mean age 41 years) with incomplete follow up had lower FEV_1 at baseline and demonstrated a significant dose-response relationship between lifetime dust exposure and decline in FEV_1. Excessive rates of decline in FEV_1 were shown in the first longitudinal analysis of lung function in the Vermont granite workers (Musk et al., 1977). However, a variety of alternative explanations for the finding have been postulated, and the spirometry data have been reviewed by others until the effect was successfully removed.

A survey of pulmonary function in the granite workers of Vermont was conducted in 1971, on 792 workers with an average age of 44 years (Theriault et al., 1974). Cumulative total granite dust exposures were measured as above, and adjustments were made for smoking (as cigarettes per day and years smoked), age and height. Total granite and respirable quartz exposure were examined separately, and both were found to be significantly associated with lower FVC, FEV_1 and TLC, with a slightly greater effect from granite than quartz. Multiple regression analyses indicated a dose-response relationship between quartz exposure and FVC. The authors concluded with the recommendation that an individual TLV for mass respirable quartz dust was warranted.

5.2.2 Gold Miners

There have been several publications on South African gold miners. Hnizdo and colleagues followed up a cohort of 2209 white gold miners who were aged 45-54 years when they underwent pulmonary function tests and compulsory medical examinations at the Medical Bureau for Occupational Diseases between 1968 and 1971. Subjects also had underground gold mining service of at least 10 years, had less than two years of service in other mines, and were residents of South Africa for at least 20 years (Hnizdo, 1992, Hnizdo et al., 1990). Pulmonary function tests were repeated on average, 4.9 years later.

Exposures commenced between 1936 and 1943 and included 30% crystalline silica in 60-80% of rock, radon daughters, and diesel fumes. Miners' occupations were categorised into 11 groups, for which dust counts were available from underground mines. Dust counts were collected by thermal precipitator and after acid treatment, produced average surface area for respirable dust particles < 5 μm (RSA). These exposure assessments may have under-estimated earlier exposures, as the dust counts were not made until the 1960's, much later than when subjects first commenced their jobs. A smoking questionnaire was administered at survey and responses were checked against smoking records kept by the Medical Bureau of Occupational Diseases. Smoking was assessed in three ways; as a categorical variable, an ordinal variable, and as pack-years (Hnizdo et al., 1990).

The cross-sectional pulmonary function data were analysed in 1990 according to dust particle-years (Hnizdo et al., 1990). Exposures were later converted into mass respirable dust (MRD) using the equation, $MRD = 0.027 \times (RSA)^{0.474}$ (Hnizdo, 1992). In 1992, both the cross-sectional and longitudinal pulmonary function data were re-analysed using exposures to cumulative respirable silica dust in gram hours/m^3 (ghm^{-3}) (Hnizdo, 1992). For this analysis, ex-smokers (n=426) were excluded because of their varied smoking habits, and those producing unsatisfactory pulmonary function tests (n=158) were excluded, leaving 1625 miners. Seventy seven percent of this number (n=1249) provided follow up pulmonary function tests (56% of the original cohort). Cumulative silica exposure was not significantly associated with longitudinal loss of FEV_1 or FVC when initial FEV_1 and FVC were included in the models. Cigarette pack-years and initial FEV_1 were associated with decline in FEV_1 and FVC. The excess deficit in pulmonary function for a 50 year old gold miner associated with 24 years of underground dust exposure of 0.30 mg/m^3 (14.4 ghm^{-3}) was estimated as 236 mL of FEV_1 (95 % CI, 134-337) and 217 mL of FVC (95% CI, 110-324) (Hnizdo, 1992). The contribution of smoking was greater than that of dust, and smoking one packet of cigarettes per day over 30 years was associated with a deficit of 552 mL of FEV_1 (95% CI, 461-644) and 335 mL of FVC (95% CI, 170-500).

Oxman and Hnizdo then re-analysed this cohort as part of a review of occupational dust exposure, and COPD mortality and morbidity in gold miners and coal miners (Oxman et al.,

1993). After adjusting for smoking, the risk of clinically important loss of lung function attributable to dust in the gold miners was significantly greater than that of coal workers (odds ratio 4.9 versus 1.5), even though cumulative respirable dust exposures were less, inferring the importance of gold miners' greater quartz exposures, or possibly reflecting a different size distribution of coal dust cloud. Emphysema at autopsy or mortality from COPD was also significantly related to cumulative respirable dust exposure, but in smokers only. However, there were only four non-smokers out of the 505 emphysema cases, and all 66 men who died from COPD were smokers (Oxman et al., 1993).

5.2.3 Hard Rock Miners

Kreiss and colleagues conducted a community prevalence survey of men who were miners and non-miners living in Leadville Colorado, a single industry hard rock mining town (Kreiss et al., 1989). Out of all eligible males aged 20 years or more (569), a random sample of 383 male participants (67%) was obtained. Two hundred and forty seven (43%) had worked at the local molybdenum (hard rock) mine. Non-participants were older, and many of these had left the town due to the mine's impending closure.

Information on respiratory symptoms and occupational history were collected, and spirometric and plethysmographic measurements of lung volume and airflow were made. Dosimeter sampling of respirable dust commenced in the 1940's. The average silica content of these samples was 19% (standard deviation, 11%). Personal samples of respirable dust were available for 26 different job titles. For the period of 1977 to 1981, 27 % these exceeded 0.1mg/m^3, and 49% of personal samples exceeded 0.05 mg/m^3. A cumulative dust exposure index was created for each subject by summing estimated exposure for each job title, weighted by months in that job. The relative dustiness of 371 jobs was ranked on a scale of 1 to 4 by a panel of experts, including an industrial hygienist and a director of health and safety previously employed at the mine. The spearman rank correlation between historic dust samples available for 26 job titles and their subjective dustiness score was 0.82. Job titles were allocated dust exposures as the average of more than five personal samples for that job. For jobs with less than five samples available, the mean of all measurements available for jobs of the same dust score was used.

Cumulative respirable dust exposure was associated with decreases in maximal expiratory flow rates after controlling for age, pack-years of smoking, current smoking category, and height. Deficits in FEV_1, FEV_1/FVC and TLC were significantly associated with increasing cumulative dust exposure. In never smokers, respirable dust exposure was associated with decreased lung volume, increased flow rates and increased single breath carbon monoxide diffusing capacity/alveolar volume (DLCO/VA). In smokers, respirable dust exposure was associated with increased lung volume, lower flow rates and lower DLCO/VA than that accounted for by smoking.

5.2.4 Construction Workers

Ulvestad and colleagues examined lung function decline and cumulative exposure to respirable silica in tunnellers and heavy construction workers who worked in any of 15 construction sites in Norway between 1991 and 1999 (Ulvestad et al., 2001). All workers from the 15 sites were invited to participate in a survey including a respiratory symptoms questionnaire, spirometry and a chest xray. A response rate was not shown, but 417 agreed to be surveyed in 1991, and 375 of

these were resurveyed in 1999. Workers aged over 55 years of age in 1991 (n=20) were excluded from the study as they would have retired (compulsory at age 63) before the follow up survey in 1999. Workers with COPD or asthma evident at the 1991 survey were also excluded (n=15). An additional 37 workers were lost to follow up (9% of the original cohort). Of the 375 resurveyed, 96 were tunnel workers, 178 were outdoor heavy construction workers and 71 were white collar employees (engineers and foremen).

Personal samplers worn by 193 participants in 15 sites between 1996 and 1999 collected exposure information on respirable dust, respirable silica, and NO_2 gas. Current job information was collected from each participant at baseline, but previous working histories were not determined. Exposure levels associated with each job were assumed to be constant between surveys, as was each subject's job. Pneumoconiosis was excluded in all but one participant who had pleural plaques. Smoking was assessed as never smoked, current smoker, or previous smoker, and pack-years were calculated at the final survey.

Tunnellers experienced moderate exposures to NO_2 (mean of 0.8 ppm, compared with Norway's OEL of 2.0 ppm) and cumulative respirable silica (mean 0.35 mg/m^3-year). Other workers experienced less than detectable (presumed equivalent to ambient air) concentrations of NO_2, and a mean cumulative respirable silica exposure of 0.029 mg/m^3-year. NO_2 exposure was highly correlated with respirable silica exposure (r=0.95). The authors stated that "cumulative exposure to NO_2 was a significant variable when tested alone" however they excluded it from the multiple regression model for change in lung function, and included cumulative respirable silica exposure and cumulative respirable dust exposure. Decrease in FEV_1 was significantly associated with cumulative exposure to respirable silica (271 mL/mg/m^3-year, p=0.02) and respirable dust (10 mL/mg/m^3-year, p<0.001). The annual decrease in FEV_1 for a non-smoking, 40 year old tunneller would be 50-63 mL, compared to a non-exposed non-smoker's decrease in FEV_1 of 25mL.

5.2.5 Brick Refractory Workers

In a cross-sectional survey of black manual workers from brick works near Capetown South Africa, pulmonary function was compared to cumulative respirable dust exposure measured by personal samplers using the Casella instrument (Myers et al., 1989). A modified version of the American Thoracic society respiratory questionnaire was used to collect occupational histories, subjective levels of dustiness for jobs, smoking habits, and respiratory symptoms. The total workforce was originally surveyed (n=575) however, ex-smokers, women, those with unsatisfactory spirometry tests, and those previously exposed to silica dust in the workplace for more than 2 years were excluded, leaving 268 subjects for analysis.

Respiratory symptoms could be predicted by category of smoking habit and exposure to respirable dust. Multiple regression analysis adjusting for age and height showed a dose-response relationship between cumulative respirable dust exposure and FVC and FEV_1. FVC was lower by 0.22 mL per log (mg/m^3) and FEV1 was lower by 0.18mL per log (mg/m^3). An unusual finding was that there was no apparent effect of smoking on pulmonary function in this analysis. The subject sample was noted for being particularly young (53% aged less than 30 years), having a short duration of employment, and being predominantly migrant (88%).

5.3 Silicosis

Silicosis results from the deposition of respirable dust containing crystalline silica in the gas-exchanging regions of the lungs. The prevalence of silicosis increases with increasing exposure to crystalline silica. Chronic silicosis is known to occur after long term exposure to crystalline silica (10 or more years). Accelerated silicosis can develop within 5 to 10 years after the first exposure. Acute silicosis is associated with high exposures to respirable crystalline silica (especially associated with sandblasting and rock drilling occupations) and symptoms may develop within a few weeks, or up to 4-5 years later.

Variations in study results and controversies surrounding the precise quantitative exposure-response relationship between respirable crystalline silica and silicosis are mainly due to uncertainties in exposure measurements, definitions of 'respirable dust', the latency of the disease process, variations in the criteria for diagnosing radiographic silicosis, and whether or not silicosis mortality or morbidity (radiographic silicosis) is the basis for ascertainment of outcome.

There has been considerable focus on the importance of exposure measurements, and the confusion that has existed in the past in measuring respirable dust, respirable silica, particle numbers (as measured by Konimeters, thermal precipitators or midget impingers), or mass (gravimetric) of dust (Gibbs et al., 1999). It has been proposed that silicosis risk estimates may be incorrect because respirable dust conversions are different for the various dusts and rock types unless side-by-side samples have been taken, and the predictive power of doing such conversions has been shown to be poor (Gibbs et al., 1999). However, serious consideration must also be given to the difficulties introduced by different sampling strategies. An understanding of the other minerals and contaminants associated with silica exposure (such as alumina powder used for silicosis prophylaxis in Australia and Canada) and ore bodies is another important consideration (Gibbs et al., 1999).

A consistent radiographic definition of silicosis has not been used, and some studies have certified silicosis only where small rounded or irregular opacities occur on chest xrays, or certified silicosis as being present only when profusion on the ILO classification is $\geq$ 1/1. Some authors have justified the use of category 1/1 rather than 1/0 on the ILO scale for silicosis diagnosis, in order to improve specificity (Gibbs et al., 1999) (at the risk of losing sensitivity), despite the explicit instructions for ILO readers. In doing so, they maintain that small irregular opacities are not a feature of classical silicosis and do not appear to provide an appropriate or valid endpoint for use in silicosis (Gibbs et al., 1999). It has been suggested that even when similar diagnostic criteria are applied, it is not possible to determine reliable estimates of silicosis risk from the available exposure-response data with any degree of confidence, as most of the reviewed studies have been limited by questionable exposure or outcome data (Gibbs et al., 1999).

As silicosis may be first detected 20 or more years after the last exposure to silica, the latency and natural history of silicosis must be considered before assessing the prevalence of silicosis within populations of exposed workers. New cases of silicosis are likely to occur after exposure has ceased, and radiographic changes may deteriorate in the absence of further exposure (Gibbs et al., 1999). Occupational cohorts should be followed up until extinction to detect all cases of silicosis resulting from the exposure. The lack of follow up of retired workers may have confounded the observed effects of crystalline silica exposure on silicosis risk in some studies.

Adjusting for the latency of disease is an important aspect of estimating the effects of exposure on disease risk (in this case, the effects of exposure to silica on risk of silicosis or lung cancer), as

the risk of disease changes with increasing time after exposure starts. Latency is usually accounted for in either or both of two ways: (i) initial person-time when the subject is not 'at-risk' of disease is ignored, often the first 2, 5 or 10 years of their time in the study; (ii) any exposure acquired shortly before onset of disease, or any specific time if not diseased (again, usually 2, 5 or 10 years, depending on the nature of the disease under study) is ignored. More precise methods can sometimes be used when modelling the disease process, such as including a separate term for time since first exposure, as well as intensity and duration of exposure in any models. Of course, in many studies, particularly concerning silicosis, duration of exposure and time since exposure are synonymous, so that they cannot be modelled separately.

Tobacco smoking has been shown to be related to a decreased latency time for silicosis onset (Rice et al., 1984), and some studies have found higher rates of silicosis among smokers (de Klerk et al., 1998, Finkelstein, 1995, Hughes et al., 1998, Rosenman et al., 1996). It is possible that these observations occur through tobacco adding insult to the injury caused in the lung by inhaled silica particles, thereby impairing the clearance of particles from the lungs, or accelerating the inflammatory processes thought to lead to fibrosis. Other studies have found smoking to be unimportant (Kreiss et al., 1996, Landrigan et al., 1986), and many studies have ignored smoking in their analyses or omitted any reference to it. Ideally, smoking should be considered in the analysis of silicosis risk and later removed if shown to be insignificant, as with any other potentially confounding variable. Information on adjustment for smoking is included accordingly in the reviews of quantitative studies on silicosis, below.

Because silicosis is rarely a fatal disease, studies on silicosis mortality underestimate the occurrence of silicosis, and are therefore inappropriate for the purpose of setting of an exposure standard for crystalline silica. An occupational exposure standard to prevent death from silicosis would probably only prevent the most severe cases, and would therefore not protect (nearly) all workers. We have therefore presented quantitative data on silicosis mortality and morbidity separately.

In conducting a review of the suitable studies on silicosis risk, Finkelstein considered that the heterogeneity of studies precluded a meta-analysis of silicosis risk. However, using the study of South African gold miners because of its long follow up times, well defined end points and reasonable exposure estimates (Hnizdo et al., 1993) he estimated that the risk of silicosis (ILO classification $\geq$ 1/1) after 20 years exposure to silica at the current OSHA standard of 0.1 mg/m^3 would be at least 5% whereas the risk after 28 years would be 25% (Finkelstein, 2000). In view of this non-linearity of response, he suggested that reduction of exposure to 0.05 mg/m^3 would reduce the risk to less than 5% (Finkelstein, 2000).

5.4 Quantitative Studies of Silicosis Morbidity

5.4.1 Gold Miners

Hnizdo's cohort of 2 235 South African gold miners with at least 10 years underground mining experience was followed up for silicosis until 1991 (Hnizdo et al., 1993). Silica exposures were calculated using methods described in *Section 5.2.2*. Three hundred and thirteen (313) miners developed silicosis at an average age of 55.9 years. In 57% of cases, the first radiological signs of silicosis (ILO $\geq$ 1/1 rounded opacities) began on average, 7.4 years after exposure stopped. After 28 years of mining at 0.3 mg/m^3 ($\approx$ 0.1 mg/m^3 of respirable quartz or 9.0 mg/m^3-year of

respirable dust) approximately 25% of the cohort had developed radiological silicosis. The risk of silicosis increased exponentially with cumulative dust doses of 7 mg/m^3-years or greater, and the latency period was independent of dose. As mentioned previously, dust exposures are likely to have been under-estimated in this study. Some miners were lost to radiological follow up due to death (more than half the cohort had died since 1970, and 85% of these had an autopsy examination for silicosis).

5.4.2 Other Miners

Muir and colleagues followed up a cohort of 2109 Ontario hard rock (gold and uranium) miners until the end of 1982, to determine their incidence of silicosis (Muir et al., 1989). The cohort originated from a list of all workers employed in Ontario who had attended the Worker's Compensation Board (WCB) for examination. Only those who started work between 1940 and 1959 and had spent 80% or more of their total mining experience in mines that had adequate dust exposure measurements were included in the cohort. More than 2000 filter samples and 9000 konimeter samples were taken over 2 years in two mines representing the main types of ore (gold and uranium), under current and simulated historical conditions. Cumulative respirable silica exposure for each miner was calculated using dust exposures obtained from a konimeter/gravimetric silica conversion curve and detailed work histories provided by the WCB.

Plain chest xrays of each cohort member were obtained from the WCB and archives of annual chest xrays taken on all miners since 1927, and were examined for onset of silicosis by five readers. There were 32 cases of silicosis classified as ILO $\geq$ 1/1 rounded opacities. Using a lag period of five years, a dose-response relationship was demonstrated between the risk of silicosis and increasing cumulative respirable silica exposure. The cumulative risk of silicosis based on 40 years of exposure at 0.05mg/m^3, 0.10 mg/m^3 and 0.15 mg/m^3 of respirable silica was 0.9 (95% CI, 0.6-1.5), 2.7 (95% CI, 1.9-3.8) and 5.0 (95% CI, 3.5-7.0), respectively.

This cohort was selectively biased towards those presenting for worker's compensation and probably represents those with the most severe forms of silicosis. This does not affect the observed dose-response relationship, although it may have biased exposures examined to those at the upper end of the distribution. It may have also included a large proportion of miners presenting with disease complicated by their smoking habit, which may have accelerated the onset of silicosis (Rice et al., 1984). The exclusion of workers from mines without dust measurements (especially smaller mines) may have selectively excluded miners working under different conditions and possibly those exposed to different fractional contents of silica (eg. nickel and copper mines have significantly lower fractional contents of silica). Furthermore, the effect of silica exposure may have been under-estimated in this study due to the inhalation therapy with aluminium particles given to many of the subjects as a 'prophylactic' against silicosis.

Kreiss and Zhen examined radiological evidence of silicosis in a random sample of 149 molybdenum (hard rock) miners who had participated in a community prevalence survey of respiratory health in the town of Leadville Colorado, described in *5.2.3* (Kreiss et al., 1996). One hundred and thirty four (134) men aged 40 years or more agreed to have a chest xray or provide one taken within the previous 2 years. Another 34 participants were 'community controls' who had not worked in the mine. Silicosis was defined as a median radiologic profusion of small opacities with ILO $\geq$ 1/0 in 32 of the 100 miners. Exposure among loaders and general labourers was thought to have exceeded the OSHA PEL for respirable silica most of the time. Cumulative

silica exposure, cumulative dust exposure, time since exposure, and years of exposure were positively associated with increasing prevalence of silicosis after adjusting for age and pack-years of smoking (which was insignificant). Thirteen percent (13%) of silicotics had average exposures of 0.025-0.05 mg/m^3. The authors concluded that the OSHA PEL of 0.1 mg/m^3 for silica did not protect against radiological silicosis.

Chen and colleagues followed up a cohort of 3010 Chinese tin miners who were employed for at least one year between 1960 and 1965 in one of four Guangxi Province underground mines (Chen et al., 2001). Radiographic silicosis was identified through annual chest xrays (compulsory for all employees exposed to silica since 1963) using the Chinese pneumoconiosis Roentgen diagnostic criteria (Stage I, II or III), which was found to have 89.3% agreement with the ILO classification in detecting the presence or absence of silicosis. Complete employment histories were maintained by each mine. Very high rates of silicosis have previously been observed in Chinese metal mines, and a monitoring scheme utilising gravimetric methods has been in place to measure total dust exposures since the early 1950's. Total dust concentrations were routinely measured at 3 year intervals between 1950 and 1986, thereafter annual measurements were made. Expert consensus was used to estimate exposures experienced prior to 1950. Surveys in 1988-9 estimated the respirable silica content of total dust to be 3.6% (SD 2.5%). A job-exposure matrix was devised based upon job title, facility and calendar year.

Follow up until the end of 1994 identified 1015 cases of radiographic silicosis. Exposures ranged from 0.2 to 6mg/m^3-year of respirable silica. For the whole cohort, mean total dust exposure was 64.7 mg/m^3-years and mean total dust concentration was 7.5 mg/m^3. The cumulative risk of silicosis was shown to clearly increase with increasing cumulative exposure to respirable silica. With an increase in total dust exposure from <10 mg/m^3-years to ≥140 mg/m^3-years, the cumulative risk of silicosis increased from 0.001 to 0.917, although no formal test for trend in these figures was shown. The silica concentrations in this study indicate a 55% lifetime risk of silicosis after 45 years of employment, based on the OSHA exposure standard of 0.05 mg/m^3.

5.4.3 Diatomaceous Earth Workers

Hughes, Weill and Checkoway examined radiographic silicosis in a cohort of 2342 workers who were predominantly exposed to the cristobalite form of crystalline silica in Lompoc, California during the extraction and calcination of diatomaceous earth (Hughes et al., 1998). Eligible cohort members had been employed for at least one year between 1942 and the end of 1987, and had experienced no known asbestos exposure elsewhere (chrysotile asbestos was used at various times in two of the plant operations). A company health surveillance program commenced in the 1930's which took xrays at the time of hire and periodically throughout the employment. An xray taken more than 1 month after hire was available for 1809 (77%) men and the analysis was based on this number. Smoking histories in the form of 'ever' or 'never' smoked were collected in the 1960's and were available for approximately half of the cohort.

Quantitative air monitoring occurred throughout 1962-1988, providing gravimetric measurements of total dust or respirable dust concentrations. Exposure measures using particle counts taken prior to 1962 were converted from mppcf to gravimetric units by linear regression modelling on companion sampling data for both measurement methods. Individual exposures to crystalline silica were estimated from job category, estimated respirable dust concentrations and the estimated percentage of crystalline silica in the product. In addition, quantitative exposure to the chrysotile form of asbestos was determined for every subject. To assess the importance of

exposure concentration, workers were divided into two categories of average silica exposure concentrations; ≤ 0.5 mg/m^3 and > 0.5 mg/m^3.

Eighty one (81) cases of silicosis (ILO $\geq$ 1/0, rounded opacities) were identified in the 1809 workers examined. Of those workers with average silica exposure concentrations ≤ 0.5 mg/m^3, the smoking status for 71% was known. Out of these, smoking was significantly related to the presence of opacities. The age-adjusted relative risk of lung opacities increased significantly with cumulative crystalline silica exposure, with the dose-response gradient greater for those with $>$ 0.5 mg/m^3 average exposure concentrations . The cumulative risk of silicosis in subjects exposed to an average of ≤ 0.5 mg/m^3 (ie. those hired after 1950) was 1.1%, and those with an average exposure > 0.50 mg/m^3 had a cumulative risk of 3.7%.

5.5 Quantitative Studies of Silicosis Mortality

5.5.1 Gold Miners

Steenland and Brown investigated silicosis mortality in a cohort study of white miners who had worked at least one year underground in a South Dakota gold mine between 1940 and 1965 (Steenland et al., 1995b). The follow up of 3330 men occurred between 1977 and 1990, and only 2% were lost to follow up. Silica dust was measured in mppcf of respirable dust for various jobs. This was converted to gravimetric units using the average respirable silica content (13%) of 82 samples of respirable dust taken over two surveys in the 1970's, which probably under-estimated earlier exposures experienced by much of the cohort (89% were first exposed before 1960, and the average length of exposure was 20.8 years). A job-exposure matrix was developed to estimate dust exposures for each job over time.

One hundred and seventy (170) cases of silicosis were identified from death certificates (n=128) or chest xrays taken during cross-sectional surveys conducted in 1960 and 1976 (n=29), or a combination of both (n=13). This limited case ascertainment to those cases severe enough to have resulted in death before death from any other cause, and those who participated voluntarily in the surveys. Silicosis was radiographically diagnosed as small rounded opacities classified as ILO $\geq$ 1/1. Adjusting for age and calendar period, the risk of silicosis was less than 1% with cumulative respirable silica exposures under 0.5 mg/m^3-years, but increased to 68-74% for the highest cumulative respirable silica exposure category of more than 4 mg/m^3-years. The authors concluded that after adjustment for other risks of death, a 45 year exposure under the Current OSHA standard (0.05 mg/m^3) would lead to a lifetime risk of death from silicosis of no less than 35-47%.

5.5.2 Industrial Sand Workers

Silicosis mortality was examined in a cohort of 2670 men who had worked in any of eight sand producing plants (7 in the US, 1 in Canada) or in an associated construction site (Hughes et al., 2001, McDonald et al., 2001, Rando et al., 2001). The criteria for inclusion in the cohort was employment for at least 3 years between 1909 and 1979, with at least one month of employment during 1940 or later. Smoking histories were obtained from medical records or by proxy for 85% of cases and controls (Hughes et al., 2001). Job histories were available from company records for 97% of cases and controls. A total of 14,249 gravimetric exposure samples were taken from

work sites between 1974 and 1998 (Rando et al., 2001). Five hundred dust counts taken between 1947 and 1955 were converted to respirable dust as; 1mppcf = 276 ug/m^3 (Rando et al., 2001). A computational algorithm was used to adjust for silica content in dust, changes in processing, and for the use of personal protection devices. A job-exposure matrix was developed on the basis of job title and calendar period. Indices of exposure (years employed, cumulative respirable silica exposure and average concentration) were lagged for up to 15 years prior to death of the case. The cohort was followed up (99%) until the end of 1994, and deaths were identified using the US and Canadian National Death Indexes. Twenty nine (29) deaths from silicosis were included in a nested case-control analysis. Silicosis mortality increased with increasing levels of cumulative exposure to respirable silica. A significant dose-response was observed across categories of lagged cumulative respirable silica exposure (trend test, p=0.03); OR=2.54, 4.55, 5.16 for >0.7 and ≤1.8 mg/m^3-years, >1.8 and ≤5.1 mg/m^3-years, and >5.1 mg/m^3-years respectively, in comparison to a baseline category of ≤0.7 mg/m^3-years (Hughes et al., 2001).

Steenland and Sanderson followed up a cohort of 4626 men who had been employed for more than one week in any of 18 industrial sand plants throughout 11 of the United States (Steenland et al., 2001b). Cohort members were identified from trade association records collected during 1987-88, and mortality follow up began in 1960, when routine data collection on multiple causes began. Between 1974 and 1996, 4269 personal samples of respirable silica were measured. The measurements taken between 1974 and until the end of 1988 (when data collection on work histories ended) were modelled to provide a job-exposure matrix that estimated exposure levels for four categories of plant (low, medium, medium-high, and high), three time periods (1974-1979, 1980-1984, and 1985-1988) and 10 job categories. An exposure assessment study in 1946 provided concentrations of particles < 5um in diameter (mppcf), which were converted to respirable-mass concentrations in ug/m^3. Respirable silica concentrations were extrapolated linearly between 1946 and 1974. Cross-sectional data on smoking was available for only 404 subjects. Eleven (11) deaths were recorded with silicosis or unspecified pneumoconiosis (which the authors attribute to "probably silicosis") as the single underlying cause. Silicosis mortality increased significantly across quartiles of cumulative respirable silica exposure (trend test, p<0.00001). The Standardised Rate Ratio (SRR) was 1.22, 2.91 and 7.39 for >0.10-0.51 mg/m^3-years, >0.51-1.28 mg/m^3-years and >1.28 mg/m^3-years respectively, in comparison to a baseline category of 0-0.10 mg/m^3-years.

5.6 Tuberculosis

The association between silicosis and tuberculosis has been firmly established. Subjects with chronic silicosis have a 3-fold increased in incidence of tuberculosis (both pulmonary and extra-pulmonary) compared with similarly aged silica-exposed groups without silicosis, and the incidence of active tuberculosis increases in direct proportion with the increase in profusion of silicotic nodules (ATS, 1997). In acute and accelerated silicosis, the incidence of tuberculosis and non-tuberculous mycobacterial disease is highest (ATS, 1997).

The relationship between silica exposure and tuberculosis has not been quantitatively defined. A recent Silica Coalition review concluded that the risk of tuberculosis does not appear to be increased in persons with radiological changes less than ILO classification 1/0 (with round opacities) (Gibbs et al., 1999).

However, studies in workers without silicosis have found that long exposures or high cumulative exposures to quartz dust may increase the risk of tuberculosis. The incidence of pulmonary

tuberculosis was found to be three times higher in non-silicotic Danish foundry workers employed for at least 25 years (Sherson et al., 1990) and non-silicotic South African gold miners with median underground exposures of 26 years (Cowie, 1994), compared to workers with shorter employment periods ((IPCS), 2000). These findings are consistent with tuberculosis being an independent result of exposure to silica, which in turn is likely to be a function of the prevalence of tuberculosis in the relevant community.

Hnizdo and Murray examined the incidence of tuberculosis in South African gold miners at autopsy (Hnizdo et al., 1999, Hnizdo et al., 1998). The smoking-adjusted relative risk of tuberculosis was 4.01 (95% CI, 2.04-7.88) in the highest quartile of cumulative dust exposure among those who were not radiographically diagnosed with silicosis, however, 'dust' was not defined.

A large case-control study of tuberculosis utilised US National Occupational Mortality Surveillance data for 1983-1992 (Chen et al., 1997). Occupational silica exposure was categorised as potentially 'high', 'intermediate' or 'low', and was determined from jobs surveyed in a National Occupational Exposure Survey and job histories recorded by a National Occupational Health Survey of Mining. The study reported a possible dose-response relationship between silica exposure and death from respiratory tuberculosis in the absence of silicosis. After identifying silica-exposed workers without documentation of silicosis on their death certificate, this study found that the OR for death from respiratory tuberculosis was 1.3 (95% CI, 1.14-1.48) among those in the 'high' potential silica exposure category, in comparison to those with no potential exposure to silica. This was after adjustment for age, gender, race, socioeconomic status and potential exposure to active tuberculosis. Unfortunately, this study was not able to adjust for the effects of tobacco smoking or individual quantitative crystalline silica exposures.

The sparseness of information on exposure-response relationships between crystalline silica and tuberculosis is striking for an occupational exposure as common as silica. This highlights the need for further study of groups whose exposures have been well characterised, and who are followed up after they have left the industry in which they were exposed to silica. The issue of tuberculosis has been essentially ignored in both the ACGIH and German MAK chemical documents on crystalline silica (ACGIH, 2000, Deutsche Forschungsgemeinschaft), 2000).

5.7 Quantitative Studies of Tuberculosis

5.7.1 Industrial Sand Workers

Mortality from respiratory tuberculosis was reported in Steenland and Sanderson's follow up of 4269 US industrial sand workers (described in *Section 5.5.2*) (Steenland et al., 2001b). Twenty one deaths were recorded; 5 had tuberculosis noted as the underlying cause of death and 16 had tuberculosis noted as one of the multiple causes of death on the death certificate. Using all of these cases, mortality from tuberculosis increased significantly across quartiles of cumulative exposure to respirable silica (trend test, p=0.01). The SRR was 0.18, 1.42 and 3.37 for >0.10-0.51 mg/m^3-years, >0.51-1.28 mg/m^3-years and >1.28 mg/m^3-years respectively, in comparison to a baseline category of 0-0.10 mg/m^3-years.

These results combine tuberculosis deaths identified from both underlying and multiple causes of death (ie. any mention of tuberculosis on the death certificate). In this study, the SMR for death

from respiratory tuberculosis as an underlying cause (n=5) was 3.39 (95% CI, 1.09-7.92) and as a multiple cause (n=16) was 4.41 (95% CI, 2.52-7.12). It is therefore unlikely that the combination of deaths from underlying and multiple causes in the case-referent analysis affects the dose-response relationship, or reduces the comparability of this study to the WA gold miners' study and others, where a single underlying cause of death is used only.

5.8 Lung Cancer

The occurrence of lung disease caused by silica exposure in Australian miners has been known since the turn of the last century, and a possible risk of lung cancer from silica exposure has been suspected since at least the 1920's (Armstrong, 1998).

Lung cancer risk has been shown to be increased in occupational populations exposed to crystalline silica including gold miners, stone, quarry, diatomaceous earth, refractory brick, pottery and industrial sand workers. Increased lung cancer risk has been associated with the presence of radiographically defined silicosis (Amandus et al., 1992, Chan et al., 2000, Checkoway et al., 1999, de Klerk et al., 1998, Dong et al., 1995, Finkelstein, 1995b, Meijers et al., 1996), increasing length of follow-up from date of silicosis diagnosis (Partenen et al., 1994), increasing peak intensity of silica exposure (Cherry et al., 1997) and increasing duration of silica exposure (Costello et al., 1995, Costello et al., 1988, Dong et al., 1995, Merlo et al., 1991, Partenen et al., 1994).

5.8.1 Direct Carcinogenicity

Although the risk of lung cancer appears to be highest among silicotics, a consistently significant relationship between lung cancer and silica exposure *per se* has proven difficult to elucidate. This is mainly because of problems in obtaining accurate retrospective measurement of exposure, the almost invariable confounding of silica exposure with cigarette smoking, frequent confounding with other lung carcinogens (ie. radon daughters, arsenic and asbestos), and the preponderance of studies confined to silicotics.

After its extensive review of the carcinogenicity of silica in 1997, IARC deemed that there was (IARC, 1997b):

a. *sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources
b. *sufficient evidence* in experimental animals for the carcinogenicity of quartz and cristobalite
c. *inadequate evidence* in experimental animals for the carcinogenicity of uncalcined diatomaceous earth
d. *limited evidence* in experimental animals for the carcinogenicity of tridymite.

The 1997 IARC carcinogen classification was based ultimately on a handful of positive epidemiological studies which had addressed potential confounding adequately, and only one showed a clear dose-response relationship (Armstrong, 1998). The IARC conclusion was however, supported by considerable evidence of the carcinogenicity of inhaled crystalline silica in rats, and *in-vitro* evidence of crystalline silica's capacity to cause cancer by generating reactive

oxygen species and stimulating cell proliferation. This body of evidence has been further extended since 1997 and recently, the results from two new cohorts of industrial sand workers have been published. The sand industry is useful for studying the carcinogenic effects of crystalline silica, as it does not involve exposures to other known carcinogens that are commonly experienced by miners (eg. radon, arsenic). Diesel exhaust exposures are known to occur among some quarry workers in the sand industry but these are thought to be negligible, as they occur outside rather than in confined spaces.

There is some argument that the toxicological evidence provided by the IARC review is inconclusive, as the exposure methods, large doses and lung overload phenomena seen in some studies do not emulate occupational exposures, and no other species has demonstrated carcinogenic responses like those seen experimentally in the rat (Holland et al., 1999). In a review of the potential carcinogenicity of crystalline silica by the Silica Coalition, it was claimed that *in-vitro* studies have been equivocal, and that most common mutagenesis assays are negative or insensitive to silica-induced changes (Holland et al., 1999). In acknowledging that cell proliferation assays suggest a functional or causal relationship between fibrosis and carcinogenesis, the review concluded that this simply raises the possibility of a threshold in the one species where tumours have been observed experimentally (Holland et al., 1999). These views were echoed in their latest report (Hessel et al., 2000).

Although most of the causal criteria have been met (Berry, 1996), some maintain that the lack of a clear dose-response relationship precludes a direct relationship between crystalline silica exposure and lung cancer (Gamble, 1999, Soutar et al., 2000, Weill et al., 1996). The Silica Coalition review alleged that there was insufficient evidence of a dose-response relationship between silica exposure and lung cancer risk, and even suggested that there was no greater risk of lung cancer among people with silicosis than those without (Gamble, 1999). In its 1998 review, the ACGIH asserted that there was little support for the hypothesis that occupational silica exposure is a direct-acting cancer initiator, although there was compelling evidence that many forms of pulmonary fibrosis constitute major risks for human lung cancer (ACGIH, 1998). The implication from this assessment was that control of workers' exposures to avoid silicosis would also prevent silica-associated lung cancer. This assessment also resulted in the reduction of the TLV-TWA from 0.1 mg/m^3 to 0.05mg/m^3 and upgrading of the rating for quartz to A2 'Suspected Human Carcinogen' designation (ACGIH, 1998, ACGIH, 2000).

Soutar rightfully argued that the disentangling of exposures related to lifestyle, such as smoking and socioeconomic class differences, had not been handled well in some studies of silica exposure and lung cancer (Soutar et al., 2000). He also maintained that weaknesses in exposure data and a resulting lack of statistical power to detect a real relationship between silica exposure and lung cancer were unlikely to explain the absence of an observed dose-effect. This is a valid proposition, however Soutar likens this to the fact that since sufficient statistical power exists to detect a relationship between silica exposure, silicosis and tuberculosis, it should therefore exist for lung cancer. However, he fails to consider that a dose-response relationship between silica and tuberculosis is yet to be elucidated, and that since the suggested exposure-response relationship between silica and silicosis is much more pronounced than that for lung cancer, the statistical power of studies on lung cancer is less.

Others focus on the human evidence and maintain that a link between crystalline silica exposure and lung cancer does exist. Goldsmith suggested a likely relationship between crystalline silica exposure and lung cancer in view of the epidemiological evidence, and that for silica exposed

workers, the relative risk levels are consistently elevated across studies within a range of 1.3 to 1.7, with relative risks higher in silicotics (Goldsmith, 1994). Steenland and Stayner pooled studies of silica-exposed workers with 'reasonably well documented' exposure and without known confounding exposures to other lung carcinogens (arsenic and radon in miners) and arrived at a combined RR of 1.3 (95% CI, 1.2-1.4) (Steenland et al., 1997). They concluded that the weight of evidence supported silica as a human lung carcinogen despite the inconsistencies, which may be related to the source of exposure eg. freshly cleaved quartz, mixed dusts or cristobalite and tridymite; the latter two being more fibrogenic than quartz, and therefore possibly more carcinogenic (Steenland et al., 1997). Furthermore, those with the highest silica exposure showed the highest risks and silica-exposed cohorts exhibit a moderately increased risk (Steenland et al., 1997).

Perhaps the most compelling evidence of a direct association between silica exposure and lung cancer comes from the more recent pooled study of 10 cohorts of silica-exposed workers which showed a small but significant monotonic increase in lung cancer risk with increasing cumulative respirable silica exposure (Steenland et al., 2001a). Furthermore, when exposure was expressed as the log of cumulative respirable silica lagged 15 years, there was a convincing uniformity across studies, despite coming from a variety of countries and industries.

There is significant toxicological evidence of the indirect genotoxic and carcinogenic effects that are stimulated by inflammatory responses induced by crystalline silica exposure. A majority of the studies on occupational crystalline silica exposure and lung cancer risk have found statistically significant associations, and given the number and nature of the epidemiological studies, some non-uniformity of results is not unusual.

5.8.2 Silicosis and Lung Cancer

The biological question still remains as to whether or not a generic relationship exists between fibrosis and lung cancer, rather than silica exposure and lung cancer. Is silicosis a marker for heavy silica exposure rather than a prerequisite for carcinogenesis, or is there a particular susceptibility for lung cancer in silicotics? The clarification of these questions would not assist greatly in the setting of occupational exposure standards or the design of monitoring and surveillance programs. It might help in medico-legal rulings if agreed criteria for determining the presence of silicosis could be established; these however, would always remain arbitrary and arguable.

Finkelstein recently estimated that the risk of lung cancer is thought to be increased by at least 30% among workers with silicosis, and that although the dose-response curve for lung cancer and silica exposure was unknown, it was likely to be non-linear if silicosis played a role in the causal pathway (Finkelstein, 2000). He concluded that silicosis is a marker for lung cancer risk, and that the reduction of dust exposures to lower the risk of silicosis would also decrease the risk of lung cancer (Finkelstein, 2000).

Leigh and colleagues modelled a dose-response relationship between silica exposure, silicosis and lung cancer (Leigh et al., 1997a). They estimated a quantitative risk for silicosis and lung cancer in Australia by applying a revised risk model derived from the study of South African gold miners (Hnizdo et al., 1991a) to the expected number of cases in the Australian labour force (based on the number of workers currently exposed to crystalline silica). The average lifetime

risk of silicosis (ILO $\geq$ 1/1) based on 40 years of exposure was estimated as 60% at 0.2 mg/m^3, 16% at <0.1 mg/m^3, and 1.5% at < 0.05 mg/m^3. The average lifetime risk of lung cancer for the same scenario was estimated as 1.87% (95% CI, 0.21-31.3) at 0.2 mg/m^3, 1.34% (95% CI, 0.20-3.98) at < 0.2 mg/m^3, 0.83% (95% CI, 0.15-1.92) at < 0.1 mg/m^3, and 0.47% (95% CI, 0.09-0.98) at < 0.05 mg/m^3.

Checkoway and Franzblau assert that using the currently available epidemiological evidence, it is not possible to address the question of whether silicosis is required for elevated lung cancer risk (Checkoway et al., 2000). They discussed the various epidemiological issues relating to the diagnosis of silicosis and study design which impede examination of this issue (described below), with which we agree (Checkoway et al., 2000).

The standard plain chest xray is a relatively insensitive method for the diagnosis of interstitial lung disease in comparison to microscopic analysis, especially when the disease is of low grade, or is patchily distributed, and may result in the under-estimation of cases (Checkoway et al., 2000). Inter-reader and intra-reader variability in plain chest xray classifications can also be considerable. Cigarette smoking is capable of producing microscopically verified pulmonary fibrosis and low grade changes on chest xrays, and the prevalence of radiographic silicosis has been shown to be increased among silica-exposed smokers (Checkoway et al., 2000). The separation of radiographic opacities (by their shape) caused by silica alone and the combined effect of silica and smoking is virtually impossible in most cases. However, the cost and higher radiation dose associated with the more sensitive high resolution computed tomography (CT) scan has precluded its use in epidemiological research until recently, and the plain chest xray presents the most efficient means of medical monitoring of silicosis. New technology applied to the high resolution CT scan (which is already being used for the early detection of lung cancer in high risk individuals) may change this assertion in the near future.

There is likely to be some under-estimation of silicosis owing to the latency of the disease, especially where cases develop long after exposure, and periods of monitoring or follow up have ceased (Checkoway et al., 2000). The importance of adjusting for disease latency in the analyses of both silicosis and lung cancer has been discussed (see *Section 5.3*). The use of silicosis registers and pneumoconiosis compensation registers rather than systematic surveillance is highly likely to limit silicosis cases to those more severe or symptomatic, and therefore more likely to have higher exposures, to smoke, and be more likely to have tests that uncover lung tumours. The time of onset of silicosis is important, and this is difficult to determine in studies depending on a single radiographic assessment, or where there has been irregular follow up (Checkoway et al., 2000). Furthermore, the lack of, or quality of quantitative exposure data severely hinders most studies (Checkoway et al., 2000). The recent re-analysis of data on Western Australian gold miners has shown that an effect of silicosis on lung cancer, independent of the effect from silica exposure, although silicosis in this study was based on compensated silicosis only (de Klerk et al., 2002a).

It may be premature to believe that the elimination of new cases of silicosis will necessarily eliminate an excess lung cancer hazard from silica exposure (Checkoway et al., 2000). A prudent approach to risk assessment therefore considers silicosis and lung cancer as separate responses to silica exposure, whose cause and effect relations are not necessarily linked (Checkoway et al., 2000). When the fundamental pathogenic nature of the carcinogenic process is known, it may become clearer as to what the relationship, if any, between silicosis and lung cancer may be. The

accurate measurement of silica exposure and cumulative lung burdens remains a priority for both epidemiology and for hazard surveillance studies (Goldsmith et al., 1995).

5.9 Quantitative Studies of Lung Cancer

5.9.1 Gold Miners

Hnizdo and Sluis-Cremer analysed the mortality of 2 209 white South African gold miners (described in *Section 5.2.2*) who were followed up for lung cancer until 1986 (Hnizdo et al., 1991a). Details on smoking habits were collected at inception of the cohort (1968-71) and current smokers amounted to about 70% of miners. There were 77 deaths from lung cancer during the follow up period (an additional 4 cases were excluded owing to uncertainty about the origin of the cancer). A significant relationship was found between death from lung cancer and cumulative respirable dust exposure measured in particle-years, with an additive effect of cigarette equivalent-years. The relative risk of lung cancer was 1.023 (95% CI, 1.005-1.042) per 1000 particle-years, with particle-years ranging from 7000 to 80000 for the whole cohort. A positive association was detected between silicosis of the hilar glands and lung cancer (OR= 3.9; 95% CI, 1.2-12.7), but no association was found between lung cancer and silicosis of the lung parenchyma. Exposures in South African gold mines include 30% crystalline silica in 60-80% of rock, but also radon daughters and diesel fumes. Increases in dust exposure may be associated with increases in radon daughter emissions (Hnizdo et al., 1991a). Exposures may have been under-estimated, as surveys of exposure were not made until the 1960's and earlier conditions are likely to have been dustier.

This study was re-analysed in 1997 as a nested case-control study, to investigate other risk factors and the incidence of different cancer cell types (Hnizdo et al., 1997). The 78 cases of lung cancer found during the follow up period to 1986 (previously reported as 77) were matched with 386 controls by year of birth. The risk of lung cancer was associated with tobacco smoking, cumulative dust exposure (lagged 20 years from exposure), duration of underground mining, and with silicosis (lagged 20 years from exposure). Tobacco smoking was the greatest predictor of lung cancer. Cumulative dust exposure and years of underground service (both lagged by 20 years) were associated with lung cancer risk and showed a dose-response trend, but when silicosis was included in the model, these were no longer significant. The authors concluded that the results could not be interpreted definitively in terms of causal association, but that possibly: (1) subjects with high dust exposure who develop silicosis are at increased risk of lung cancer; (2) high levels of exposure to silica dust on its own are important in the pathogenesis of lung cancer, but the presence of silicosis is coincidental; or (3) high levels of silica exposure may be a surrogate for the exposure to radon daughters (Hnizdo et al., 1997). The best predictive model included pack years of cigarette consumption (adjusted RR = 1.0 for < 6.5 pack years, 3.5 (95% CI, 0.7-16.8) for 6.5-20 pack years, 5.7 (95% CI, 1.3-25.8) for 21-30 pack years, and 13.2 (95% CI, 3.1-56.2) for more than 30 pack years, and silicosis (RR = 2.45 (95% CI, 1.2-5.2)). A multiplicative combined effect of smoking and the presence of silicosis on lung cancer risk was shown. There was no association with overall uranium production at the time of employment (radon daughters were not measured).

A another cohort of South African gold miners has been followed up, including 4 925 white miners born between 1 January 1916 and 31 December 1930, who were working in the Witwatersrand mining area near Johannesburg in 1970 (aged 39-54 years at the time), and had attended the Medical Bureau for Occupational Diseases in 1969 for a compulsory medical

examination (Reid et al., 1996, Wyndham et al., 1986). These subjects differ from the Hnizdo cohort by age, area of recruitment, and methods for recruitment, however there was some overlap between studies. Forty one of the 78 lung cancer cases found in Hnizdo's study were also cases in this cohort, in which there were 159 cases (personal communication, Eva Hnizdo).

According to a 30% sample of all work histories, gold miners defined as having worked at least 85% of their shifts in gold mines were thought to make up approximately 87% of this cohort. Total years of underground service and particle-years of cumulative dust exposure measured by thermal precipitator count of respirable particles (<5μm) were analysed as separate exposure variables. Dust counts were converted to cumulative dust exposures using the same methods as those in the Hnizdo studies (Hnizdo et al., 1991a). Smoking of cigarettes, pipe, or cigars recorded in 1960, 1965 and 1969 was converted to cigarettes per day. Average cigarettes per day from these three assessments was used to characterise smoking for the analyses (Wyndham et al., 1986).

Mortality has been presented according to both SMR and case-control analyses after nine years and then after twenty years of follow up (Reid et al., 1996, Wyndham et al., 1986). The reference group was the total white male population in South Africa. A healthy worker effect was expected owing to cohort members undergoing a compulsory medical examination before commencing work as a miner, and those overtly diseased or grossly overweight being denied the right to work legally as a miner. Two controls were matched to each case by year of birth only. There were 2032 deaths in total; 464 were excess deaths, with more than half of these due to ischaemic hearth disease (IHD), lung cancer or COPD. Only four of the lung cancer cases were non-smokers, including one who had known asbestos exposure.

The risk of lung cancer was not significantly raised by the number of underground shifts worked, or by estimated cumulative dust exposure. The lung cancer risk associated with cumulative exposure calculated up until 5 years before the case's death (mg/m^3-year) was 1.08 (95% CI, 0.94-1.2) when smoking was not included in the model, and 1.12 (95% CI, 0.97-1.3) when smoking was included. The risk of lung cancer associated with amount smoked (packs of 20/day) was 2.41 (95% CI, 1.4-4.2, p=0.002).

The unhealthy lifestyle habits of these miners were considered to be mainly responsible for the excess deaths observed. Eighty six percent (86%) of the cohort had smoked at some time and most smoked on average, a pack of 20 cigarettes per day. IHD was the biggest contributor to mortality, and the fourth highest cause of death was liver cirrhosis. This study did find that dust exposure contributed to COPD mortality, however probably not without an effect from smoking. Because of the non-significant risk between underground exposure and lung cancer (1.0, 95% CI, 0.78-1.3) it was thought that any potential confounding in lung cancer risk due to exposure from radon daughters was not of concern, or was too small to be demonstrable. More studies are planned to examine radon exposures in detail.

5.9.2 Diatomaceous Earth Workers

Checkoway and colleagues followed up lung cancer mortality in 2266 male diatomaceous earth workers in California from 1942 to 1994 (Checkoway et al., 1997). Exposure to the cristobalite form of crystalline silica was predominant, and asbestos exposure was associated with two plant operations. The white male workers in this follow-up form a subset of the original cohort

described in *Section 5.4.3* (n=2570), who had worked in the larger of two plants and who had not experienced asbestos exposures in any previous jobs. The prevalence of smoking ('ever' or 'never' smoked) was available for only 50% of the cohort, and the authors attempted to overcome this by applying statistical methods to estimate any resulting confounding bias.

Follow up was 91% complete and the certified cause of death was obtained for 96% of all 749 deaths, of which there were 77 due to lung cancer. Adjustments for age, calendar year, duration of follow up and ethnicity were made and exposure was lagged by zero and 15 years. The rate ratio (RR) per mg/m^3-years (trend slope) was 1.05 (95% CI, 0.99-1.11). There was evidence of a dose-response relationship (although not strong) between cumulative silica exposure and lung cancer risk, and the RR for lung cancer at the highest level of cumulative silica exposure ($\geq$ 18.3 mg/m^3-years) was 2.15 (95% CI, 1.08-4.28). When adjusted for the lack of complete quantitative smoking data and assuming a 20-fold increase in risk among smokers compared with non-smokers, this RR was reduced to 1.67 (95% CI, *not shown*). Serious confounding due to smoking was not thought to be responsible for the result, because of similar smoking prevalence in the two highest categories of silica exposure and their differing risks of lung cancer. Furthermore, confounding is thought mostly absent when internal comparisons are made, as the smoking habits of workers are unlikely to vary according to level of exposure (Steenland et al., 1997). In occupational epidemiology, a risk ratio of 1.4 or more is thought unlikely to be elevated due to confounding by smoking (Steenland et al., 1997). There was no association between asbestos exposure and lung cancer risk, nor was a synergistic effect of asbestos and silica exposure on lung cancer risk evident.

The authors concluded that their study supported the hypothesis that crystalline silica is a human carcinogen although not a potent one, but noted that this study may not be directly comparable with others because cristobalite was the principal silica polymorph, and not quartz. Although hindered by this and the quality of its smoking data, this study gleans merit for the transparency in its exposure assessment methods.

Re-analyses of these data have since clarified the dose-response relationship between silica exposure and lung cancer mortality previously observed among Californian diatomaceous earth workers (Rice et al., 2001). Various exposure lag times were examined (using both Poisson regression and Cox proportional hazards methods) and a 10 year lag period was found to best fit the models, rather than 15 years used in earlier analyses. Asbestos exposure was not taken into account in the analysis as it was not associated with lung cancer risk in the earlier analysis. Background rates of lung cancer according to age and calendar time in both the US population (external standardisation) and study population (internal standardisation) were modelled so that adjustments could be made for differences between the study population and US population due to any healthy worker effect and the ethnicity of the cohort (Hispanic vs non-Hispanic). All risk models showed a dose-response relationship between silica exposure and lung cancer mortality. The model of best fit was a linear relative rate model (using Poisson regression) that predicted a lung cancer mortality rate ratio of 1.6 at the mean level of cumulative respirable silica exposure, and a rate ratio of 6.0 at the maximum exposure level (using internal standardisation). The dose-response slope for this model was 0.16 (p=0.006). The excess lifetime risk of death due to lung cancer for white men exposed to respirable cristobalite dust for 45 years at the current OSHA standard (0.05 mg/m^3) with a 10 year lag period was 1.9% (95% CI, 0.5% - 4.6%).

5.9.3 Industrial Sand Workers

Hughes and colleagues examined lung cancer mortality in their cohort of 2670 men who had worked in any of eight sand producing plants (7 in the US, 1 in Canada) or in an associated construction site (Hughes et al., 2001). Detail on this study has been described in *Section 5.5.2.* Smoking histories were obtained from medical records or by proxy, for 85% of cases and 85% of controls (Hughes et al., 2001). The cohort was followed up (99%) until the end of 1994 and deaths were identified through the National Death Index.

Ninety (90) lung cancer deaths were included in a nested case-control analysis. Lung cancer risk increased significantly across categories of cumulative respirable silica exposure when using lagged (15 years) and non-lagged exposures. Odds ratios for lagged exposures were 0.84, 2.02, 2.07 for categories of >0.3 and $\leq$1.1 mg/m^3-years, >1.1 and $\leq$3.3 mg/m^3-years and >3.3 mg/m^3-years respectively, in comparison to the baseline category of $\leq$0.3 (Hughes et al., 2001). An interactive effect between smoking and silica exposure was not found. Significant trends in increasing lung cancer risk were also observed across categories of average exposure concentration (non-lagged), but not across categories of employment duration.

Steenland and Sanderson followed up their cohort of 4626 men who had been employed for more than one week in any of 18 industrial sand plants throughout 11 of the United States (described in *Section 5.5.2*) for lung cancer mortality (Steenland et al., 2001b). Cross-sectional data on smoking was available for only 404 subjects, so the authors used an indirect adjustment method for estimating the impact of smoking differences on lung cancer mortality for these 404 subjects, in comparison with the US population (using smoking data collected in the 1987 National Health Survey). Excess lung cancer mortality due to smoking in this cohort was estimated at 10-20%.

Follow up from 1979 until 1996 identified 109 lung cancer deaths. The average length of employment was 9 years, and estimated average exposure to respirable silica was 0.05 mg/m^3 (NIOSH REL). A nested case-control analysis excluded short term workers (<6 months of employment) who had high overall mortality. Lung cancer mortality increased across quartiles of cumulative respirable silica exposure lagged for 15 years (test for trend, p=0.08); OR=1.35 (95% CI, 0.72-2.54), 1.63 (95% CI, 0.83-3.18), and 2.00 (95% CI, 1.00-4.01) for >0.18-0.59 mg/m^3-years, 0.59-1.23 mg/m^3-years and >1.23 mg/m^3-years of cumulative exposure to respirable silica respectively, in comparison to a baseline category of 0-0.18 mg/m^3-years. When cumulative respirable silica exposures were not lagged, odds ratios were lower but demonstrated a significant increasing trend across quartiles (p=0.04). Lung cancer mortality significantly increased across quartiles of average exposure to respirable silica (test for trend, p=0.003); OR=0.92 (95% CI, 0.42-2.00), 1.44 (95% CI, 0.72-2.86), and 2.26 (95% CI, 1.17-4.38) for >0.023-0.046 mg/m^3, >0.046-0.065 mg/m^3 and >0.065 mg/m^3 average exposure to respirable silica respectively, compared to a baseline category of 0-0.023 mg/m^3.

5.9.4 Pooled Studies

Steenland and Stayner pooled 16 studies of lung cancer and reported a summary risk of 1.3 (95% CI, 1.2-1.4) (Steenland et al., 1997). Unfortunately, this meta-analysis was non-quantitative and could only report a significantly increased risk of lung cancer among silica-exposed workers. Furthermore, we accepted only two of their pooled studies (Checkoway's US diatomaceous earth workers and Hnizdo's South African gold miners) as being suitable for a meta-analysis, as in addition to being non-quantitative, most did not control for smoking.

A recently published IARC-sponsored study was able to pool and analyse lung cancer data from many of the cohort studies described above (Steenland et al., 2001a). The ten industrial cohorts included US diatomaceous earth workers; South African, US and Australian gold miners; US industrial sand workers; US (Vermont) granite workers; Chinese pottery workers, tin and tungsten miners; and Finnish granite workers. As there was much overlap between the two US studies on industrial sand workers (Hughes et al., 2001, Steenland et al., 2001b), the authors included only Steenland *et al* in their pooled analysis, as this includes the greater number of subjects. This pooled analysis represents the largest study of lung cancer and silica exposure conducted to date, including over 1000 lung cancer cases.

Much of the raw data not previously accessible through publications was made available for the authors to conduct this pooled analysis. While numerous exposure metrics and dose-response functions were fitted to the data, the best goodness of fit to all cohorts was one that modelled log cumulative respirable silica exposure lagged 15 years, with a heterogeneity p-value between cohorts of 0.34, indicating good homogeneity. The log relative risk of lung cancer increased by 0.062 (with standard error 0.015) per log(mg/m^3-year) of cumulative respirable silica exposure, and the relative risk was 1.064 (95% CI, 1.033-1.096) per log(mg/m^3-year) of cumulative respirable silica exposure. An excess lifetime (to age 75) lung cancer risk of 1.8% to 2.8% for 45 years' exposure to a concentration of 0.1 mg/m^3 respirable silica was also estimated.

5.10 Auto-immune Disease

Statistically significant excess deaths or cases due to auto-immune diseases have been reported in several epidemiological studies examining silica-exposed workers.

Increased numbers of systemic sclerosis (SSc) cases have been reported in gold miners (Sluis-Cremer et al., 1985), ceramic workers (Rapiti et al., 1999), foundry workers (along with systemic lupus erythematosus) (Rosenman et al., 1999), and registers of SSc sufferers have shown a high number of cases having occupational histories of silica exposure (Haustein et al., 1998, Haustein et al., 1994, Haustein et al., 1990). Rheumatoid arthritis has been associated with silica exposure in gold miners (Cowie et al., 1990, Cowie et al., 1987, Sluis-Cremer et al., 1986, Tager et al., 1999), foundry workers (Rosenman et al., 1999), and industrial sand workers (Steenland et al., 2001c). An increased risk of end-stage renal disease (ESRD) has been reported in groups of granite workers (Ng et al., 1993), gold miners (Steenland et al., 1995a), ceramic workers (Rapiti et al., 1999), fibreglass factory employees (Chiazze et al., 1999) and industrial sand workers (Steenland et al., 2001c). In 1996, the United States Environmental Protection Authority (USEPA) noted that repeated exposure to high concentrations of crystalline silica may be associated with auto-immune disease and/or renal damage, either with or in the absence of pulmonary disease (USEPA, 1996). Goldsmith reviewed US occupational cohort studies with

information on mortality attributable to renal disease, and concluded that occupational exposure to silica is associated with the likelihood of having treatable ESRD (Goldsmith et al., 1993).

Observations of auto-immune disease arise mainly from occupational settings in which exposures have been sufficient to result in silicosis, and there are still doubts about true cause and effect relationships between silica and auto-immune diseases. Although there is toxicological evidence to support causality, there is a paucity of suitable dose-response data from epidemiological studies. It has been suggested that the link between silica exposure and auto-immune disease may have been missed in cohort mortality studies because auto-immune disease is rarely an underlying cause of death, and case-control studies of auto-immune disease have often failed to consider occupational exposure to silica (Steenland et al., 1995c).

Hogan et al examined the prevalence of occupational exposures to silica in a case-control study in North Carolina, of 65 patients with glomerulonephritis, 51 with systemic lupus erythematosis (SLE) nephritis and 176 controls with other renal disease, but without nephritis (Hogan et al., 2001). All subjects were recruited through a linked database of nephropathology results. The analysis was adjusted for smoking and exposures to gasoline or other fuels, pesticides, cleaning agents, solvents, degreasers, glues or adhesives, paint and paint products. The odds ratio for glomerulonephritis was 4.4 (95% CI, 1.36 to 14.38) among those cases who were exposed to silica on the basis of their job titles. Previous silica exposed jobs were not associated with SLE nephritis.

In a case series report, an increased prevalence of glomerulonephritis was observed among residents from a remote area in the UK where fluorspar mining and processing was the major occupation for most of the 20th century (Fenwick et al., 2000). The authors suggested that the most likely cause for the excess renal disease was exposure to silica, as fluorospar seams are reached by drilling through quartz beds, and prior to the introduction of wet drilling in this industry, the death rate from pulmonary silicosis was high.

An Australian population-based case-control study has estimated an OR of 3.93 (95% CI, 1.84-8.54) for SSc among males who had been exposed to silica occupationally at any time in their working lives (Englert et al., 2000). This analysis was based on 160 cases of SSc, and silica exposure was documented as occurring well before the first onset of symptoms and diagnosis, for the majority of cases.

Other recent publications that add weight to the quantitative evidence of a relationship between silica exposure and ESRD in particular, are reviewed below.

5.11 Quantitative studies of Auto-immune Disease

5.11.1 Gold Miners

Using a register of individuals receiving medical benefits for the treatment of end-stage renal disease (ESRD), Calvert and colleagues followed up the NIOSH cohort of 3 332 white male miners from a South Dakota gold mine (described in *5.4.1*) for ESRD incidence until 1992 (Calvert et al., 1997). Eligible gold miners had worked underground for at least one year between 1940 and 1965. As the ESRD register started in 1977, only those cohort members alive

as of January 1, 1977 (according to the National Death Index) were followed up against the register. Two percent of the cohort were lost to follow up, and 2 412 subjects were deemed eligible for this study.

Silica exposures in the South Dakota gold mine are thought to have exceeded the current OSHA PEL prior to 1951, and decreased thereafter. Although most of the cohort was employed before 1949, the median level of exposure was below the OSHA PEL. Underground exposures included non-asbestiform mineral fibres, low levels of arsenic and radon daughters. It is thought that these exposures are not related to renal damage, except for arsenic and radiation at high levels (Calvert et al., 1997).

Eleven cases of treated ESRD were identified. The standardised incidence ratio (SIR) for treated ESRD in the cohort was 1.37 (95% CI, 0.68-2.46), using the United States ESRD incidence rate to calculate expected numbers of cases. The SIR was much greater for nonsystemic ESRD (glomerulonephritis or interstitial nephritis) at 4.22 (95% CI, 1.54-9.19), and increased to 7.7 (95% CI, 1.59-22.48) for those with 10 or more years of underground employment. The SIR for treated nonsystemic ESRD in gold miners exposed to greater than 0.22 and less than 0.55 mg/m^3 -year was 11.05 (95% CI, 3.01-28.3). The authors concluded the current OSHA PEL may not provide adequate protection against the nephrotoxic effects of silica, since most exposures in this cohort were below the OSHA PEL.

5.11.2 Industrial Sand Workers

In the biggest study so far on defined silica exposure and auto-immune disease, Steenland et al examined renal disease and rheumatoid arthritis in the cohort of 4626 men were employed for more than one week in any of 18 industrial sand plants throughout 11 of the United States (described in *Section 5.5.2*) (Steenland et al., 2001c). Subjects were followed up until the end of 1996, using a national registry of treated ESRD patients to ascertain ESRD incidence, and the National Death Index to ascertain mortality from ESRD and rheumatoid arthritis. Twenty three percent of the cohort had died and the cause of death was established for 95% of decedents. Data on smoking was limited, but this is not believed to be related to renal disease or arthritis.

A dose-response analysis on incident ESRD included 18 cases with adequate work histories (out of 23 identified from the national register). Rate ratios for incident ESRD were 2.68, 4.00 and 4.38 for quartiles of cumulative respirable silica exposure; 0.10-0.51 mg/m^3-years, 0.51-1.28 mg/m^3-years and 1.28+ mg/m^3-years respectively, in comparison to a baseline of >0-0.10 mg/m^3-years.

ESRD mortality was presented separately for chronic and acute renal disease (as mentioned on the death certificate). For chronic renal disease (n=30), the SRR was 1.57, 2.62 and 2.02 for quartiles of cumulative respirable silica exposure; 0.10-0.51 mg/m^3-years, 0.51-1.28 mg/m^3-years and 1.28+ mg/m^3-years respectively, in comparison to a baseline of >0-0.10 mg/m^3-years (slope not significant). For acute renal disease (n=11), the SRR was 1.65, 1.56 and 4.13 across the same quartiles of cumulative respirable silica exposure (slope significant). Rheumatoid arthritis was mentioned on 18 death certificates. The SRR for rheumatoid arthritis (death) was 1.73, 3.73 and 6.91 for quartiles of cumulative respirable silica exposure; 0.10-0.51 mg/m^3-years, 0.51-1.28 mg/m^3-years and 1.28+ mg/m^3-years respectively, in comparison to a baseline of >0-0.10 mg/m^3-years (slope significant). The authors utilised both underlying and multiple causes of

death in ascertaining mortality from rheumatoid arthritis and ESRD, and have analysed chronic and acute renal disease separately. Therefore these results are incomparable to the West Australian gold miners' data and other studies where the cause of death is based on single underlying cause only.

Table 2. Quantitative Studies of Chronic Obstructive Pulmonary Disease

Study	*Study Type*	*Cases*	*Subjects*	*Occupation, country*	*Age*	*Sex*	*Adjustments*
(Myers et al., 1989)	cross-sect	P	268	brick refractory workers, South Africa	mean 29 yrs	M	age, smoking, height
(Hnizdo, 1992, Hnizdo et al., 1990, Oxman et al., 1993)	cross-sect	P	2209	gold miners, South Africa	45-54	M	age, smoking, height, weight
de Klerk, *see Appendix 2*	cohort	P	2215	gold miners, W. Australia	16-84	M	smoking, bronchitis
(Theriault et al., 1974)	cross-sect	P	792	granite workers, Canada	25-65	M	age, smoking, height
(Eisen et al., 1995)	cohort	P	353	granite workers, Canada	25-65	M	age, smoking, height, demonstrated healthy worker bias
(Kreiss et al., 1989)	cross-sect	P	383	hard rock miners, USA	20-81	M	age, smoking, height
(Ulvestad et al., 2001)	cohort	P	375	tunnellers and construction workers, Norway	mean 40 yrs	M	age, height, smoking,

P = prevalent cases

Table 3. Other Studies of Chronic Obstructive Pulmonary Disease

Reference	*Occupation, country*	*Limitations*
(Ruckley et al., 1984)	coal workers, Scotland	coal miners
(Harber et al., 1998)	diatomaceous earth workers, California	lack of quantitative exposure data
(Ulvestad et al., 2000)	tunnellers, Norway	no dust exposure measurements
(Meijer et al., 2001)	concrete factory workers, The Netherlands	dose-response not presented
(Annesi et al., 1986)	factory workers (not spec.), France	no dust exposure measurements (yes-no)
(Wang et al., 1997)	foundry workers and coal miners, China	lack of quantitative exposure data
(Irwig et al., 1978)	gold miners, South Africa	lack of quantitative exposure data
(Becklake et al., 1987)	gold miners, South Africa	lack of quantitative exposure data
(Cowie et al., 1991)	gold miners, South Africa	lack of quantitative exposure data
(Hnizdo et al., 1991b)	gold miners, South Africa	lack of quantitative exposure data
(Hnizdo et al., 1994)	gold miners, South Africa	dose-response not presented
(Holman et al., 1987)	gold miners, Western Australia	no dust exposure measurements
(Malmberg et al., 1993)	granite workers, Sweden	dose-response not presented
(Graham et al., 1994)	granite workers, Vermont	dose-response not presented
(Costello et al., 1995)	granite workers, Vermont	lack of quantitative exposure data
(Begin et al., 1995)	silicotic register, Quebec	no dust exposure measurements

Table 4. Quantitative Studies of Silicosis

Study	*Study Type*	*Cases*	*Subjects*	*Occupation, country*	*Age*	*Sex*	*Adjustments*
(Kreiss et al., 1996)	cross-sect	P	32/100	hard rock miners, USA	40+	M	age, smoking, time since exposure
(Muir et al., 1989)	cohort	I	32/2109	hard rock miners, Canada	n/avail	M	none
(Hughes et al., 1998)	cohort	I	81/1983	diatomaceous earth workers, USA	20+	M	age, smoking (50% of cohort), asbestos exposure
(Chen et al., 2001)	cohort	I	1015/3010	tin miners, China	mean 48 yrs	M	age, facility, calendar year
(Hnizdo et al., 1993)	cohort	I	313/2235	gold miners, South Africa	45-54	M	age
de Klerk, *see Appendix 2*	cohort	I	643/2215	gold miners, W. Australia	16-84	M	smoking, time since 1st exposure
de Klerk, *see Appendix 2*	cohort	D	50/2215	gold miners, W. Australia	16-84	M	smoking, time since 1st exposure
(Steenland et al., 1995b)	cohort	D	170/3330	gold miners, USA	mean yob 1920	M	age, calendar period
(Hughes et al., 2001)	cohort	D	29/2670	industrial sand workers, USA	mean 30	M	age, smoking, facility, date first hired
(Steenland et al., 2001b)	cohort	D	11/4027	industrial sand workers, USA	mean yob 1941	M	limited smoking data, ethnicity

P = Prevalent Cases

I = Incident Cases

D = Deaths

Table 5. Other Studies of Silicosis

Reference	*Occupation, country*	*Limitations*
(Legrand-Cattan et al., 1998)	Ceramic workers, France	no information on methods to calculate dust exposure
(Swaen et al., 1988)	Ceramic workers, The Netherlands	no dust exposure measurements
(Cavariani et al., 1995)	Ceramic workers, Italy	lack of quantitative exposure data
(Miller et al., 1998)	coal workers, Scotland	coal miners
(Seaton et al., 1981)	coal workers, UK	coal miners
(Rosenman et al., 1996)	Foundry workers, USA	inadequate statistical data; no standard error
(Lo, 1998)	Construction and quarry workers, Hong Kong	dose-response not presented
(Lim et al., 1998)	Diatomaceous earth workers, Korea	dose-response not presented
(Chia et al., 1991)	Granite workers, China	no dust exposure measurements
(Graham et al., 2001)	Granite workers, Vermont	dose-response not presented
(Paul, 1961)	Copper miners, Northern Rhodesia	no dust exposure measurements
(Sluis-Cremer et al., 1985)	gold miners, South Africa	lack of quantitative exposure data
(Cowie et al., 1991)	gold miners, South Africa	lack of quantitative exposure data
(Murray et al., 1996)	gold miners, South Africa	no dust exposure measurements
(Trapido et al., 1998)	gold miners, South Africa	no dust exposure measurements
(Steenland et al., 1995a)	gold miners, South Dakota	SMR's only; no smoking adjustment
(de Klerk et al., 1998)	gold miners, Western Australia	lack of quantitative exposure data
(Chen et al., 1990)	Haematite miners, China	spurious dust levels; silica content unknown
(Martin et al., 1988)	iron ore miners, Canada	dose-response not presented
(Chen et al., 1992)	metal mine and pottery workers, China	lack of quantitative exposure data
(Paretto, 1971)	silver miners, Peru	cases ascertainment not described; prevalent or incident cases unclear
(Pang et al., 1992)	Tungsten miners, China	case definition and number of cases not given
(Honma et al., 1997)	Pneumoconiotic and silicotic autopsies, Japan	lack of quantitative exposure data
(Finkelstein, 1995)	Silicotic register, Ontario	no dust exposure measurements
(Maxfield et al., 1997)	Silicotic register, USA	no dust exposure measurements

Table 6. Quantitative Studies of Tuberculosis

Study	*Study Type*	*Cases*	*Subjects*	*Occupation, country*	*Age*	*Sex*	*Adjustments*
(Steenland et al., 2001b)	cohort	D	21/4626	industrial sand workers, USA	mean yob 1941	M	limited smoking data, ethnicity,
de Klerk, *see Appendix 2*	cohort	D	6/2215	gold miners, W. Australia	16-84	M	smoking, time since first exposure

D = Deaths

Table 7. Other Studies of Tuberculosis

Reference	*Occupation, country*	*Limitations*
(Sherson et al., 1990)	foundry workers, Denmark	no dust exposure measurements
(Cowie, 1994)	gold miners, South Africa	lack of quantitative exposure data
(Hnizdo et al., 1999, Hnizdo et al., 1998)	gold miners, South Africa	"dust exposure" only
(Chen et al., 1997)	miners, USA	lack of quantitative exposure data

Table 8. Quantitative Studies of Lung Cancer

Study	*Study Type*	*Cases*	*Subjects*	*Occupation, country*	*Age*	*Sex*	*Adjustments*
(Rice et al., 2001)	cohort	D	77/2342	diatomaceous earth workers, USA	15-60	M	age, calendar year, ethnicity, follow up duration, smoking (50%), asbestos exposure, exposure lagged 10years
(Hnizdo et al., 1997, Hnizdo et al., 1991a)	cohort	D	78/2209	gold miners, South Africa	45-54	M	smoking, exposure lagged 20 years
(Reid et al., 1996)	cohort	D	159/4925	gold miners, South Africa	39-54	M	smoking
de Klerk, *see Appendix 2*	cohort	D	136/2215	gold miners, W. Australia	16-84	M	smoking, bronchitis, time since 1st exposure
(Steenland et al., 2001b)	cohort	D	109/4626	industrial sand workers, USA	mean yob 1941	M	limited smoking data, ethnicity, exposure lagged 15 years
(Hughes et al., 2001)	cohort	D	90/2670	industrial sand workers, North America	mean 30	M	age, smoking, facility, date first hired
(Steenland et al., 2001a)	pooled cohorts	D	1072/65980	mixed		M/F	age, sex, calendar period, study

D = Deaths

Table 9. Other Studies of Lung Cancer

Reference	*Occupation, country*	*Limitations*
(Puntoni et al., 1988)	brick refractory workers, Italy	lack of quantitative exp data; SMR only; no smoking adjust
(Merlo et al., 1991)	brick refractory workers, Italy	no dust exposure measurements
(Merlo et al., 1995)	brick refractory workers, Italy	no dust exposure measurements; silicotics
(Dong et al., 1995)	brick refractory workers, China	lack of quantitative exposure data
(Tsuda et al., 1998)	brick refractory and quarry workers, Japan	no dust exposure measurements
(Forastiere et al., 1989)	ceramic workers, Italy	no dust exposure measurements; silicotics
(Meijers et al., 1996)	ceramic workers, The Netherlands	lack of quantitative exposure data
(Sherson et al., 1991)	foundry workers, Denmark	no dust exposure measurements
(Andjelkovich et al., 1994)	foundry workers, USA	exposure levels not provided
(Rosenman et al., 1995)	foundry workers, USA	no dust exposure measurements; silicotics
(Koskela et al., 1987)	granite workers, Finland	dose-response not presented
(Costello et al., 1988)	granite workers, Vermont	lack of quantitative exposure data
(Costello et al., 1995)	granite workers, Vermont	lack of quantitative exposure data
(Chia et al., 1991)	granite workers, China	no dust exposure measurements
(Neuberger et al., 1986)	metal industry, glass, pottery, stone, ceramic workers, Austria	no dust exposure measurements
(Guenel et al., 1989b)	stone workers, Denmark	dose-response not presented
(Zambon et al., 1987, Zambon et al., 1986)	tunnel and quarry workers, Italy	no dust exposure measurements; silicotics
(Ng et al., 1990)	tunnel and quarry workers, Hong Kong	no dust exposure measurements
(Nakagawa et al., 1998)	tunnel construction workers, Japan	no dust exposure measurements
(Chen et al., 1990)	Haematite workers, China	spurious dust levels; silica content unknown
(Ebihara et al., 1998)	copper miners and stone masons, Japan	no dust exposure measurements
(Kusiak et al., 1991)	gold miners, Ontario	no dust exposure measurements
(Hessel et al., 1990)	gold miners, South Africa	lack of quantitative exposure data
(Steenland et al., 1995a)	gold miners, South Dakota	SMR's only; smoking adjustment not reported
(Brown et al., 1986)	gold miners, USA	no dust exposure measurements

Table 9 (cont'd). Other Studies of Lung Cancer

Reference	*Occupation, country*	*Limitations*
(de Klerk et al., 1995)	gold miners, Western Australia	no dust exposure measurements
(de Klerk et al., 1998)	gold miners, Western Australia	lack of quantitative exposure data
(Armstrong et al., 1979)	gold and coal miners, Western Australia	no dust exposure measurements
(Cocco et al., 1994b)	lead and zinc mine workers, Sardinia	few cases; females only; no smoking information
(Cocco et al., 1994a)	lead and zinc miners, Sardinia	silicotics
(Kawabata et al., 1998)	Manganese mine and other dusty workers, Japan	no dust exposure measurements; silicotics
(Carta et al., 1991)	metal miners, Sardinia	lack of quantitative exposure data
(Carta et al., 1994)	metal miners, Sardinia	no quantitative data
(Schuler et al., 1986)	metal mine, foundry, quarry, tunnel workers, Switzerland	no dust exposure measurements; silicotics
(Westerholm et al., 1986)	metal mine, foundry, quarry, tunnel workers, Sweden	no dust exposure measurements; silicotics
(Fujii et al., 1998)	metal & coal mine, quarry, tunnel & stone workers, Japan	no dust exposure measurements; silicotics
(Wang et al., 1996)	metal mine, foundry and brick refractory workers, China	no dust exposure measurements; silicotics
(Chen et al., 1992)	metal mine and pottery workers, China	lack of quantitative exposure data
(McLaughlin et al., 1992)	metal mine and pottery workers, China	Extremely low exposure measures; arsenic and PAH collinear with silica exposures
(Higgins et al., 1983)	taconite miners, USA	unclear exposure measurement; taconite fibres included.
(Cooper et al., 1992)	taconite miners and millers, USA	no dust exposure measurements
(Hua et al., 1992)	tin miners, China	spurious dust levels; silica content unknown
(Hua et al., 1994)	tin miners, China	lack of quantitative exposure data
(Samet et al., 1994)	uranium miners, Mexico	silicotics
(Thomas et al., 1987)	pottery workers, USA	no dust exposure measurements
(Cherry et al., 1998)	pottery workers, UK	matching on year of hire; incomparable with others
(Takagi et al., 1998)	pottery workers, Japan	no dust exposure measurements
(Finkelstein et al., 1982, Finkelstein et al., 1987)	silicotic register, Ontario	no dust exposure measurements; silicotics
(Finkelstein, 1998)	silicotic register, Ontario	lack of quantitative exposure data; silicotics
(Kurppa et al., 1986)	silicotic register, Finland	no dust exposure measurements; silicotics
(Partenen et al., 1994)	silicotic register, Finland	Silicotics
(Infante-Rivard et al., 1989)	silicotic register, Quebec	no dust exposure measurements; silicotics
(Amandus et al., 1995)	silicotic register, North Carolina	no dust exposure measurements; silicotics

Table 9 (cont'd). Other Studies of Lung Cancer

Reference	*Occupation, country*	*Limitations*
(Starzynski et al., 1996)	silicotic register, Poland	lack of quantitative exposure data; silicotics
(Brown et al., 1997)	silicotic register, Sweden and Denmark	no dust exposure measurements; silicotics
(Honma et al., 1997)	Pneumoconiotic and silicotic registers, Japan	lack of quantitative exposure data; silicotics
(Chan et al., 2000)	silicotic register, Hong Kong	no dust exposure measurements; silicotics

Table 10. Quantitative studies of End-Stage Renal Disease

Study	*Study Type*	*Cases*	*Subjects*	*Occupation, country*	*Age*	*Sex*	*Adjustments*
(Steenland et al., 2001c)	cohort	I	18/4626	industrial sand workers, USA	mean	M	age, race, facility, calendar year
		D*	41/4626	industrial sand workers, USA	yob 1941	M	age, race, facility, calendar year
(Calvert et al., 1997)	cohort	I	6/2412	gold miners, USA	f/u 1977 - 1992	M	none
de Klerk, *see Appendix 2*	cohort	D	13/2215	gold miners, W. Australia	16-84	M	smoking

*multiple cause analysis - not comparable to other studies

D = Deaths

I = Incident Cases

Table 11. Other Studies of Auto-immune Disease

Reference	*Disease, occupation, country*	*Limitations*
(Rapiti et al., 1999)	ESRD, ceramic workers, Italy	SMR's only
(Chiazze et al., 1999)	ESRD, fibreglass workers, USA	matching problems, unclear measure of exposure
(Fenwick et al., 2000)	renal disease, fluorspar miners, UK	no dust exposure measurements
(Steenland et al., 1995a)	chronic renal disease, gold miners, South Dakota	SMR's only
(Ng et al., 1993)	nephrotoxicity, granite workers, Hong Kong	lack of quantitative exposure data
(Rosenman et al., 1999)	SLE, SSc, RA, foundry workers, USA	no dust exposure measurements
(Sanchez-Roman et al., 1993)	SLE, SSc, scouring powder factory, Spain	no dust exposure measurements
(Hogan et al., 2001)	SLE, glomerulonephritis, population based study	lack of quantitative exposure data
(Haustein et al., 1990)	SSc, dusty workers, East Germany	no dust exposure measurements
(Haustein et al., 1994)	SSc, dusty workers, East Germany	no dust exposure measurements
(Haustein et al., 1998)	SSc, dusty workers, East Germany	no dust exposure measurements
(Sluis-Cremer et al., 1985)	SSc, gold miners, South Africa	lack of quantitative exposure data
(Cowie, 1987)	SSc, gold miners, South Africa	no dust exposure measurements
(Cowie et al., 1990)	SSc, gold miners, South Africa	no dust exposure measurements
(Tager et al., 1999)	SSc, gold miners, South Africa	no dust exposure measurements
(Englert et al., 2000)	SSc, population based study	lack of quantitative exposure data
(Turner et al., 2000)	RA, pottery workers, UK	matching on year of hire; incomparable with others
(Sluis-Cremer et al., 1986)	RA, gold miners, South Africa	lack of quantitative exposure data

SSc - Systemic Sclerosis (scleroderma) SLE - Systemic Lupus Erythematosus

ESRD – End Stage Renal Disease RA – Rheumatoid Arthritis

6.0 COMBINATION OF THE QUANTITATIVE EVIDENCE

To assist with standard setting, we combined the suitable quantitative studies discussed in Section 5.0, to determine the dose-response relationships between crystalline silica exposure and associated adverse health effects.

6.1 Summary

Great differences in all methodological aspects of the majority of studies examined in this review indicate that differences in study results are more likely to have been due to unmeasured deterministic differences, rather than stochastic variability. It was therefore decided by the authors that formal meta-analyses (or pooled analyses) were not justified for most putative silica-related diseases, and would probably only serve to confuse rather than elucidate. Therefore, we quantitatively summarised studies by graphical means, which gives a clear picture of important similarities and differences between studies. In addition to graphical analysis, a meta-analysis was originally undertaken (in 2000) for lung cancer but has since been superseded by the large IARC pooled analysis.

In addition to the studies discussed in *Section 5.0*, we have included results from a recent analysis of a cohort of West Australian gold miners, commissioned by the Advisory Committee for this Review (see *Appendix 2).* These provided additional quantitative dose-response relationships for all of the disease responses discussed. It should be noted however that these dose-response analyses have not yet been fully published (published only as an extended abstract, (de Klerk et al., 2002a)), but have been reviewed by members of the Advisory Committee and two selected international experts.

6.2 Methods

6.2.1 Dust Measurement Conversions

To account for the different methods used to determine silica and dust exposures in different studies, we converted exposures from each study to mg/m^3 years of cumulative exposure to respirable silica according to BMRC methodological criteria, to enable interpretation in the Australian context. In general, this meant multiplying non-Australian exposure estimates by 1.95, including those exposures for the Hnizdo studies converted by Leigh and colleagues (Leigh et al., 1997a). See *Appendices 4-5* for background information on converting dust exposures estimated using different methodological criteria.

6.2.2 Graphical Comparisons

Where the methodological differences and heterogeneity between studies is evident, a meta-analysis is inappropriate. By plotting the dose-response relationships for each of the accepted studies, the different effects estimated from each study and their variability can be appreciated. This was undertaken for silicosis, lung function decline, and lung cancer. We have not graphically combined the studies on auto-immune disease or tuberculosis. Although the consistency of positive findings across several studies indicates that there is likely to be

some association between silica exposure and these outcomes, given the magnitude of the associations between silica and other diseases, the association with ESRD and tuberculosis need not be considered for standard setting.

6.2.3 Use of a single pooled study

The IARC pooled study of 10 cohorts *(Section 5.9.4)* included some 65,980 subjects to explicitly examine silica exposure and lung cancer risk, and is by far the largest such analysis ever conducted, including over 1000 cases (Steenland et al., 2001a). The pooled exposure-response relationships derived in that study are therefore appropriate for consideration in this review.

6.3 Results

6.3.1 Pulmonary Function

Quantitative studies relating dust exposure to decline in FEV_1 are listed in *Table 2* of *Section 5.0*. Some of the studies relate to total respirable dust rather than respirable silica and a variety of different exposure measures have been used.

It has not been established that respirable silica *per se* rather than total dust exposure is the important risk factor for lung function loss, but comparisons of the different exposure-specific decrements showed more uniformity when total dust rather than respirable silica was used as the exposure variable (not shown). The studies of WA gold miners, Kreiss *et al* (1989) and Myers *et al* (1989) expressed results in terms of log cumulative respirable silica exposure, so that slopes were unaffected by conversion either of exposure units or from total dust to respirable silica. In *Figure 3*, the ranges of total dust exposure approximate those found in the respective studies, and even the shallowest slope was statistically significantly different from zero, indicating that any meta-analysis would estimate a magnitude of reduction at least as great as this, and more statistically significant. There have been numerous studies that have shown strong associations between exposure to dust and subsequent COPD (defined in various ways) and clear gradients of increasing response with increasing exposure have been demonstrated (see *Section 5.2*).

6.3.2 *Silicosis Incidence and Prevalence*

The differences between studies on silicosis are even more marked than those noted for FEV_1 decrement, again making a formal meta-analysis of doubtful relevance. The quantitative studies of radiographic silicosis in *Table 4, Section 5.0* are graphed in *Figure 4*.

The paper by Hughes *et al* (1993) is the only one out of these studies that found (or probably looked for) differences in exposure-response relationships for different concentrations of respirable silica, and this is certainly more appropriate when attempting to apply the data to current situations. Since the aim of this review of the evidence is for applications in standard setting, we have only shown the exposure gradient for low concentrations of exposure rather than high concentrations from this study.

As might be expected, the WA studies showed the lowest risk estimates because they were based on compensated cases of silicosis rather than xray diagnoses ascertained via systematic surveillance. However, they are similar to the study by Muir *et al* (1989), where the relationship for the majority of xray readers' findings has been used. The WA study also examined the different effects of duration and intensity of exposure, as well as the more usual cumulative exposure. It also allowed for adjustment for time since first exposure as distinct from duration of exposure. The majority of studies have assumed these two time axes are equivalent.

The closeness of some of the studies and the wide range between them suggested showing the same relationships on a log scale in *Figure 5*.

6.3.3 *Lung Cancer Mortality*

Graphical representation

The quantitative studies of lung cancer mortality in *Table 8, Section 5.0* are graphed in *Figure 6*, including the IARC pooled study. To estimate the relative risk from the pooled study, we anchored it using the odds ratio of 1.04 for their category of 0.4-2.0 mg/m^3-years cumulative respirable silica exposure and then used the best fitting relationship with the 15 year lag: log(RR)=0.062*log(cumulative exposure) as in seen in Table 3 of the pooled analysis (Steenland et al., 2001a).

The agreement between studies according to their graphical representation is much more evident than for the other diseases, indicating a small but steady increase in risk of lung cancer with increasing cumulative silica exposure. This uniformity of study results, while demonstrating some divergence between the two South African studies (Hnizdo et al., 1997, Hnizdo et al., 1991a, Reid et al., 1996), which had a small proportion of their subjects in common (personal communication, Eva Hnizdo), and the two others (Checkoway et al., 1999, de Klerk et al., 1999), indicated that a formal meta-analysis might be appropriate and this was previously carried out (see Appendix 3). The IARC study was however used for all risk estimation and setting the standard.

6.4 Conclusions

a. Exposure to dust containing silica leads to loss of lung function, but the precise amount is unclear, as is the difference if any, between silica and other dusts.

b. The amount of silicosis resulting from silica exposure in different study populations is extremely varied, making uniform recommendations to prevent silicosis inappropriate. Whether silicosis is a necessary precursor for silica-induced lung cancer has not yet been adequately addressed by any study. It is hoped that the imminent addition of 5 years of follow-up of the WA gold miners' cohort, together with the ongoing reading of all their xrays, may provide this.

c. Our previous meta-analysis of lung cancer risk and the IARC pooled analysis (Steenland et al., 2001a) concurs with the IARC classification of crystalline silica as a human carcinogen because of the uniformity of study findings, and lack of contrary evidence. The effect of increasing cumulative silica exposure on lung cancer is small but statistically significant. Because of the similarity between dose-response relationships in studies presented in *Figure 6*, we have decided to use the most precise estimate of lung cancer risk, that from the pooled study, for risk assessment in this review.

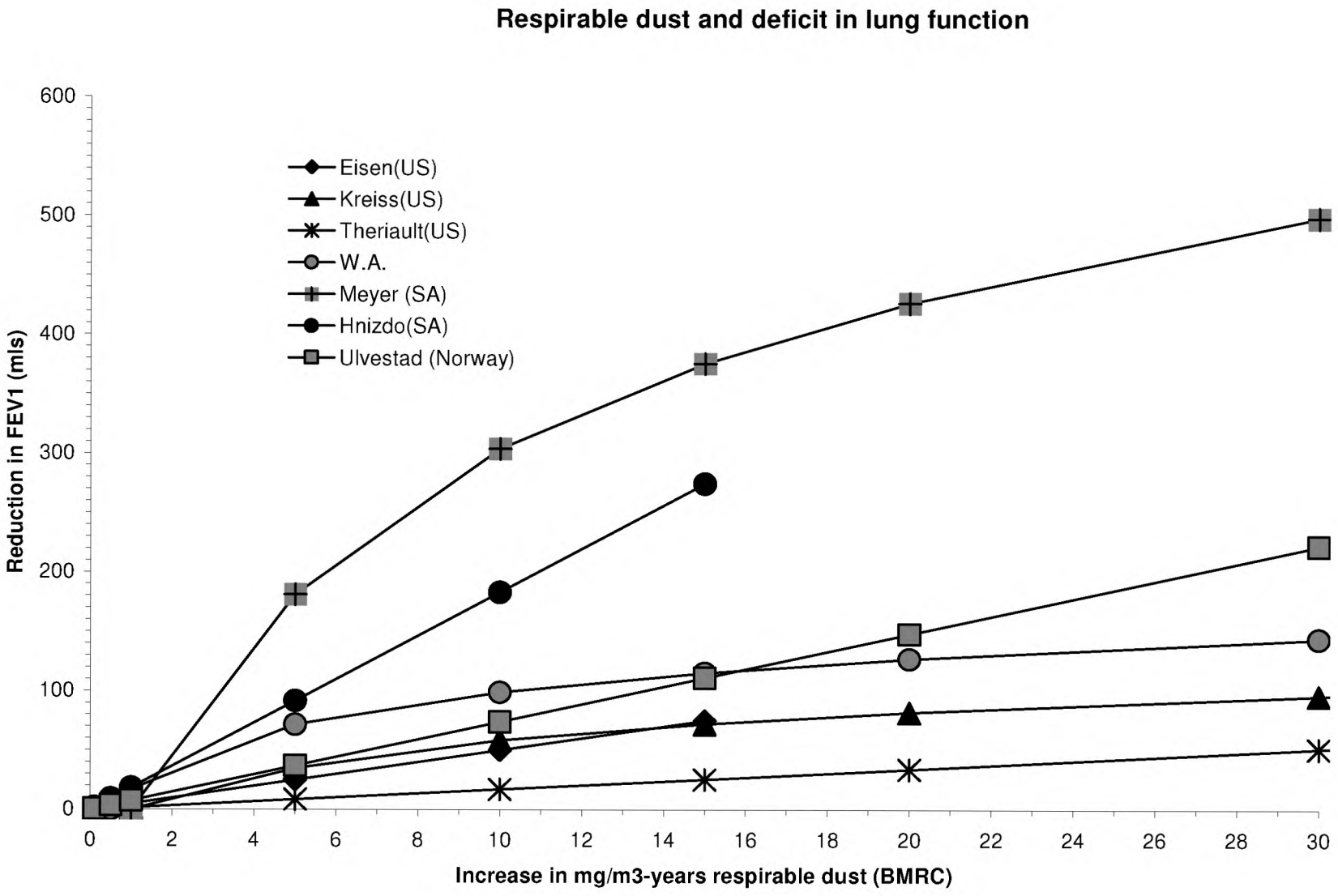


Figure 3. Estimated reduction in FEV_1 and cumulative exposure to respirable dust.

All exposure assessments converted to BMRC/Johannesburg curve (Appendix 5)

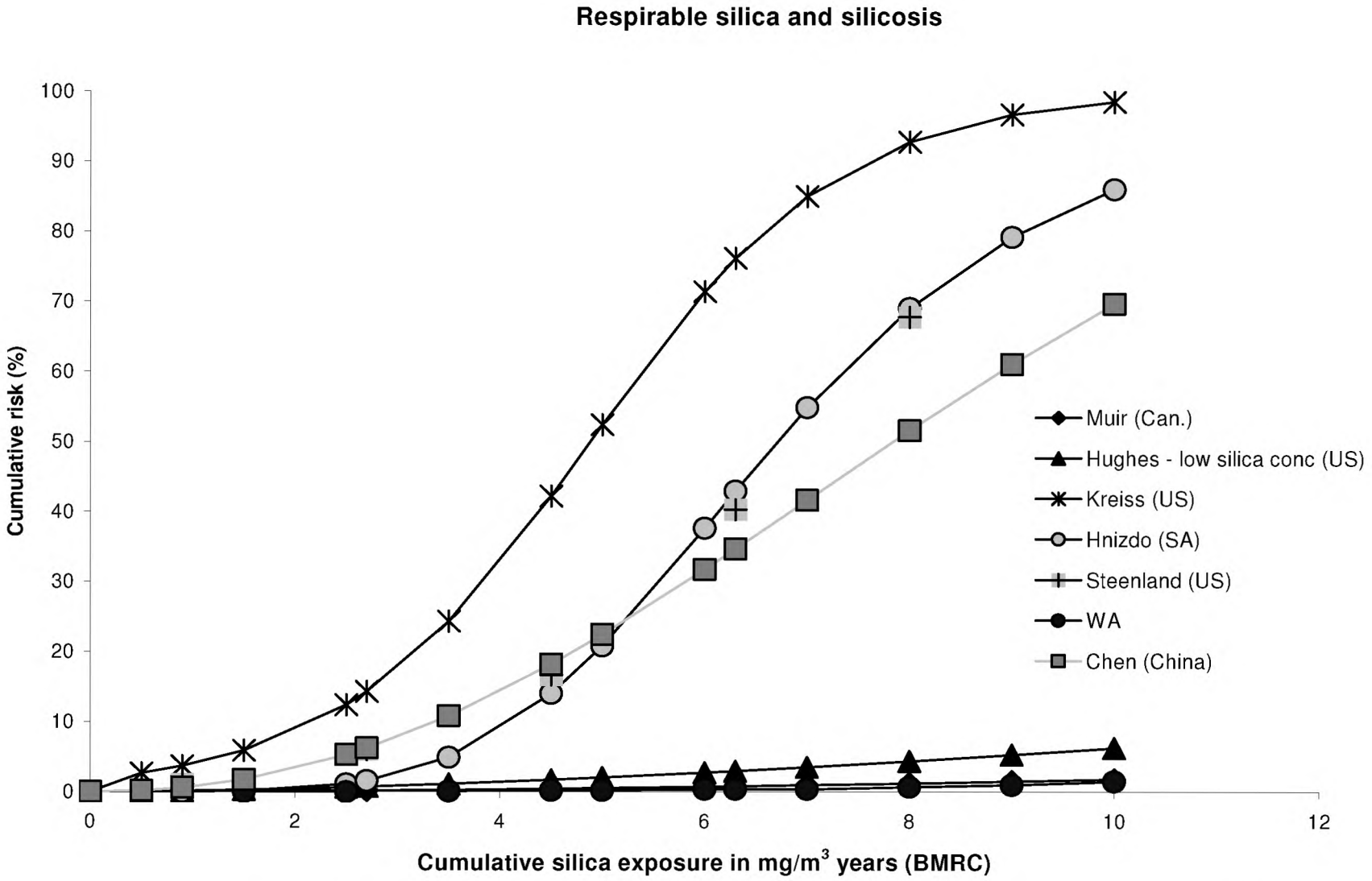


Figure 4. Estimated cumulative risk of silicosis and cumulative exposure to respirable silica.

All exposure assessments converted to BMRC/Johannesburg curve (Appendix 5)

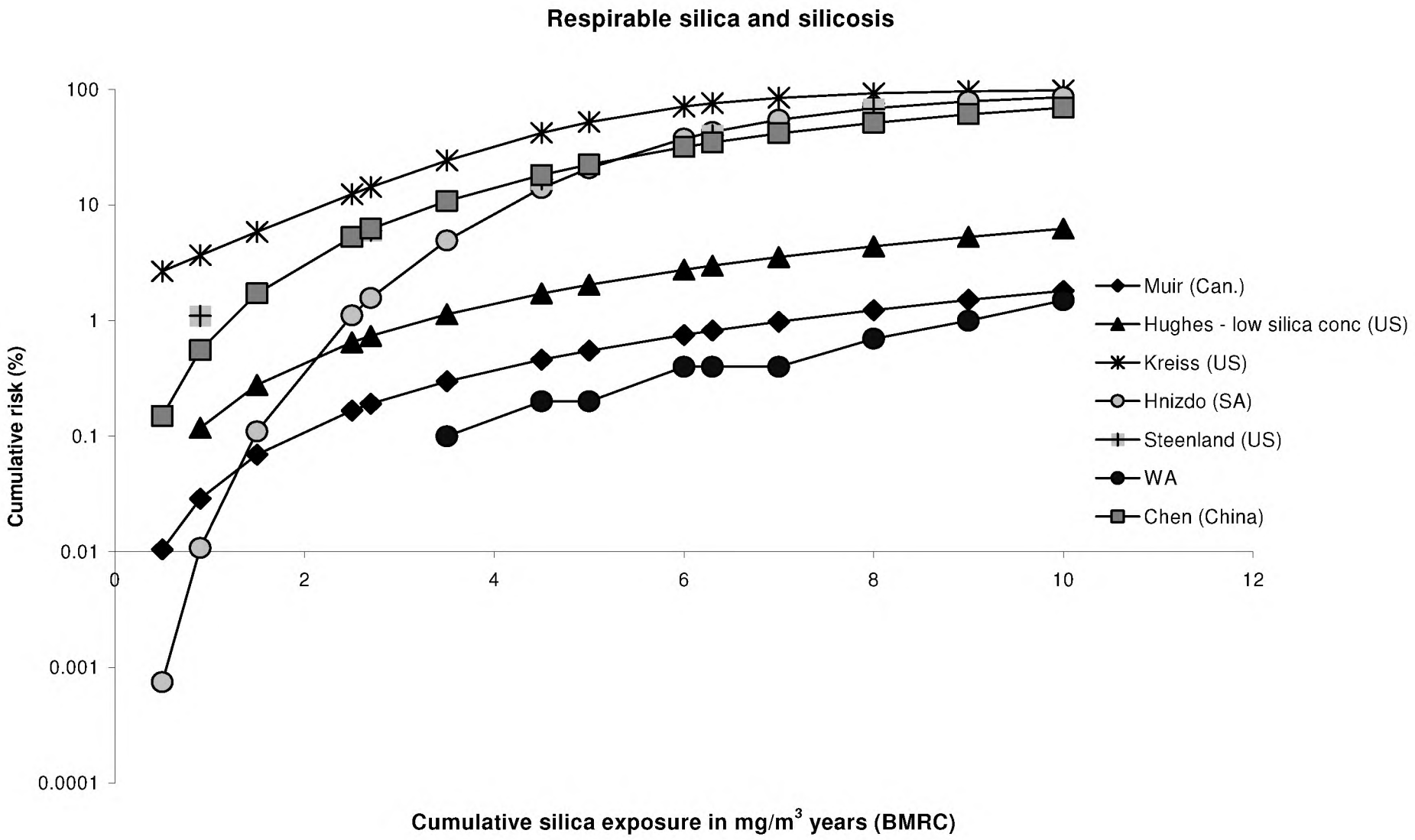


Figure 5. Estimated cumulative risk of silicosis (expanded log scale) and cumulative exposure to respirable silica.

All exposure assessments converted to BMRC/Johannesburg curve (Appendix 5)

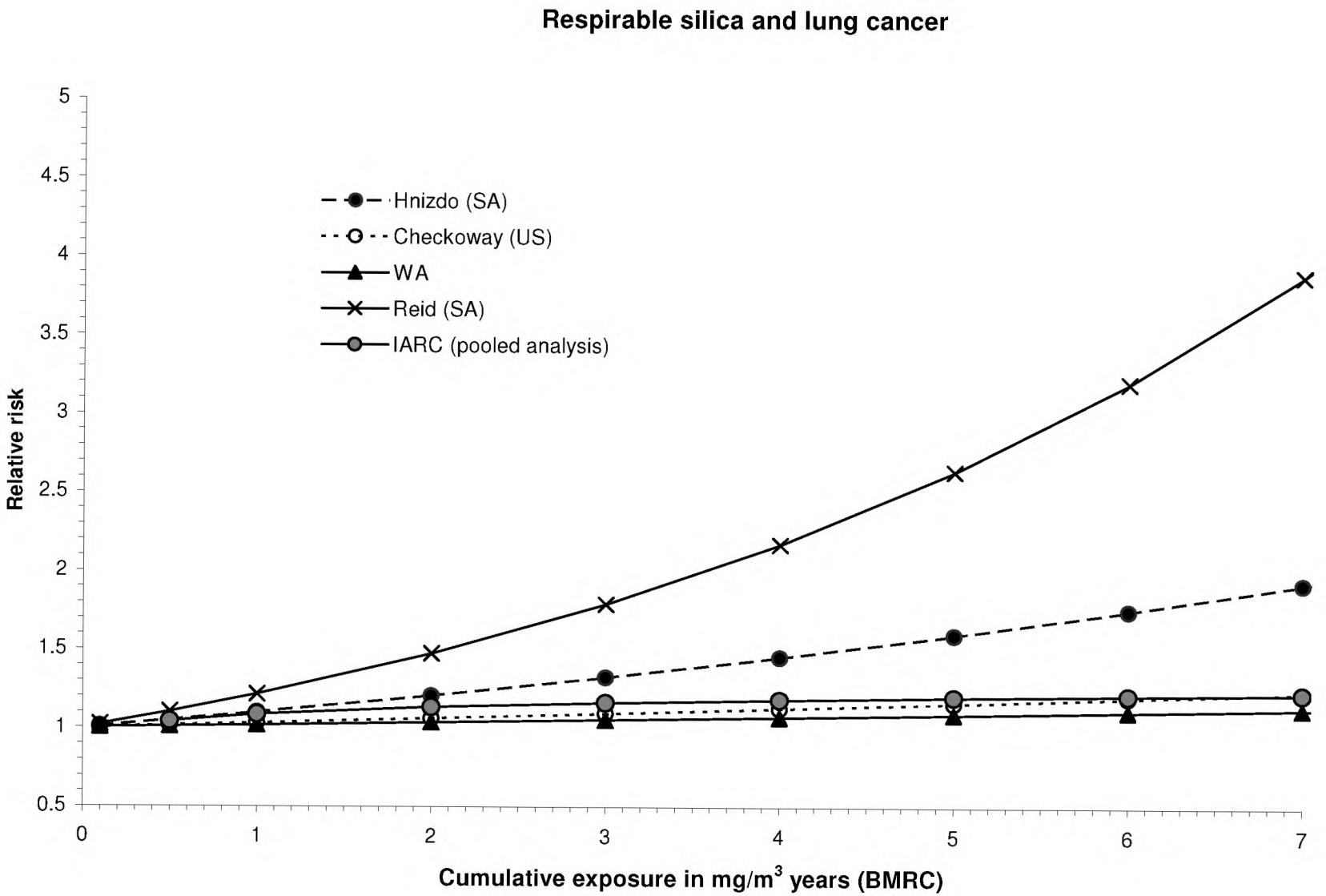


Figure 6. Estimated relative risk of lung cancer and cumulative exposure to respirable silica.

7.0 SYNTHESIS

This chapter recommends an exposure standard for crystalline silica and documents the logic for this recommendation.

7.1 Evidence

7.1.1 Chronic Obstructive Pulmonary Disease

Morphological changes in airways and functional changes in air-flow have been observed experimentally in animals after silica exposure. There have been numerous studies showing strong associations between occupational exposure to silica dust and/or crystalline silica and abnormal decline in pulmonary function, bronchitis, emphysema and other obstructive pulmonary diseases. Although these health effects are often associated with tobacco smoking, they are present to a significant extent in non-smokers who have had occupational exposure to quartz, and do not have silicosis. Whether silica acts differently from other 'nuisance' respirable dusts in this respect is not clear.

Significant dose-response relationships between crystalline silica exposure and COPD have been shown in studies of granite workers, gold miners, hard rock miners and brick refractory workers, and a synergistic effect between tobacco smoking and crystalline silica exposure on mortality from COPD has been demonstrated (Hnizdo, 1990).

The impairment of respiratory function in workers exposed to dusts containing crystalline silica is an important cause of disability that can significantly affect quality of life, especially in smokers who are likely to have smoking-induced losses in lung function. Our review of the quantitative evidence shows that although there have been a variety of dose-responses observed, dust containing silica causes decrements in FEV_1 and FVC, and this is certainly dose-dependent. The shallowest dose-response is still highly significant (Kreiss et al., 1989). We therefore recommend that an exposure standard should try to consider the prevention of excessive loss of lung function.

7.1.2 Silicosis

The toxicological and epidemiological evidence of crystalline silica being a causative agent in silicosis is well established (hence the name). Silica causes silicosis in a dose-dependent manner. Dose-response relationships between crystalline silica and silicosis have been observed in studies of gold miners, hard rock miners, foundry workers, diatomaceous earth workers and ceramic workers.

In our overview of all the suitable dose-response studies, we observed a large degree of variation in the dose-response relationships, which we believe makes the setting of an exposure standard based on silicosis problematic when using the epidemiological evidence available at present, unless standards are made specific to particular industries or situations. For example, using Australian gold-mining data to establish limits for Australian gold-mines or, arguably, for industries in Australia that use the same methods of exposure measurement.

7.1.3 Tuberculosis

The risk of tuberculosis increasing after the development of silicosis has been well established by epidemiological evidence. There is also evidence of increased risk of tuberculosis in silica-exposed foundry workers and gold miners without silicosis. However, the paucity of quantitative data on tuberculosis precludes any worthwhile examination of a dose-response relationship with crystalline silica exposures. It can therefore only be concluded at this stage, that an exposure standard that protects against silicosis is also likely to protect against tuberculosis.

7.1.4 Lung Cancer

There is significant toxicological evidence of indirect genotoxic and carcinogenic effects that are stimulated by crystalline silica exposure. Other epidemiological criteria for causality including temporal sequence, dose-response, magnitude of effect and consistency of findings (Rothman, 1988) have been met. Crystalline silica (quartz and cristobalite) has been formally classified as a human carcinogen by the IARC and other regulatory bodies.

Lung cancer incidence is increased in people who have been exposed to silica dust, and the increase is dose-dependent. The IARC pooled study of lung cancer found a uniform combined risk of 1.064 (95% CI, 1.033-1.096) per log(mg/m^3-year) increase in cumulative silica exposure, with exposures lagged 15 years. The uniformity in findings in the reviewed studies and lack of contrary evidence supports this small but significant dose-response relationship. Because of the similarity between the various dose-response relationships shown in *Figure 6*, we have decided to use the most precise estimate, that from the pooled study, for risk assessment in this review.

7.1.5 Silicosis and Lung Cancer

There is a large body of evidence indicating that the risk of lung cancer is greater among those with silicosis. The toxicological data indicate that inflammatory and fibrotic responses to crystalline silica have the potential to induce carcinogenic processes, which supports the biological plausibility of silicosis being a precursor for lung cancer.

However, owing to uncertainties in silicosis ascertainment, exposure assessments, and the occurrence of lung cancer among silica-exposed workers without silicosis, it is not possible to adequately address this issue using the data available at present.

Therefore, for the purpose of setting an exposure standard for crystalline silica, silicosis and lung cancer should be treated as separate diseases, whose cause and effect relations are only linked by a common exposure.

7.1.6 Auto-immune Disease

The toxicological evidence supports the ability of crystalline silica to migrate to extra-pulmonary tissue and accumulate in the lymph nodes, whereby an auto-immune response may be stimulated. The consistency of positive epidemiological findings across several studies indicates that there is likely to be some association between crystalline silica exposure and auto-immune disease. Given the magnitude of the associations between silica and other diseases, the association with auto-immune diseases need not be considered for standard setting. It can be assumed with some confidence that the risk of auto-immune disease is greater among subjects with silicosis.

7.2 Standard Setting

We have chosen to base our recommendation for the setting of an exposure standard for crystalline silica on the relationships between exposure to crystalline silica and lung cancer, for the following reasons:

a. The International Agency for Research on Cancer classified crystalline silica (quartz and cristobalite) as a human carcinogen in 1997, and crystalline silica was given an A2 'Suspected human carcinogen' rating by the American Conference of Government Industrial Hygienists in 1998 (ACGIH, 2000, IARC, 1997b);

b. lung cancer is the least acceptable adverse health effect that may arise after exposure to crystalline silica, as it is very likely to be fatal;

c. the dose-response relationships between crystalline silica and lung cancer, while varied, represent the most consistent relationship in the epidemiological data available at present.

When setting standards it is important to acknowledge that the risk for a given standard is always less than the risk for the same given level of exposure. In setting a standard, the expectation is that it should not be exceeded and examination of statutory measures in Western Australian industry supports this, especially if sanctions can be imposed when standards are breached. Therefore, the average exposure of any workforce will be less than the standard and their associated risk will also be less. This is exemplified in the dust data from WA mines presented in Table 4 of Hewson (1993), where, from 1979 to 1993, all average levels are less than the standard of 0.2 mg/m^3, and from 1991 to 1993, 3% of samples are over the limit. This means that while for a small proportion of workers the risk is increased to that conferred by the standard, the excess risk applied to the overall workforce is that conferred by the average exposure. There will be different acceptable levels of risk that can be imposed by peak levels to a small proportion of the workforce from those that can be imposed by average levels on the whole workforce.

Acceptable levels of risk for silicosis and FEV_1 loss have not been defined locally, but are discussed below. For example, the commissioned study of compensation for silicosis in Western Australia (*Appendix 2 and (de Klerk et al., 2002b)*) concluded that under the current exposure standard, the rate of onset of silicosis was zero and almost certainly less than 48 per

million. Such a rate could well be acceptable but acceptance requires a collective decision of all interested parties.

As there is no consensus on what level of risk of mortality from lung cancer is acceptable, we have followed the risk assessment guidelines set out by the Royal Society (Warner, 1983), where it is stated that an annual excess risk of death of:

1 per million person-years (py) is considered negligible, with any form of control unjustified,

1 per 100,000 py is considered low, such that 'very few would consider action necessary',

1 per 10,000 py is considered moderate, such that 'few would commit their own resources to reduce risk',

1 per 1000 py is considered high and

1 per 100 py is considered unacceptable.

The HSE, OSHA and EPA have all attempted to define regions of tolerable or acceptable risk resulting from workplace and general community activities ((HSE), 1999b, McClellan, 1999). Superimposed on a background annual risk of death of 1 per 100 py averaged over the lifetime, an additional residual risk of 1 per 1,000,000 py imposed by an occupational exposure is considered "extremely small" and "acceptable" such that further effort to reduce the risk is not likely to be required, as resources to do so would be grossly disproportionate to the risk reduction achieved. Meanwhile, a residual annual risk of 1 per 100 py cannot be justified except in extraordinary circumstances, and would therefore be classed as unacceptable.

Between the extremes of 1 death per 100 and 1 death per 1,000,000 py lies a tolerable region which may vary with different activities or exposures, depending on societal values and the ease or cost of achieving further risk reduction. For substances for which hazardous properties have a threshold, a NOAEL may be determined and then translated into an occupational exposure standard - the level of exposure to which there is minimal risk to the health of the workforce. In contrast, for substances for which there is no identifiable threshold of exposure (and health effects produced are of serious concern), a maximum exposure limit (MEL) may be set as a boundary between the unacceptable and tolerable regions of exposure, ie. exposure above the MEL is deemed intolerable.

The HSE (based on the Royal Society's 1983 recommendation) argues that an individual risk of death of 1 per 1,000,000 py for both workers and the public corresponds to a very low level of risk and should be used as a guideline for the boundary between broadly acceptable and tolerable regions. On the other hand, OSHA has suggested that risks greater than or equal to 1 per 1,000 py are clearly significant and deemed "unacceptably high". The HSE concurred, suggesting that an individual risk of death of 1 per 1,000 py should on its own represent the dividing line between what could be just tolerable for any substantial category of workers for any large part of a working life, and what is unacceptable for any but fairly exceptional groups. For members of the public who have a risk imposed on them in the wider interest of society, this limit was judged to be an order of magnitude lower - at 1 per 10,000 py.

We have therefore concluded that risks higher than 1 per 10,000 py are unacceptable and risks lower than 1 per 100,000 py are acceptable. Thus we recommend an exposure standard for

silica that would limit the population average excess risk of lung cancer to between 1 and 5 per 100,000 py, and the peak excess risk to less than 10 per 100,000 py (ie. 1 per 10,000 py), as this appears to be a reasonable level of risk to be imposed on an employee as a condition of his or her employment.

7.3 Recommended Exposure Standard

Table 12 shows the risks of lung cancer that would result from adherence to different exposure standards, where unacceptable risks are shaded. For reasons stated in *Section 7.2 a*, *b*, and *c*, these risks are confined to lung cancer deaths and do not take the other silica related diseases into consideration. These have been calculated using the various assumptions described below, and are based on a 40 year working-life from age 20. The epidemiological data did not suggest any difference in level for cristobalite, and no evidence was found to suggest a different level for tridymite.

The assumptions are:

a. *The level of the existing risk of lung cancer on which the risk from silica exposure is superimposed*: we have assumed the population rate of lung cancer to be the 1994 Australian *mortality* rate (all studies used lung cancer mortality as their 'end-point') for 65 year old males adjusted to the level we anticipate in 2035. Lung cancer mortality has been declining steadily since the 1980s and we have assumed that the same proportional rate of decline that has been observed from 1980 to 1995 will continue into the future, giving a value of 80 per 100,000 py. While the vastly different rates for smokers and non-smokers could be incorporated into the standard, the Advisory Committee made it clear that such a dual standard would be unworkable.

b. *The dose-response function used*: we have used the pooled IARC study (Steenland et al., 2001a) as it is the most reliable.

c. *How well the standard is adhered to (ie. the proportion exceeding the standard)*: in WA this varied from 30%in 1979-80 down to 3% in 1991-3 (Hewson, 1993).

d. *The variability and distribution of measurements made to assess exposure levels*: we assumed a log-normal distribution with a standard deviation of either 0.75 or 0.85. Table 4 of Hewson (1993) indicated values from 0.7 to 0.9.

Table 12 shows that the choice of an acceptable exposure standard varies greatly, depending on the different assumptions. Based on the pooled IARC study, an acceptable exposure standard was found to be approximately 0.13 mg/m^3 of respirable silica, ***based on current Australian measurement methods***, where shaded risks are definitely unacceptable and others could be acceptable.

Table 12. Excess risk of lung cancer per 100,000 py for peak and average exposure after 40 years of estimated respirable crystalline silica exposure based on IARC study.

Proportion of samples over limit	*Log-normal SD*	***Mg/m^3 of respirable silica using current Australian (BMRC) methodology***																					
		0.2	0.2	0.15	0.15	0.13	0.13	0.12	0.12	0.11	0.11	0.10	0.10	0.09	0.09	0.08	0.08	0.07	0.07	0.06	0.06	0.05	0.05
		Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave	Peak	Ave
0.05	0.75	12.8	2.8	9.5	2.1	8.1	1.8	7.5	1.7	6.8	1.5	6.2	1.4	5.5	1.2	4.9	1.1	4.3	1.0	3.7	0.8	3.0	0.7
0.05	0.85	13.3	2.4	9.8	1.8	8.4	1.5	7.7	1.4	7.1	1.3	6.4	1.2	5.7	1.1	5.1	0.9	4.4	0.8	3.8	0.7	3.1	0.6
0.1	0.75	13.4	3.7	9.8	2.7	8.4	2.4	7.8	2.2	7.1	2.0	6.4	1.8	5.8	1.6	5.1	1.5	4.4	1.3	3.8	1.1	3.1	0.9
0.1	0.85	13.9	3.2	10.2	2.4	8.8	2.1	8.1	1.9	7.4	1.8	6.7	1.6	6.0	1.4	5.3	1.3	4.6	1.1	3.9	1.0	3.3	0.8
0.2	0.75	14.2	5.2	10.4	3.8	9.0	3.3	8.2	3.1	7.5	2.8	6.8	2.5	6.1	2.3	5.4	2.0	4.7	1.8	4.0	1.5	3.3	1.3
0.2	0.85	14.9	4.7	10.9	3.5	9.4	3.0	8.6	2.8	7.9	2.6	7.1	2.3	6.4	2.1	5.7	1.9	4.9	1.6	4.2	1.4	3.5	1.2

7.4 Conclusions

(1) At the level of 0.13 mg/m^3 of respirable silica (based on current Australian measurement methods), using the pooled IARC study for lung cancer and the WA data for silicosis and lung function decrement, and based on a 40 year working life from the age of 20 years, this standard will :

a. ensure that the excess risk of lung cancer is kept below 1 per 10,000 py, and should be considerably less than this,
b. ensure that the cumulative risk of silicosis after a 40-year working lifetime be less than 1%,
c. ensure that the total excess decrement in lung function should be less than 200 mL,

It should be noted that the presented risk estimates for lung cancer in *Table 12* will be appreciably lower for non-smokers.

(2) Given the current exposure standard operating in the mining industry in Western Australia, the study of compensated goldminers in WA indicates that:

a. The actual incidence of silicosis for levels of exposure under the current standard and exposure conditions is almost certainly less than 4.8 cases per 100,000 py.
b. The observed number of cases of silicosis arising in men exposed only after the current standard was introduced is significantly less than the number expected from the same model used to estimate the above incidence of silicosis (8 per 100,000 py). That is, at current levels of operation within the mining industry today, significantly less cases of silicosis (ie none) have occurred than would have been expected based on risk models fitted to the earlier cohort of goldminers. Exposure-response relationships from other studies would have predicted even more cases and appear therefore to be even less appropriate for the current situation.
c. Combining results from both studies, the cohort study of gold-miners (*Appendix 2, Section 9.1*) indicated that the risk of lung cancer after a diagnosis of silicosis was 1.6 (and that the relative risk for lung cancer after this adjustment was 1.0). The observed risk of silicosis in the study of silicosis compensation (*Appendix 2, Section 9.2*) was zero with an upper 95% confidence limit of 4.8 per 100,000 person-years, so that an upper 95% confidence limit for lung cancer could be set at: 4.8 x (1.6-1)/1.6 = 1.8 per 100,000 person-years. That is, current standards should ensure a maximum excess risk of lung cancer well within the 'acceptable' range.

This review provides a health based exposure standard based on considerations of the effects of exposure at various levels, the known incidence of the health outcome in question, and what might be an 'acceptable' level of risk (Vincent, 1998).

The recommended exposure standard for crystalline silica is 0.13 mg/m^3, using current (2001) Australian measurement protocols.

8.0 APPENDIX ONE

AUSTRALIAN TECHNICAL REPORT ON CRYSTALLINE SILICA (1996)

APPENDIX 1. AUSTRALIAN TECHNICAL REPORT ON CRYSTALLINE SILICA (1996)

This appendix describes the work previously conducted towards the review of the occupational standard for crystalline silica in Australia.

8.1 Summary of the Draft Australian Technical Report on Crystalline Silica (1996)

In 1993 an Expert Working Group was asked to evaluate the international and Australian experience with crystalline silica, in order to provide some guidance in terms of the most appropriate controls for crystalline silica in the workplace in Australia. The group produced the Draft Technical Report on Crystalline Silica (1996) (NOHSC, 1996) which was based on information available up until 1993.

The findings with respect to the terms of reference are:

a. *To examine the applicability of overseas data and standards in Australia.*
Diseases of both the lung parenchyma (silicosis) and airways (chronic obstructive pulmonary disease, chronic bronchitis and cancer) are associated with crystalline silica exposure.

b. *To examine the statistics of dust disease in Australia relating to exposure to crystalline silica.*
The current health effect data collected for compensation purposes, which reflects conditions in the past, indicates a reduction in the numbers and severity of silicosis. Health data for airway diseases attributed to dust is not collected.

c. *To study current crystalline silica exposure data in relevant industries in Australia with a view to formulating a health-based exposure standard.*
Exposure data for the respirable fraction is available for only 19 per cent (mining sector) of the estimated 140, 000 crystalline silica exposed workers in 20 different occupations in 50 different industries (70 per cent Construction, 19 per cent Mining, 12 per cent Manufacturing). A risk characterisation model incorporating estimated respirable mass fractions predicts 1000 cases of early mild silicosis and an extra 630 cases of lung cancer in the next 40 years.

d. *To make recommendations on options for exposure standards for crystalline silica.*
Rationale is provided for two respirable exposure standards, 0.1 mg/m^3 and 0.2 mg/m^3, based on exposure data, health effects, measurement aspects and control measures.

e. *To identify particular areas that may be appropriately addressed by codes of practice or guidance notes.*
Data collection: Uniform national methods need to be developed, which comprehensively monitor all the health outcomes in the total exposed workforce. Air monitoring needs to be standardised and linked to health outcomes.
Airways disease: Needs to be surveyed, other respirable hazards controlled, and research

into appropriate particle size-selection monitoring.
Risk factors: Sectors such as small business need special control strategies and information.

Not all members of the EWGCS endorsed all sections of the report. The areas where consensus was not reached were those relating to risk modelling and extrapolation based on historical dust measurements. In November 1993 a scientific forum on crystalline silica was hosted by NOHSC. Two international and 7 local researchers on occupational effects of silica presented their findings to 61 attendants from industry, employee associations and other sectors. The updated collected findings of the meeting were reviewed by the Chairperson (Berry, 1996) and are presented in the subsection, *Report from The Scientific Forum on Crystalline Silica* later in this Appendix.

Between 1988 and 1996, no national exposure standard for crystalline silica existed. However, some mining and occupational health and safety authorities established their own exposure standards. In view of the absence of an enforceable exposure standard for the other jurisdictions, on 2 April 1996 the National Commission reinstated the original NHMRC atmospheric exposure standards, that is:

Quartz	0.2 mg/m^3
Tridymite	0.1 mg/m^3
Cristobalite	0.1 mg/m^3

In declaring the above exposure standards the National Commission recommended that for those jurisdictions where existing legislation specifies lower exposure standard values than above, that those exposure standards be retained in accordance with that legislation. The commission decided that a further review of the standard would be made within 12 months of declaration of this 'interim' standard. It was considered that additional new information might enable consensus to be reached on those technical issues that were yet to be resolved and that this new data might also have an impact on the exposure standard.

Since 1996 the NOHSC Epidemiology Unit has briefed the National Commission regularly by a series of updates on crystalline silica. The Hazardous Substances Unit (now a part of the Chemical Assessment Division) has been working under the guidance of the Hazardous Substances Sub Committee (HSSC) to develop new methods for reviewing and maintaining exposure standards. The question of the review of the interim silica exposure standard has been referred by NOHSC to the Hazardous Substances Sub Committee (HSSC) for consideration.

In April 1998, the HSSC agreed to recommend that a review of the crystalline silica exposure standards was warranted. The objectives and proposed outcomes of the review are defined in the Objectives and Outcomes section in the main document.

8.2 Membership of the Expert Working Group on Crystalline Silica

Dr Gary Baker (Chairperson)	WorkSafe Australia
Mr Barry Chesson	Alcoa of Australia
Dr Eva Francis	WorkCover Authority
Dr Jim Leigh	WorkSafe Australia
Mr Geoff Pickford	Pickford Consulting Pty Ltd
Mr Alan Rogers	WorkSafe Australia

8.3 Membership of the Reference Group on Crystalline Silica

Dr David Kilpatrick	Kilpatrick and Associates Pty Ltd
Ms Kathryn Walton	Confederation of Australian Industry

8.4 Terms of Reference

The terms of reference of the Expert Working Group on Crystalline Silica are to:

a. examine the statistics of dust disease in Australia relating to exposure to crystalline silica;
b. study current crystalline silica exposure data in relevant industries in Australia with a view of formulating a health-based exposure standard;
c. examine the applicability of overseas data and standards in Australia;
d. identify particular areas that may be appropriately addressed by codes of practice or guidance notes; and
e. make recommendations on options for exposure standards for crystalline silica.

8.5 Report from The Scientific Forum on Crystalline Silica

A scientific forum on occupational health and safety issues associated with crystalline silica was hosted by WorkSafe Australia on November 9 and 10 1993. The purpose of the forum was to discuss the draft technical report on crystalline silica. The forum was chaired by Professor Geoffrey Berry, with presentations by Prof Berry, Dr Gary Baker, Dr Jim Leigh, Dr Eva Francis, Dr KC Wan, Mr Geoff Pickford and Mr Alan Rogers, Dr Gregory Wagner and Dr Eva Hnizdo.

The forum was widely advertised and attended by 61 people, from the construction and mining industries, occupational hygiene consultancies, regulatory bodies, employer and employee associations and medical professions. The forum program was divided into two sections:

- presentations by national and international speakers summarising and reviewing the scientific evidence
- syndicate group discussion and presentation of group findings, followed by a general discussion, relating to the health effects of exposure to crystalline silica.

8.5.1 Presentations

Professor Berry reviewed the position of the International Agency for Research on Cancer IARC on silica. In 1987, IARC classified silica as a Group 2A carcinogen, that is, crystalline silica is probably carcinogenic to humans. This was based on sufficient evidence showing cancer in animals and limited evidence of carcinogenicity in humans from epidemiology studies.

Professor Berry noted that in the six years since the IARC monograph had been published, there had been a number of epidemiology studies investigating the possible association between silica exposure and cancer and that it might now be timely for IARC to review the classification in the light of the new epidemiology and toxicology data available.

Dr Gary Baker had chaired the Expert Working Group on Crystalline Silica and summarised the findings of the report:

a. the health effects of silica exposure include airways diseases other than silicosis, such as lung cancer, obstructive airways disease and bronchitis;
b. the current surveillance for health outcomes and crystalline silica exposure is poor, with particular shortfalls for exposure data in the manufacturing and construction industries and for the incidence of airways disease in all industries;
c. workers in small industries in equipment handling occupations appeared to be at the highest risk of exposure; and
d. the risk model developed provided a way to quantify the findings with predictions for silicosis and lung cancer cases per year over the next 40 years, at exposure levels of 0.1 mg/m^3 of 11 silicosis cases and 10 extra lung cancer cases and at exposure levels of 0.2 mg/m^3 of 20 silicosis cases and 14 extra lung cancer cases.

The draft report made recommendations for:

a. systematic pro-active monitoring and health surveillance;
b. industry specific control strategies; and
c. standardised classification in data collection.

Dr Jim Leigh explained the basis for the risk modelling and prediction formulae used in the draft technical report to calculate the predicted cumulative incidence rate of silicosis and lung cancer in the occupationally exposed population, noting:

a. the model used calculated median exposure intensities and durations in a industry-by-occupation exposure matrix;
b. the risk ratio for lung cancer and silicosis were calculated from the incidence data in studies of South African gold miners; and
c. as the risk ratio in the South African gold miners had been developed using respirable surface area particle years, an equation to convert this to mg/m^3 was derived from data on simultaneous measurement counts.

Dr Leigh also provided a synopsis of the papers presented at the 2nd International Symposium on Silica, Silicosis and Cancer, held in San Francisco, in October 1993.

Dr Eva Francis reviewed the past and present techniques for measurement of crystalline silica, noting that the current measurement was the gravimetric respirable dust standard, and this method is published in Australian Standard 2985 - 1987.

Dr KC Wan, reviewed 110 cases of silicosis certified for workers compensation by the Western Australian Pneumoconiosis Medical Panel to determine the relationship to airborne silica in mining. The review concluded that there had been no compensation claims for silicosis in miners who had commenced mining work after 1974 when the current exposure standard of 0.2 mg/m^3 was introduced.

Messrs Pickford and Rogers spoke of the difficulties of using and interpreting historical exposure data, and compared Australian and United States sampling methodologies.

Dr Gregory Wagner reviewed the scientific evidence for health effects of silica and health outcomes, especially lung cancer. He noted that although there was an increasing number of epidemiology studies which looked at the association between exposure to crystalline silica, silicosis and lung cancer, the issue was still being debated. His paper considered some of the methodological issues which may explain the differences in study results. He noted that the evidence supporting the concern for cancer risk in people has overall coherence.

Dr Eva Hnizdo, reviewed the risk of silicosis, emphysema and chronic obstructive pulmonary disease in relation to silica dust exposure in South African gold miners. She noted that the risk of silicosis increased exponentially with increasing silica exposure, and that in comparison to Canadian miners the South Africans had a substantially higher cumulative risk. The studies of chronic obstructive lung disease established that the level of respirable dust to which gold miners are exposed is associated with a significant loss of lung function. Silica dust was associated with the prevalence of emphysema diagnosed at autopsy but in non-smokers only an insignificant degree of emphysema was found.

8.5.2 Syndicate Groups

The forum was split into three syndicate groups and led by Prof Berry, Dr Leigh and Dr Wagner. Each group addressed the same questions and these responses were discussed and consolidated in the general discussion as follows:

Is there a causal link with silica and cancer in the whole work force?

There is a credible hypothesis supported by animal data and epidemiology data that there is a causal link, but the evidence needs to be reviewed by an expert group.

Is there an increase risk of lung cancer in people with silicosis?

In people with silicosis there is evidence of an increased risk of lung cancer but this is not sufficient to establish a causal association.

Does protection against silicosis protect against all airways disease, including cancer?

There is evidence that protecting against silicosis will reduce the incidence of all airways conditions but further studies are needed to elucidate a level to protect against all airways disease.

Syndicate group leaders also gave brief reports on matters raised in considering the questions and these were further considered in the general discussion. These have been grouped together below. They reflect the range of matters discussed and in some cases indicate the extent of agreement but are not intended as a consensus report from the forum.

Silica and Cancer

It was noted that the current IARC classification of crystalline silica as a Group 2A carcinogen was very unlikely to be downgraded.

There was substantial agreement that elimination of silicosis would reduce the excess cancer risk, if indeed there is an excess risk, although not necessarily protect against all of any excess risk, and that the main evidence which can be used to define a protective work environment is data on the incidence of silicosis.

The evidence supporting cancer risk for people with silicosis is consistent, temporally appropriate, demonstrates in some instances a dose-response gradient, and is consistent with laboratory models. It was noted that there was not a great deal of information to separate out the effects of smoking from silica exposure and that there was insufficient information on the interactions between silica exposure, silicosis and lung cancer.

There was some evidence for a causal relationship between cancer and silica, predominantly silicosis, but there were limitations to the data. A review of the new data by IARC was needed.

Health effects other than silicosis

There was a diversity of view as to what presented the most appropriate No Observable Adverse Effect Level (NOAEL), with some considering that all adverse effects should be taken into account and others considering that only silicosis should be considered, as there was a view that preventing silicosis would protect against other adverse health effects.

Loss of lung function from silica exposure was an important and well documented health effect and needed to be given greater recognition, particularly where other adverse health factors are present.

Data Collection

The data sources to properly assess exposure were lacking and there was a great deal of disparity in the monitoring and health surveillance requirements.

Improvements are needed for all stages of data collection with consistent analytical methods, diagnostic standards in medicine and disease classification.

There was international variation in what is considered as silicosis, for example, ILO 1/0 radiology readings were sometimes rated as silicosis instead of a 1/1 reading being taken as a threshold for silicosis.

Use of Compensation Data

The disadvantages in using mining compensation data to determine the incidence of silicosis was raised and it was noted that compensation-based data underestimated the incidence of disease, because of under reporting due to factors such as the disincentives to claim compensation for early silicosis, lack of follow up for those who left the mining industry and exposure occurring in other industry sectors such as construction and manufacturing.

Measurement of silica exposure

There was concern about the reliability of exposure monitoring data.

There was concern that the draft technical report reached conclusions on the risks associated with particular levels of exposure that were dependent on conversion factors over which there is some disagreement. It was considered appropriate that the uncertainty this produced should be introduced into the range of possibilities.

There was also discussion on the conversion factors used in the draft technical report for extrapolating from the United States measurement of respirable silica to Australian measurements of respirable silica, noting that including a second extrapolation factor to take 1.4 to 1.8, to allow for portal to portal sampling as distinct from crib room to crib room, would not always be correct as this would not apply to measurements taken in above-ground mining, construction or manufacturing industries and whether this sampling strategy was never used in Australia.

There were a range of opinions on the adequacy of training for those monitoring for exposure and also whether the Australian Standard for monitoring was adequate.

Characterisation of silica species

There was a need for better characterisation of the physico-chemical properties of alpha-quartz, cristobalite and amphibole particles to understand the differences in toxicity between them. There also appeared to be a toxicity gradient within alpha-quartz species with different surface chemistry. There was a need to review the research needs for crystalline silica in this area.

Control of Silica exposure

The current best practice for control of silica exposure in workplaces is not consistently achieved in many workplaces. There was a need to improve both compliance sampling and assessment of workplace silica hazards to minimise exposures. Information on health hazards and education and training in control measures, for employers and employees using crystalline silica, were important to reducing adverse health effects. While a number of scientific questions remained unanswered, action to prevent adverse health effects from silica exposure could and should proceed.

8.5.3 Summary

The Forum concluded with a summary by Professor Berry of what he considered were the main points of the meeting:

Silicosis has been recognised as a consequence of exposure for several decades but the question today is whether current conditions limit exposure to levels that should prevent silicosis occurring. Dr Wan's results are encouraging but the group exposed after 1974 has to be followed up for a longer period before it can definitely be concluded that the problem is solved. Lung cancer is not a proven consequence of exposure to silica, but recent studies have provided some supportive evidence. In Western Australia there seems to be the opportunity for studies of populations exposed to silica that will contribute to the international data on this topic. A problem with attributing airways disease to silica exposure is lack of specificity; Dr Hnizdo's data showed a gradient in relative risk of 50-fold in relation to smoking but of less than two-fold for silica exposure for emphysema.

There are problems in using historical estimates of exposure levels. The draft technical report presents a range of estimates of disease outcome in relation to exposure, constituting good estimates of what can be achieved with the data available. But there are clearly some problems because the history of the situation is that exposure information is required according to modern measurement methods from periods when different ways of measuring airborne dust and silica were used. This problem has occurred in other settings; certainly it has been a problem in asbestos. Probably we will never have an answer that satisfies everyone but as Dr Wagner stated earlier in the meeting 'Prudent public health practice requires that action is taken in the face of uncertainty.'

Whatever might be done in defining exposure standards and work practices a problem is compliance, whether this is done by enforcement or through an educative approach. The main problem seems to be the small industries which between them employ a large number of workers. The danger is that concentrating 'enforcement' resources on the larger industrial concerns, where there is already a reasonable measure of control, to try and make marginal

improvements may take attention away from areas where major improvements are possible and ought to be achieved.

9.0 APPENDIX TWO

STUDIES OF WESTERN AUSTRALIAN GOLD MINERS

APPENDIX 2. STUDIES OF WESTERN AUSTRALIAN GOLD MINERS

Two analyses of Western Australian data were commissioned by the Advisory Committee and conducted by the Consultants, to assist in this review by adding to the body of dose-response data.

9.1 Introduction

The follow up of Western Australian (WA) gold miners has previously been reported using non-quantitative silica exposures according to job and duration of work (de Klerk et al., 1998, de Klerk et al., 1995). The first analysis in this appendix describes the conversion of non-quantitative exposures into quantitative estimates of crystalline silica exposure (mg/m^3), to determine dose-response relationships between silica-related diseases and cumulative exposure to respirable silica, and to contribute to the data suitable for the review of the exposure standard for crystalline silica. The results of these analyses were presented for the first time in earlier drafts of this document and have since been published as an extended abstract (de Klerk et al., 2002a).

The second analysis re-examines the incidence of silicosis in Western Australia until 1998 using the work histories of all compensation claimants after 1974, when regulation of the current exposure standard for crystalline silica (0.2 mg/m^3 using British MRC methodological criteria) began in the mining industry in Western Australia. It is reported that up until 1993, there have been no cases of silicosis among workers first employed in the industry after 1974 (Wan et al., 1999). This implied that with the current silica exposure standard, workplace practices were adequate for protecting the health of workers in the industry. However, several potential shortcomings of that study have been identified. The aims of this study were to determine if any new cases of silicosis had occurred since 1993 in workers whose exposures started after 1974. Furthermore, Mines Department Annual Reports containing annual numbers of miners in WA were used establish the expected number of cases, to estimate the upper confidence interval for the risk of silicosis in WA with the operation of the current exposure standard for crystalline silica. These results have also been published (de Klerk et al., 2002b) since first being presented in earlier drafts of this document.

9.2 A quantitative analysis of the major health sequelae associated with crystalline silica exposure in West Australian gold miners

9.2.1 Abstract

A subset of 2215 of the 2297 West Australian goldminers previously described in de Klerk and Musk (de Klerk et al., 1998) who had complete work and smoking histories were selected, and their data re-analysed with a view to examining quantitative exposure-response data for major adverse health effects from respirable crystalline silica exposure.

Cumulative exposures to respirable silica were derived using a method to standardise over 550 dust particle counts taken from mines in WA during the 1950s with subjective dust exposure rankings for over 400 jobs. Survival analyses for mortality from lung cancer, auto-immune disease, end-stage renal disease, incidence of compensated silicosis, as well as tuberculosis and silicosis mortality were performed using age- and year-matched conditional logistic regression analyses. Determinants of change in FEV_1 were also determined for the subset of subjects (n=91) who attended 2 successive surveys of lung function. We also analysed FEV_1 effects using only cross-sectional data from each subject's first survey where FEV_1 was measured.

There was a strong and consistent effect of estimated exposure to respirable silica on incidence of silicosis and the prevalence of bronchitis, and the risk of lung cancer was raised, but not significantly. The presence of silicosis was associated with increased lung cancer mortality as described previously, and was very strongly associated with auto-immune disease, but not with end-stage renal disease. Its association with tuberculosis mortality was fairly high, but not statistically significant.

9.2.2 Background

A cohort of 2297 goldminers working in the Kalgoorlie region of WA was established from workplace surveys of respiratory symptoms, smoking habits and lung function, which were performed in 1961, 1974 and 1975. Among these subjects, the incidence of silicosis has been clearly related to duration of silica dust exposure, with the onset of silicosis conferring a significant increase in risk for subsequent lung cancer (de Klerk et al., 1998). Among the more recently employed goldminers, it has been shown that duration of exposure to silica dust is significantly related to the prevalence of bronchitis and airflow obstruction (Holman et al., 1987), and to measures of lung parenchymal function in non-smoking miners (Musk et al., 1992). Chest xray abnormalities indicative of silicosis were also associated with duration of underground employment and smoking history (Musk et al., 1993).

The aims of this re-analysis were to calculate exposure-response relationships for the major health sequelae of silica exposure, using quantitative exposures.

9.2.3 Methods

9.2.3.1 Outcome assessment

The surveys of 1961, 1974 and 1975 included a slightly modified version of the BMRC questionnaire on respiratory symptoms. Bronchitis was defined as cough and phlegm for periods of at least 3 months in a year, for at least 2 years. FEV_1 and FVC was measured by dry wedge spirometer, using the best of 3 readings (Cotes et al., 1997).

In 1993, ninety percent of the cohort could be traced to either the West Australian electoral roll or the West Australian death registry. Deaths from lung cancer, tuberculosis, silicosis, auto-immune disease (AID) and end-stage renal disease (ESRD) were identified from the coded cause of death in the WA Death Registry records. Existing Pneumoconiosis Medical Board (PMB) records were searched in 1993 to identify cohort members who had received compensation for silicosis.

9.2.3.2 Exposure assessment

Smoking

Non-smokers were defined as never having smoked one cigarette a day, one cigar a week, or one ounce of tobacco a month, for as long as one year. Ex-smokers had stopped smoking at least three months before the survey. Smokers were categorised as smoking 1-14 cigarettes per day, 15-24 cigarettes per day or 25+ cigarettes per day. Rolled tobacco and pipe tobacco use was converted to cigarette equivalents, assuming one cigarette for every gram of tobacco.

Employment Records

Full employment details for each of the gold miners were recorded on miners' record cards held at the Perth Chest Clinic (PCC). These included details of dates of employment at each mine and job descriptions, as well as other clinical information which had been recorded each time a subject returned for compulsory annual chest x-ray films, which were required as long as he continued work as a miner. These records were found to be much more detailed than the survey employment histories and were therefore used to provide each subject's full employment history in the goldfields.

Job Ranking

A panel of experts including several former mines inspectors, industrial hygienists, occupational physicians and public health practitioners was convened to make a subjective ranking (on a scale of 1 to 10) of all jobs that all men had done according to their PCC records. Rankings were made specific for each calendar period where the panel felt that changes in engineering procedures and controls might have led to changes in dust levels. This ranking was compiled and then re-verified by one of the mines inspectors.

Dust Counts

There were two sources of dust count data: dust particle counts according to an assortment of jobs in specific WA mines, and average annual dust particle counts from all WA mines sampled for compliance regulation.

Several particle counts (ppcc) made for an assortment of jobs in West Australian mines during the 1950s were obtained from regulatory measurements made since 1925, by the West Australian Department of Minerals and Energy. Particle counts for almost all mines in the Kalgoorlie region were available for 1957 and 1958. However when compared, there was virtually no correlation between dust counts for particular jobs and their subjective ranking, even when restricted to the year when dust particle counting was most complete (1958). It was clear on examination of the readings that the job-specific dust counts for each year were based on tasks that were thought to be especially dusty at that time. That is, compliance samples had mostly been taken and the dust counts were therefore biased towards the upper limits of exposure.

Annual average dust particle counts from WA mines (Hewson, 1993) were available from West Australian Mines Department Annual Reports, and it was thought that these could be used to examine longitudinal trends in dust exposures experienced by WA gold miners, once standardised with the job-specific dust counts. However, these included dust counts from all mines in WA covered by the particular legislation, so that extremely dusty operations such as the asbestos mine at Wittenoom (where reported counts were regularly above the detectable maximum of 1000 ppcc) were included in calculating these average yearly dust levels, as well as exposures experienced by both underground and aboveground workers.

Silica Exposures

The job-specific dust particle counts therefore represented the distribution of dust levels experienced in West Australian mines at the time, but could not be depended upon to indicate dust levels associated with the specific job or task being carried out at the time of the sample. The assumption then had to be made that the jobs sampled at each mine in each year were similar and an allocation procedure was used as follows:

The dust particle counts collected for all jobs sampled during 1958 (when almost all Kalgoorlie mines were surveyed) were plotted on a probability scale. The average dust particle count for 1958 was then equated with the average rank for all of the jobs sampled in that year (over 400 were accorded an agreed rank score classification). The average rank for all jobs with corresponding dust counts in 1958 was 6.74, and the average dust particle count for 1958 was 153 ppcc (based on 569 recorded dust levels). It was assumed that this method of 'standardisation' was applicable to all other sampled years and not only to the jobs that were sampled in 1958.

The distributions of the dust counts were almost identical between the 10^{th} to the 70^{th} percentiles for the years 1953/54, 1957 and 1958. The job rankings (1-7) were therefore superimposed onto each of these deciles. For the average rank, the difference between deciles of dust counts using a combination of all available dust surveys from 1953/54, 1957 and 1958, was 35 ppcc. For example, the average rank for 1957 was 6.7, and this was equated to the mean dust count of 153 ppcc. A rank of 5.7 (one percentile lower in the dust count distribution) could then be defined as 153-35 = 118 ppcc. The difference between other ranks was then estimated as a proportion of that decile difference (35 ppcc) between the mean rank and the next.

The average dust count for underground mines recorded in the Mines Department Annual report for 1957 was 177 ppcc, so that for all other years the rank score mean of 6.7 was

equated to the annual average multiplied by (153/177) ppcc. A table of rank to dust concentration conversions for some typical years is shown in *Table A2.1.*

Dust counts were then converted to gravimetric estimates of crystalline silica exposure using Hewson's methods (Hewson, 1993). That is, all pre-1961 dust counts were multiplied by 1.6 (to adjust for changes in dust counting), 1 ppcc = 0.01 mg/m^3, and 20% silica in dust was assumed. Regression techniques using the annual average dust counts that were standardised with job-specific dust counts, produced an exponential curve, and translated job rankings into dust exposures. Personal silica exposures by job were then expressed as:

Respirable crystalline silica (mg/m^3) = ((186.64exp(0.2563*job rank))*exp(-0.0223*year of work))/500

Table A2.1. Estimated Dust Exposure According to Job Rank by Year in WA Gold Mines, ppcc.

	Rank score									
Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1925	135	175	226	294	381	494	640	830	1000+	1000+
1935	117	152	196	255	330	428	555	720	933	1000+
1940	95	124	160	208	269	349	453	587	762	987
1950	73	94	122	158	205	266	345	448	580	752
1960	66	85	111	143	186	241	313	406	526	682
1970	55	71	92	120	155	201	261	339	439	569
1975	42	54	70	91	117	152	198	256	332	431

Exposures = (underground average dust count for year) x (153/118)$^{(\text{Rank score} - 6.7)}$ sampled as dust particle counts, expressed as ppcc of dust; divide by 100 for mg/m^3, further divide by 5 for respirable silica.

9.2.3.3 Statistical methods

A nested case-control design was used where subjects could be controls for more than one case and cases could be controls in years prior to the onset of their disease. Controls were age matched to cases.

Variables compared between cases and controls were smoking status, duration and concentration of respirable crystalline silica exposure, the product of these (cumulative exposure), time since first exposure (years) and time since last exposure. Apart from smoking, all of these variables were calculated up until the date of death. Smoking habit was categorised as that given at the time of survey, and could only be assumed not to have changed since. The presence of bronchitis at survey was included as a covariate. When lung cancer was the outcome, the onset of silicosis was also included as a time-dependent covariate.

The frequencies of the variables of interest in the matched sets of cases and controls were compared by conditional logistic regression analysis using the Cox regression program from SPSS for Windows, and stratified on combined values of current age and year at risk with a constant survival time variable. Non-linearity of effects was subsequently examined using fractional polynomial regression (command fracpoly) in STATA (STATA, 1999).

The association of cumulative respirable silica with bronchitis was examined using logistic regression, and with lung function, using linear regression. The majority of studies examining the association between mining dust exposure and level of FEV_1 have done so using cross-sectional data estimated at single surveys. So that comparisons could be made and studies combined, we examined the association of silica exposure and lung function deficit both longitudinally and cross-sectionally.

9.2.4 Results

The distributions of basic variables were as described previously (de Klerk et al., 1998). *Table A2.2* shows the estimated increase in occurrence of disease. All rates are per log(mg/m^3-year) of cumulative respirable silica.

Bronchitis and pulmonary function

The relative rate for prevalent bronchitis was 1.4 (95% CI, 1.2-1.6).
Table A2.3 shows that when examined longitudinally within subjects, lung function declined at a rate of 66mL per year, per log(mg/m^3-year) of cumulative respirable silica exposure (95% CI, (-235) - 103 mL). FEV_1 was lower on average by 42 mL per log (mg/m^3-year) cumulative respirable silica exposure according to cross-sectional data.

Silicosis mortality and morbidity

The relative rate of silicosis incidence was 4.8 (95% CI, 4.1-5.7). For comparison with other studies we estimated the relative rate of silicosis mortality as 2.2 (95% CI, 1.2-3.9). The effects of intensity of respirable silica exposure appeared linear and the effects of duration more exponential when these two exposure effects were included in models for silicosis instead of cumulative silica exposure (*Figures A2.1* and *A2.2*). This suggests that cumulative exposure may be the wrong metric for examining exposure effects. These models of the relative rate (RR) of silicosis also included effects of time since first exposure which showed a steep rise till 10-20 years after exposure, then a plateau till about 50 years after first exposure, and then a gradual decline (*Figure A2.3*).

Lung Cancer

The relative rate of lung cancer mortality was 1.2 (95% CI, 0.9-1.6). The effect of silicosis (time-dependent) rather than respirable silica exposure on lung cancer was 1.6 (95% CI, 1.1-2.2). When silicosis was included in the lung cancer model, the RR for cumulative respirable silica exposure reduced to 1.00 (95% CI, 0.72-1.40).

Other disease

The relative rate of tuberculosis mortality per log(mg/m^3-years) was 2.5 (95% CI, 0.5-11.4). Mortality from auto-immune diseases (systemic sclerosis, scleroderma, lupus erythematosus,

not including ESRD) was 1.3 (95% CI, 0.5-3.6) and ESRD mortality was 1.2 (95% CI, 0.4-3.1). The effect of silicosis (time-dependent) rather than respirable silica exposure on auto-immune disease was 7.3 (95% CI, 1.9-28.6) *(Table A2.2)*. The RR of ESRD for silicotics was 1.4 (95% CI, 0.4-4.8).

Table A2.2. Change in Risk and Cumulative Respirable Silica Exposure, WA Gold Miners.

Outcome	*N cases*	*Adjusting factors*	*Relative rate per log (mg/m^3)* [§] *(95% CI)*	*Effect of silicosis*[ϕ] *as time-dependent variable (95% CI)* [§]
Silicosis incidence[ϕ]	643	Smoking, years since first employed	4.8 (4.1-5.7)	
Silicosis mortality	50	Smoking, years since first employed	2.2 (1.2-3.9)	
Lung cancer mortality	136	Smoking, bronchitis	1.2 (0.9-1.6)	1.6 (1.1-2.2)
Tuberculosis mortality	6	None	2.5 (0.5-11.4)	2.7 (0.5-14.6)
AID mortality	12	None	1.3 (0.5-3.6)	7.3 (1.9-28.6)
ESRD mortality	13	None	1.2 (0.4-3.1)	1.4 (0.4-4.8)
Bronchitis prevalence	1071	Smoking, age, years since first employment	1.4 (1.2-1.6)	

[ϕ] compensated silicosis cases

[§] relative rate per log (mg/m^3) cumulative respirable silica exposure

Table A2.3. Change in FEV_1 and Cumulative Respirable Silica Exposure, WA Gold Miners.

Pulmonary Function	*N subjects*	*Adjusting factors*	*Regression coefficient*	*95% CI*
Annual FEV_1 decline [§] (mL/year)	95	Smoking, weight, age	- 66	-235, 103
FEV_1 deficit (mL) [§] (cross-sectional)	368	Smoking, height, weight, age	- 42	-130, 45

[§] per log (mg/m^3) cumulative respirable silica exposure

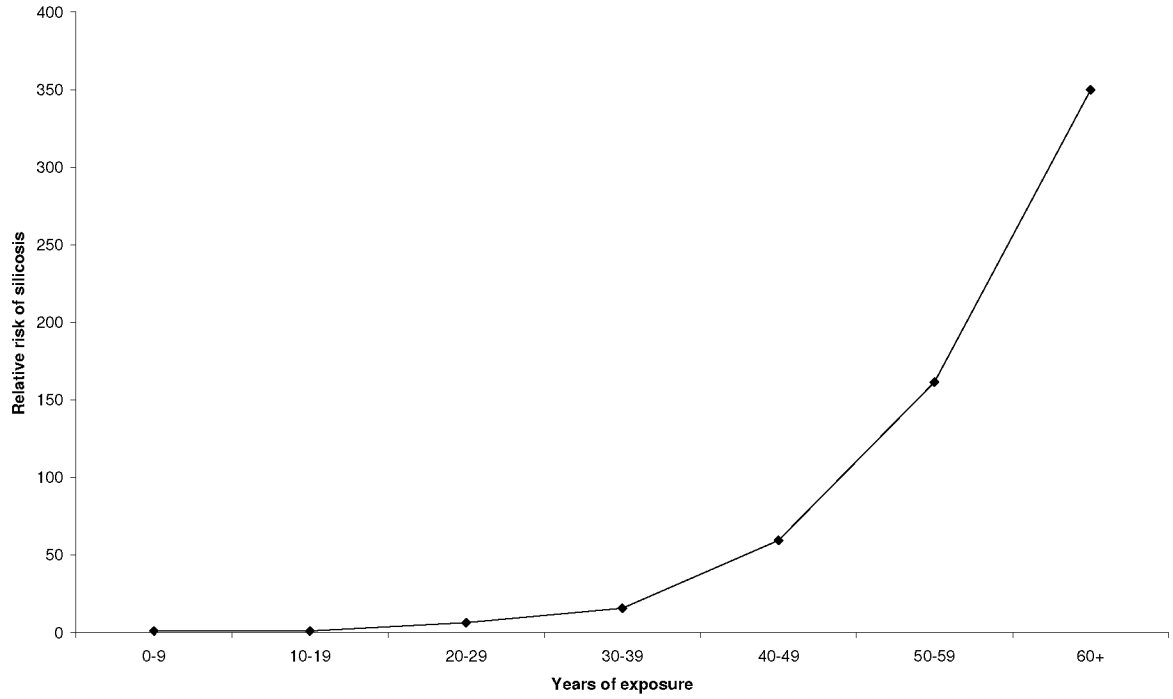


Figure A2.1 Relative rate of compensated silicosis and duration of silica exposure
(adjusted for exposure intensity, bronchitis, and smoking).

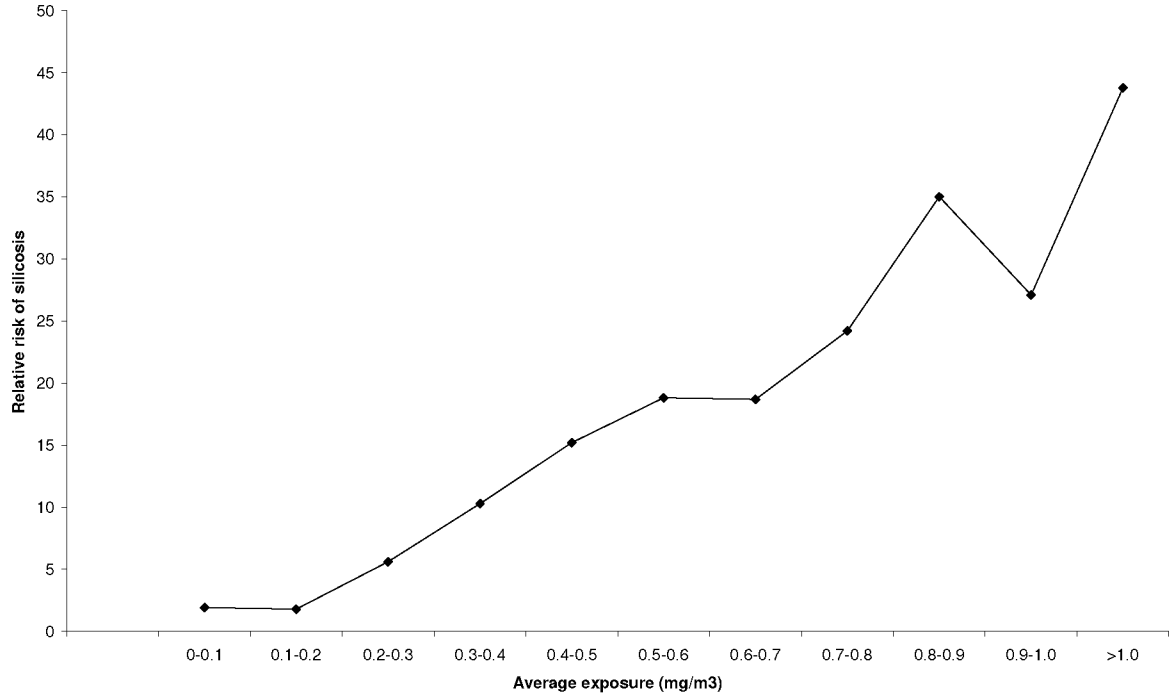


Figure A2.2 Relative rate of compensated silicosis and average respirable silica exposure

(adjusted for duration, bronchitis, and smoking).

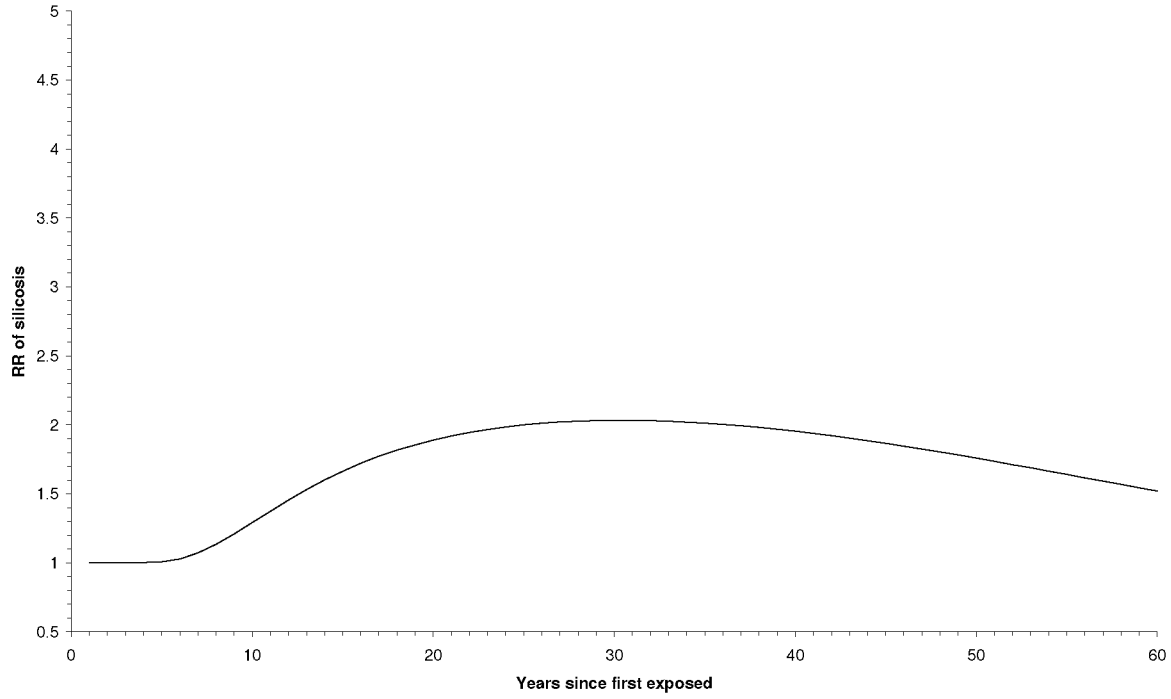


Figure A2.3 Relative rate of compensated silicosis and time after first silica exposure
(adjusted for duration, intensity, bronchitis and smoking)

9.2.5 Conclusions

After refinement of cumulative respirable silica exposures to mg/m^3, silicosis incidence and mortality, and bronchitis prevalence in the WA gold miners' cohort were clearly and significantly related to respirable crystalline silica exposure.

Mortality from lung cancer (adjusted for smoking), AID and ESRD were not significantly related to cumulative respirable silica exposure, however the non-significant increase in risk of lung cancer was similar to that found in other quantitative studies (Checkoway et al., 1997, Hnizdo et al., 1991a, Reid et al., 1996). Both lung cancer and AID mortality were significantly increased once silicosis had been diagnosed, with the risk for AID considerably high (RR = 7.3), suggesting immunity related problems arising from silicosis.

After allowing for smoking, weight and age, annual decline and cross-sectional deficit in FEV_1 was not significantly related to cumulative respirable silica exposure, however the number of subjects available for this analysis is small. Again, the reductions observed were similar to those found in other quantitative studies (Eisen et al., 1995, Hnizdo, 1992, Hnizdo et al., 1990, Kreiss et al., 1989, Myers et al., 1989, Oxman et al., 1993, Theriault et al., 1974)

The detailed comparison of the silicosis results found here with those from other studies must await completion of a study of corresponding ILO xray diagnoses on the study subjects, as has been used in most other studies.

9.3 Silicosis Compensation in Western Australian Miners, 1974 - 2000.

9.3.1 Abstract

Silicosis in Western Australia is thought to have been eliminated since the advent of the West Australian Ventilation Board and regulated implementation of the current exposure standard for crystalline silica in 1974 (Wan et al., 1999). However, there are several potential inadequacies in this assessment: compensated cases and incomplete coverage of the exposed population, insufficient information concerning exposure, a lack of denominator information, and the effects on rates of disease latency.

The aims of this study were to re-examine the incidence of new cases of silicosis in workers whose exposures began after 1974 and using estimates of the population at risk, to estimate the upper confidence limit for the risk of silicosis in WA where the current exposure standard for crystalline silica is in operation.

The number of workers employed in mining industries in WA has increased overall, however the number employed in mining for more than 10 years has decreased dramatically. There were no cases of compensated silicosis whose first dust exposure in the WA mining industry began during or after 1974. Under current workplace practices, the maximum number of cases expected (the upper confidence interval for silicosis risk) is estimated to be 4.8 per 100, 000 person-years.

9.3.2 Background

In 1974, the WA Ventilatory Board was set up to regulate surveillance of implementation of the current exposure standard for silica (0.2 mg/m^3 using BMRC criteria) in the WA mining industry. It has been reported that no cases of silicosis have occurred among workers first employed in the industry since that date, based on compensation for silicosis (Wan et al., 1999). This implies that with the current silica exposure standard, workplace practices are adequate for protecting the health of workers in the industry. There are several issues to be considered with this conclusion:

Compensation data contains some information regarding occupational history (date first employed, where employed etc), occurrence of the disease and level of compensation awarded. However, no denominator data are collected so that disease rates may be calculated, and therefore the confidence interval for this observed zero value is unknown. Alternatively, if cases do occur, it is clear that the exposure standard is not a 'No Observed Adverse Effect Level' (NOAEL). The degree to which people successfully applying for compensation represent all exposed subjects with silicosis in a defined area is generally unknown. For example, the majority of West Australian goldminers in the past have known about the existence of the Pneumoconiosis Medical Board (PMB) and may have looked upon silicosis compensation as a kind of pension for which there is no penalty for applying. In other industries the tendency to make an application at the time of retiring from the industry is almost certainly less.

An attempt at complete annual x-ray screening was made in the mining industry at least until recently, but not in most other industries, and coverage has changed over time. It is well accepted that the majority of workers exposed to crystalline silica are in the construction industry (Nurminen et al., 1992). Furthermore, it is almost certain that people with concomitant diseases (especially smoking-related airway disease) would be more likely to apply to the PMB. The significant effects of smoking habit on silicosis incidence described in the WA goldminers study (de Klerk et al., 1998) were considered to be due to this. Alternatively, many people could have diagnosable silicosis without feeling sufficient symptoms to warrant seeing a doctor and obtaining a chest x-ray. To summarise, unknown numbers of cases of silicosis could occur without being detected.

There are also problems of disease latency. It is known that silicosis (except the acute form which can occur shortly after very heavy exposure) usually takes many years to develop after exposure has started and may not occur until after a subject has left the industry (Glover et al., 1982). *Figure A2.3* (*Section 9.2*) shows the change in relative risk of silicosis with follow-up time after adjustment for duration and intensity of exposure. It is clear that there is no disease within 5 years of exposure, and the risk then increases rapidly to a maximum at approximately 30 years after exposure started. Many studies (particularly industry-based cross-sectional studies) are unable to distinguish latency time from exposure time, and it is quite feasible that latency might increase as exposure decreases. To be able to say that the risk of disease is zero after a standard has been brought in then requires follow-up well after any possible latent periods. It is not clear that this time has yet been reached in Australia.

In order to assess the reliability of the NOAEL or zero rate (if one is found), an estimate of the population at risk is required, so that for example, an upper confidence interval can be placed on the zero value (analogous to a detection limit in industrial hygiene dust sampling). However, a simple estimate of the annual net workforce is not sufficient because the risk of silicosis increases with cumulative silica exposure (a combination of duration and intensity of exposure) and with time since exposure ceased, so that rather than reducing the risk of disease by reducing the exposure, the risk might be reduced by increasing staff turnover. Some information on staff turnover and its association with age and duration of employment is therefore needed.

Knowledge of what the levels of exposure to silica have actually been, is also important. For example, if workplace hygiene conditions are such that the standard is often exceeded, or the standard is never even approached, generalisability to other industries is questionable.

The aims of this study were to determine if any new cases of silicosis have occurred in workers whose exposures began after 1974, and to estimate the upper confidence limit for the risk of silicosis in WA at the current exposure standard for crystalline silica.

9.3.3 Methods

Identification of claimants and their work histories.

The Pneumoconiosis Board (PMB) of WA consists of a panel of physicians who meet monthly to assess applications for compensation due to disability associated with pneumoconioses acquired through occupational exposures. The assessment involves a review

of the applicant's medical and occupational histories and diagnostic results of any xrays, CT scans, histo-pathology and pulmonary function tests ordered by the referring doctor. Data retained by the PMB include: name of applicant, date of birth, awarded compensation (if any) as well as a brief job history, all of which was collated by year of application.

Because of a legal ruling brought in after action from lawyers representing former asbestos producers, the PMB was not allowed to make a diagnosis of silicosis after June 1992, and had to record 'pneumoconiosis' as the diagnosis. We searched the PMB records for all subjects awarded compensation for either silicosis or pneumoconiosis from the end of 1998, working backwards. The working history in the PMB record for each case was checked to see if their occupational exposure to silica dust in Western Australia had occurred prior to 1974. Work histories were also sought from miners' record cards held at the Perth Chest Clinic. The miners' records include details of dates of employment at each mine, job descriptions, and other clinical information which had been recorded each time a subject returned for compulsory annual chest x-ray films, which were required as long as he continued work as a miner. These records were found to be much more detailed than the PMB data.

Exposure assessment

Gravimetric dust sampling of various mines throughout WA has been undertaken by the West Australian Government's Department of Mines since 1974 and recorded in the CONTAM Database since 1976. The silica content of these samples has been estimated using either x-ray diffraction or infra-red spectroscopy. How well actual measures of silica levels conform with the standard could be assessed on a job specific basis and each claimant's job history could be assigned a 'post-standard' estimate of exposure, however, without this information for all subjects without disease (or at least a sample of them), estimates of overall levels of compliance with the existing standard, and how these have changed over time, must suffice. Such estimates have been comprehensively estimated up until 1993 by Hewson (Hewson, 1993), but exposures after 1993 are not currently available. However, there is no reason to believe that they do not continue the steady decline reported by Hewson. In his report, average levels have been maintained below 0.2 mg/m^3 since 1977, and have steadily declined each year (Hewson, 1993). Even 'high exposure jobs' have been kept below 0.2 mg/m^3 since 1989 (Hewson, 1993).

Estimation of person-years at risk of silicosis.

Estimates of the proportion of miners in each year was obtained by regression smoothing using data from published cross-sectional surveys of the mining industry (de Klerk et al., 1999, de Klerk et al., 1998, Holman et al., 1987, Musk et al., 1992). The mean age in each sub-group was similarly obtained.

The 'eligible' workforce may be considered as those knowingly exposed to dust and eligible to apply for dust related compensation. As a proportion of the total workforce (ie. in minerals industries), the 'eligible' workforce is considered to be the fraction of the total workforce for whom x-rays are currently mandatory. According to the 1995 survey of whole mining industry in WA (Miner's Health Surveillance data, Department of Minerals and Energy, WA) this would be 6318/46216, or 14%. The figure of 14% is in approximate agreement with the coverage rate of previous surveys of Kalgoorlie gold miners. For example, in the 1975 cross-sectional survey of WA gold miners, a total of 348 people attended, 19% of all WA workers in the gold industry and 3% of all employees in minerals industries (Musk,

unpublished data). In the 1989 Kalgoorlie gold miner's survey 1363 attended, which comprises approximately 10% of all employees in the gold and nickel industries, or 4% of all employees (Musk et al., 1992).

Life-table methods were then applied with the following approximating assumptions:

a. The total population at risk each year was 14% of the total mining workforce
b. Age-specific death rates were those for males living in WA in 1991
c. The age was the mean interpolated age in each duration of exposure sub-group
d. Those leaving the workforce died at the same rate as those who stayed

Statistical Methods

The expected number of silicosis cases was calculated according to the duration of work and time when exposure occurred in the eligible workforce. Assuming cases occur randomly with a Poisson distribution, then zero cases will occur 5% of the time if 3 cases are expected. Therefore, 3 divided by the person-years observed can be interpreted as an upper 95% confidence limit for the true rate when observing zero cases.

9.3.4 Results

The search for compensated cases stopped after reaching PMB records for 1978, as it became evident that no cases compensated prior to 1979 had commenced their exposures before 1974. There were 408 compensation applications between 1979 and 1998, with a fairly dramatic decline in these numbers over time *(Figure A2.4)*. All work histories for these cases were located at the Perth Chest Clinic. There were 2 cases who first started work in the West Australian mining industry in 1974 or later, but had previous mining exposure elsewhere. There were no cases whose first dust exposure occurred in the WA mining industry during, or after 1974.

Table A2.4 shows the duration of employment in gold mining according to the Kalgoorlie cross-sectional surveys of 1974, 1985 and 1989, and Miner's Health Surveillance data of 1995. Staff turnover has increased in the industry since 1972 *(Table A2.5)*. Whereas the total workforce has steadily increased, the mid 1970s saw the least number of men employed in the Kalgoorlie gold mines in the last 100 years *(Table A2.5)*. Thus, while the proportion of new starters in the total workforce has increased necessarily with increasing overall staffing levels, the proportion of workers employed for under 10 years has increased dramatically and there have been concomitant declines in long-stay employees *(Table A2.4)*. The workforce as a whole appeared to be getting older, also.

Table A2.6 provides an estimate of the expected numbers of cases from the risk model derived above (Table A2.2) and various estimates of the actual exposure level operating in the mines. Based on the observation of zero cases, and by applying equal weight to all person-year strata, an upper limit for the incidence rate of silicosis under current WA workplace practices is estimated at 4.8 cases per 100,000 person-years.

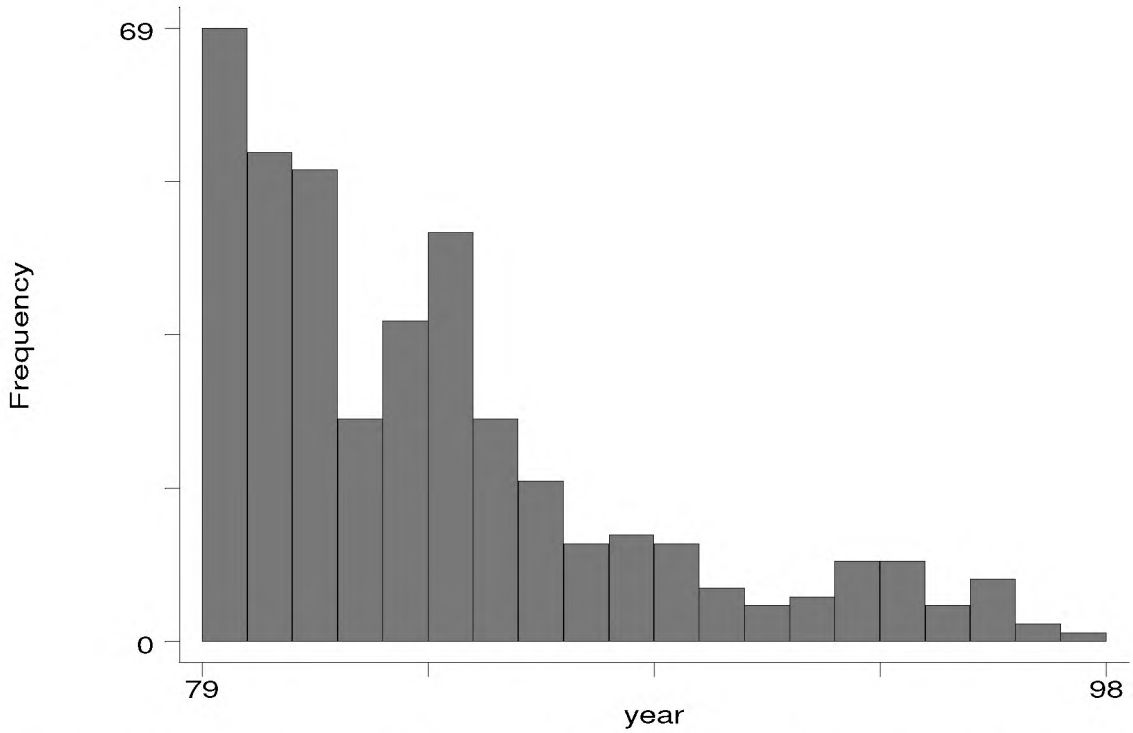


Figure A2.4. Numbers of Pneumoconiosis Compensation Applications in WA, 1979-1998.

Table A2.4 Duration of Employment in Gold Mining in WA, 1974-1995.

	% of Total Surveyed (mean age) [1]			
# Years Employed	1974	1985 [2]	1989	1995 [3]
<1	3 (21.2)	17 (-)	2 (28.1)	10 (31.3)
1-9	19 (29.4)	44 (-)	64 (30.6)	80 (34.2)
10-19	33 (40.0)	22 (-)	20 (42.1)	7 (44.4)
20-29	30 (48.3)	10[§](-)	9 (49.1)	3 (52.1)
30+	15 (56.9)	7[§](-)	5 (57.5)	0.2 (58.3)

[1] cross-sectional surveys of Kalgoorlie gold miners in 1974, 1985 and 1989, and Miners' Surveillance data from 1995

[2] includes nickel smelter workers

[3] all designated workers in mining operations

[§] inferred from different grouping in publication

Table A2.5 Persons Employed in West Australian Minerals Industries, 1972-1998.

Year	*Gold Mining*	*All mines*
1972	1982	9947
1973	2001	11495
1974	2027	12268
1975	1808	13686
1976	1153	13346
1977	871	13596
1978	960	13066
1979	996	13400
1980	1480	20251
1981	2450	24193
1982	2358	23628
1983	2968	24242
1984	3931	25548
1985	4136	26492
1986	4498	29691
1987	6757	30581
1989-90	13348	33074
1995	15999	34794
1996	13080	39599
1997	12569	40098
1998	12614	45429

Taken from Annual Reports of the West Australian Department of Minerals and Energy, 1972-98

Table A2.6 Expected Number of Silicosis Cases in WA, 1979-1998

Years of exposure [ϕ]	*Person-years*	*Expected number of Silicosis Cases* [ϕ]		
		Actual exposure level (mg/m^3)		
		0.05	0.15	0.25
1-9	54 917	2.98	4.87	16.2
10-19	6 818	0.49	0.80	2.66
20-29	175	0.07	0.11	0.38
30+	0	0	0	0
TOTAL	61910	5.8 (0.003) [§]	19.2 (<0.0001) [§]	19.2 (<0.0001) [§]

[ϕ] subjects with more than 5 years since first exposure, first exposed after 1972.

[§] p-value for significance from 0

9.3.5 Conclusions

It is clear that there have been significantly less cases than expected, whatever the actual level. It should be noted that West Australian dose-response data predicts the lowest number of expected cases out of all other dose-response studies discussed earlier (*Sections 5.0* and *6.0*), so that any other predictions of disease risk using WA data may be even further from that expected. Errors could have arisen in: the estimate of person-years, the exposure-response equation, and/or exposure estimates, and it is not possible to identify which way these errors would go or by how much. However, they do suggest that continued monitoring of the numbers of workers joining, leaving and remaining in the industry, and their work histories, forms an essential part of maintaining adequate industry surveillance, in addition to exposure monitoring.

10.0 APPENDIX THREE

METHODS FOR A REVIEW OF THE LITERATURE

APPENDIX 3. METHODS FOR THE LITERATURE REVIEW

The aims of this review were to review the toxicological and epidemiological literature on the adverse health effects of crystalline silica, and also to ascertain relevant data that would be suitable for meta-analyses, in order to determine dose-response relationships for each of the health effects. This appendix describes the methods used to identify and review the literature, and briefly outlines the fundamentals of meta-analysis.

10.1 Systematic Literature Reviews

An extensive reference database of epidemiological and toxicological studies on the health effects of crystalline silica was developed in order to review the current Australian Occupational Exposure Standard for crystalline silica. Of the relevant studies that were accepted after critical examination of study design and exposure issues, those epidemiological studies presenting interpretable dose-response data and toxicological studies published after 1996 (after the 1997 IARC Monograph on the Evaluation of Carcinogenic Risks to Humans (IARC, 1997b)) were included in this review.

10.1.1 Literature Searches

Bibliographies from the 1996 Draft Technical Report (NOHSC, 1996) and the 1997 IARC Monograph (IARC, 1997b) were used as starting point for references. Key reports and proceedings were obtained directly from the authorities producing them eg. IARC, ACGIH, EPA, International Programme on Chemical Safety.

For epidemiological studies, electronic searches were made from 1990 onwards of Current Contents, Medline (Ovid), Toxline and PubMed (National Library of Medicine, USA). Toxicological studies were searched from 1996 onwards, using the same resources. Searches were based on:

- Text words: silica, quartz, tridymite or cristobalite
- Medical Subject Heading (MeSH) terms: 'adverse effect', 'pharmacokinetics', 'toxicity', 'administration and dosage' associated with any of the above chemical substances
- MeSH terms: silicosis, fibrosis, pneumoconiosis, cancer, auto-immune diseases, chronic obstructive lung disease, bronchitis or lung disease associated with any of the above chemical substances.

10.1.2 Identification of Relevant Studies

Over 1000 studies were identified through the electronic searches. Articles relevant to the objectives of the review were identified by scanning their abstracts. The full text of these articles was obtained and then critically appraised with regard to the design and exposure measurement issues listed below (which are non-exhaustive). Each appraisal was abstracted onto a pro-forma table to facilitate selection of those studies suitable for inclusion, particularly those suitable for the examination of dose-response relationships.

Not all published studies are described in this review. Those thought to be irrelevant to the objectives of the review have been omitted. Studies included in the reviews of epidemiological and toxicological studies (*Chapters 4* and *5*) are those deemed acceptable according to the design and exposure measurement issues below.

10.1.3 Study Design Issues

- study design, eg. longitudinal or cross-sectional data
- a well-defined study population
- number of cases and controls, exposed and non-exposed
- methods for the ascertainment of cases, preferably independent of exposure
- source of cases and potential selection bias, eg. silicosis compensation records, hospital admissions, necropsy studies, death certificates, selection of cohorts eg. exclusion of workers who have left industry or exposure source
- source of controls and potential selection bias, eg. reference groups for SMR's, control groups from other industries
- measurement of potential confounding factors, eg. smoking, other occupational hazards (eg. coal, radon, arsenic, diesel, asbestos, talc)
- appropriate statistical methods

10.1.4 Exposure Issues

- dosage and route of administration to laboratory animals
- specification of silica form, ie. dust, quartz, cristobalite or tridymite (mixed dust, amorphous silica etc. ignored)
- silica source and presence of modifying effects, eg. coal dust, high temperature operations and conversion of quartz to cristobalite.
- presence of other carcinogens in the workplace eg. radon daughters, polycyclic aromatic hydrocarbons (PAH)
- presence and effect of attempts at workplace exposure controls eg. wet working, ventilation, aluminium dosing
- analyses including quantitative exposure data
- method of exposure measurements, ie. gravimetric or particle counts
- inspirable or respirable exposure measurements (use of BMRC or ACGIH definitions)
- temporal analyses, information on latency, eg. time since exposure
- calculation of cumulative exposures and conversion techniques
- the calculation of dose-response relationships

10.1.5 Abstract Pro-forma: Epidemiological Studies

Reference								
Study type								
Study group (study base)								
Industry								
Country								
Calendar period								
Outcomes	Diseases							
	Type of case							
Number of cases								
Control/reference group								
Age range								
Sex								
Confounders/Other exposures								
Interactions examined								
Latency/time course examined								
Exposure	Units							
	Measuring technology							
	Measuring strategy							
	Particle fraction							
	Quartz content							
Response rate								
Exposure-response: Exp level								
RR, 95% CI or								
cases/(person-yrs or controls)	/	/	/	/	/	/	/	/
General validity and relevance								

10.1.6 Abstract Pro-Forma: Review Studies

Reference	
Aims/Purpose	
Search methods	
Inclusion/exclusion criteria	
Validity/quality criteria	
Methods for summarising	
Conclusion criteria	
Review conclusions	
Main influences	
General validity and relevance	

10.1.7 Abstract Pro-forma: Toxicological Studies

Reference		
Study type		
Species		
Outcomes		
Exposure	Dust	
	Administration route	
Number of cases		
Follow-up time		
Dose-response present?		
Study conclusions		
General validity and relevance		

10.1.8 Abstract Pro-forma: Exposure Assessment Studies

Reference		
Substance(s) measured		
Sampling protocol		
Measurement protocol		
Studies applied to		
Reported accuracy		
Relevance	Historical studies	
	Current standards	
Biomarkers used		
Study conclusions		
General validity and relevance		

10.2 The Concept of Meta-analysis

A meta-analysis can be broadly defined as the quantitative review and synthesis of results of related but independent studies. Meta-analyses are usually conducted in order to 'pool' studies and thereby increase the precision of the estimate of an effect (Normand, 1999). However, the process of combining different studies in order to obtain an 'average effect' has been criticised by many, and there are several important issues to consider.

The process of the meta-analysis is thought to be no different from conducting primary research. It is a multidisciplinary task involving the processes of developing a selection criteria for studies to be included (eg. only cohort studies), the identification of subject matter, the critical review of studies retrieved (eg. assessment of bias and confounding), the extraction of relevant data and finally, appropriate statistical analyses.

The variation in study design, sampling, analyses, and point estimates creates several difficulties for the statistician especially when pooling observational studies, as these usually lack the opportunity for the scientific rigour afforded by experimental studies. In the context of this review, SMRs, relative risks and linear regression coefficients are most commonly reported, depending upon the study design. In order to pool studies, a point estimate of effect is needed from each study along with its standard error, which may be imputed from confidence intervals or a p-value to 2 decimal points (Greenland, 1987). Methods have been developed for converting different point estimates into a consistent format. Adjustments for the limitations in study design, such as the lack of adjustment for confounders, sampling bias and misclassification have also been suggested, however it is likely that these problems will persist in contributing to heterogeneity among study results (Greenland, 1987).

Depending on the variability in study design, study populations, case ascertainment, statistical analysis, etc, the confidence intervals about a pooled or summary estimate may be very large. In this case, even after combining the studies to increase statistical power, there is still a large degree of uncertainty about the risk estimate. The first step in a meta-analysis is to examine inter-study variation by conducting a test of homogeneity. This is also done in order to be reasonably certain that each study is attempting to measure the same parameter. The test of homogeneity has the null hypothesis that the means from all studies are equal (Normand, 1999). Although the test of homogeneity indicates statistical agreement between studies (regarded by some as artifactual reassurance for the statistician), their actual comparability rests on less quantifiable information that only a description of each study can provide.

The fundamental statistical process performed in a meta-analysis is one of weighted regression, which treats each study result (such as a log relative risk or a coefficient) as the dependent variable with an accompanying weight (Greenland, 1987). The weight is the inverse variance or 'precision' of the result, which is calculated using the standard error (SE), as $1/(SE)^2$ (Greenland, 1987). Down-weighting is sometimes undertaken, usually where the uncertainty of a study's result is thought not to be sufficiently reflected in its SE. An alternative to down-weighting 'suspect' studies is to conduct a sensitivity analysis. By omitting these studies from the analysis, one can assess their impact on the pooled result. These aspects of course, should also be clearly spelled out in the methods section of the meta-analysis. Alternatively, a pooled summary can be calculated as the weighted sum of all results divided by the sum of weights. However, this method depends on the fairly stringent

assumption that all the studies are estimating the same value for an effect, ie. that the same effect would be expected on average from each study, and that any variation in effect is due entirely to random error (Greenland, 1987). Graphical representations are also acceptable, usually in the form of a weighted histogram of results, or a funnel plot of study result versus precision eg. weight or sample size (Greenland, 1987). As well as providing a 'picture' of results, publication bias can be identified on a graph as a sparsity of results around the zero effect level.

A major problem with the meta-analysis is publication bias. This includes a reliance on published studies only, or a selective bias towards published studies that report a positive result. It is advised that unpublished data be sought wherever possible by searching the relevant research registers and databases. Rules for the inclusion of studies need to be scientifically rigorous.

The meta-analysis assumes that the estimated pooled risk is constant across populations. However, there seems no basis for this assumption, as the risk is thought more likely to be heterogenous (Greenland, 1987). Bias in observational studies is very likely to vary across studies and will contribute to a variation in exposure effect. For example, lag times included for the development of silicosis vary between studies and calculations to convert dust counts to respirable silica vary between studies. It has been suggested that the homogeneity assumption be regarded as extremely unlikely to be met, given the differences in included covariates, bias, and exposure variables (Greenland, 1987).

The meta-analysis cannot provide a substitute for the qualitative evaluation of each of the studies, as this is outside the scope of a statistical device (Greenland, 1987). Causal explanations of similarities and differences among study results noted in the meta-analysis are a qualitative aspect of the review and depend on the skill of the reviewer. This concept is analogous to the fact that the statistical analysis of data cannot explain cause and effect, but simply represents a fallible device capable of recognising patterns in the data (Greenland, 1987). Whereas, a purely qualitative description of reviewed studies lacks precision, and may overlook small but significant patterns or associations.

In summary, the pooled estimate derived from a meta-analysis is probably most useful for detecting the *existence* of an effect, as the inherent variation between studies limits the likelihood that the magnitude of effect is constant across studies. Publication bias is a common problem, and the onus is on the reviewer to provide a description of the search methods and selection criteria, and to individually review each of the included studies, to assist the reader in accepting or rejecting the pooled estimate.

10.3 Meta-analysis of Lung Cancer and Crystalline Silica

We conducted a meta-analysis of lung cancer risk using a one-way random effects model with the 'Meta' program in STATA (Stata, 1999). Because there is some contention that the South African gold-miners (Hnizdo et al., 1997, Hnizdo et al., 1991a, Reid et al., 1996) were exposed to other carcinogens (uranium, radon etc) and the diatomaceous earth workers were exposed principally to the cristobalite form of crystalline silica, inclusion of various combinations of studies into the analyses enabled some assessment of the sensitivity of the final random effects estimate.

Details of the relative risk of lung cancer per mg/m^3-year increase in cumulative respirable crystalline silica exposure for each study included in the meta-analysis is shown in *Table A3.1*. The WA gold miners' data were analysed with exposure on a linear scale in common with the other three studies, so that weighting of each study's contribution by way of the estimate of variance would be consistent.

The combined estimate for the relative risk of lung cancer from all quantitative studies is 1.034 (95% CI 1.006-1.063, p=0.01) per mg/m^3-year increase in cumulative respirable crystalline silica exposure (*Table A3.2*). The uniformity of results was confirmed by the test of heterogeneity with a p-value of 0.29, indicating good agreement between studies (Normand, 1999). The sensitivity analyses showed little variation in the risk estimate and had no impact on its statistical significance.

The quantitative lung cancer studies included in this meta-analysis are a subset of those included in IARC pooled analysis (Steenland et al., 2001a), which included some studies that we excluded as part of our review because they lacked quantitative exposure data or dose response data, ie. studies on US Vermont granite workers (Costello et al., 1995, Costello et al., 1988) , US gold miners (Brown et al., 1986, Steenland et al., 1995a), and Chinese pottery workers, tin miners and tungsten miners (Chen et al., 1992). However, the IARC-commissioned study was able to obtain further data on each of these studies (via the authors) to enable their inclusion in the pooled analysis. Because of the similarity between dose-response relationships shown graphically in *Figure 6*, we used the most precise estimate of lung cancer risk, that from the pooled study (*Table A3.2*), for risk assessment in this review.

Table A3.1 Details of Lung Cancer Studies Included in the Meta-analysis

Study	*n cases*	*Log RR* [§]	*SE (log RR)*
Hnizdo 1991 & 1997 [ϕ]	78	0.0933	0.0378
Checkoway, 1997 [ϕ]	77	0.0299	0.0124
de Klerk, 1999 [ϕ]	136	0.0173	0.0115
Reid, 1996 [ϕ]	159	0.194	0.128

[ϕ] respirable crystalline silica (BMRC adjusted)

[§] per mg/m^3-year increase in cumulative respirable crystalline silica exposure

Table A3.2 Statistics for Meta-analysis and IARC Pooled Analysis

Statistic	*Hnizdo, Reid, Checkoway, de Klerk*	*Reid omitted*	*Reid, Hnizdo omitted*	*IARC Pooled Analysis*
Rate Ratio per mg/m^3-year cumulative silica	1.034	1.031	1.023	1.064
95% confidence interval for RR	1.006,1.063	1.005,1.057	1.007,1.040	1.033, 1.096
p value from *Z*	0.018	0.018	0.006	n/a
Homogeneity chi squared (X^2_h)	5.54	3.83	0.556	n/a
Homogeneity degrees of freedom	3	2	1	10
Homogeneity *p* value	0.136	0.147	0.456	0.34

11.0 APPENDIX FOUR

WORKPLACE EXPOSURE MONITORING

APPENDIX 4. WORKPLACE EXPOSURE MONITORING

This appendix describes the methods used for measuring workplace exposures, including sampling and analytical techniques, and their commonly applied standards.

11.1 Sampling Strategies for Workplace Monitoring

Over the years, a considerable portion of the available data on silica exposure in industry has come from samples conducted predominantly for dust control or regulatory purposes. The choice of sampling equipment, location of sampling device, and duration of the sampling period has depended on the proposed application of the collected data. Therefore, a number of different approaches continue to be used to sample dusty atmospheres.

Different sampling strategies are likely to produce significant differences in measured dust concentrations. These differences should be taken into account when setting and comparing exposure standards. There are three main approaches to dust sampling; engineering dust control sampling, regulatory sampling and exposure assessment.

11.1.1 Sampling for Engineering Dust Control

This uses a variety of sampling and analytical methods to determine the effectiveness of dust control measures, such as exhaust ventilation, equipment design, equipment operation and work practices. These methods are often chosen as they indicate the amount of dust present at a particular time and point in space.

Engineering dust control sampling places emphasis on tasks, processes and particular work practices which give rise to high dust levels. Most samples are static samples and therefore, most are not taken in the breathing zone of a worker.

For engineering control purposes, short-period or instantaneous 'grab' sampling is sometimes used, for example, a sample is taken in less than a second, or up to six or so 'grab' samples are taken and combined to make a single sample. These samples may be taken either in the general atmosphere for dust control or in the breathing zone of employees.

The results of such sampling generally would not provide a reliable estimate of worker's exposure to crystalline silica, because:

- only trouble spots are generally chosen;
- samples are not usually taken in the breathing zone of employees; and
- workers are variably protected to an unknown degree.

While short-period samples have assisted in the control of dust concentrations in the workplace, there are major limitations on the use of these results for estimating silica exposure of employees.

11.1.2 Regulatory Sampling

Many regulatory authorities specify the sampling strategy, field equipment and analytical method to be used for monitoring in a particular industry. Sampling for such monitoring generally requires continuous sampling in the workers' breathing zone, for between one half and a full working shift. A comparison of dust concentrations with specified standards of exposure is then used to determine legal compliance.

Alternatively, in some industries, sampling is conducted in a general working area to test operational system compliance with empirical standards, which have been developed to provide safe conditions for the employees involved. The results of such static sampling may not be representative of a worker's exposure to dust, but the effectiveness of, for example, a ventilation system. Appropriate research for validated correction factors specific to that industry is required for estimating personal exposure.

11.1.3 Exposure Assessment

To be most useful, exposure assessment should be representative of workers' exposure over an extended period of time.

11.1.3.1 Respirable personal sampling

Silicosis is caused by particles of crystalline silica which pass through the intrathoracic conducting airways of the lungs and deposit in the alveolar region. Size selective samplers mimic the size selection process that occurs in the respiratory tree (particles less than five micrometers aerodynamic diameter). The collected 'respirable dust' can then be analysed for crystalline silica content.

The most appropriate samples for epidemiological purposes are those taken in the workers' breathing zones for at least half and preferably, the whole of a representative shift. Shift-to-shift variations in dust concentrations should be taken into account to arrive at a representative exposure. Sufficient numbers of samples should be taken so that the long term exposure profile of individual employees (or groups of employees doing the same type of job) can be assessed with reasonable accuracy and confidence. The number of samples necessary will be determined by the variability of the measurements.

It is rare to find data on dust concentrations which have been specifically collected to provide information to support epidemiological studies.

11.1.3.1 Inspirable personal sampling

Airways disease such as bronchitis may be caused or aggravated by larger particles that deposit in the conducting airways. Size selective samplers can mimic the inspirable size selection process that occurs in the combined upper and lower respiratory tract (generally less than 130 micrometers aerodynamic diameter).

Unfortunately, there is a poor and variable correlation between the inspirable and respirable dust fraction across processes and industries. This occurs with mass measurements, because of the extreme influence of heavy inhalable dust particles greater than approximately 50 µm in diameter, in comparison with respirable particle of 5 to 7 µm in diameter. Exposure to large particles increases as workers move closer to the source of the dust generation. As the distance increases, the dust becomes finer until the only dust present is in the respirable size range. While the ratio of inhalable to respirable dust is highly variable, a value of three to one is often used.

11.1.3.2 Sampling practices

There are important differences between sampling practices of some sections of the mining industry, which are important in the interpretation of airborne dust measurements. For example, in underground mines in the United States of America, full-shift, personal samples are taken from 'portal to portal' (that is, from time at the entrance of the mine, usually some distance from the work-face, during work time and then after exit from the mine). However, the majority of Australian mine sampling is based on full-shift personal samples taken from 'crib room to crib room' (that is, time near to the work-face during work time, then removed before exit from the mine). Travel distances underground may reach up to one and half hours in a full shift. Tomb et al (1978) determined that 2 mg/m^3 'portal to portal' may be equivalent to approximately 2.7 mg/m^3 'crib room to crib room' (Tomb et al., 1978). Walton (1978) stated that,

"…based on 1970/75 samples, the average ratio between face mean concentrations (portal to portal) and control point (time at face) concentrations has remained close to 1.4." (Walton, 1978)

In other words, 'crib room to crib room' results are higher than 'portal to portal' results by around 30 to 40 per cent. Therefore different sampling strategies do not give numerically comparable average values.

11.1.3.3 Exposure estimation approaches

As referred to in the section on respirable personal sampling, long term personal sampling of the respirable fraction of airborne dust is most appropriate for the estimation of a worker's exposure to crystalline silica. Long term sampling means that a representative estimate of an employees cumulative respirable silica exposure can be obtained by summing the product of each dust concentration and respective time period. The result is expressed in milligrams per cubic metre years (mg/m^3/yr). Peak and average dust concentrations are also estimated. Knowledge of the silica-related disease and individual accumulated doses can assist in the development of a dose-response relationship upon which an exposure standard can be based.

11.1.3.4 Australian standardised sampling methods

While some Australian occupational health and safety legislation specifies sampling and analytical procedures for various mining situations, this is not generally true for all industries.

The NHMRC, in its document 'Methods for Measurement of Quartz in Respirable Airborne Dust by Infrared Spectroscopy and X-ray Diffractometry' (1984) (NHMRC, 1984) recommends strategies for collecting personal samples, static samples and engineering control samples. In 1987, Australian Standard AS 2985 *Workplace Atmospheres—Method for Sampling, Gravimetric Determination of Respirable Dust* formalised that breathing zone samples, taken by a sampling device conforming to BMRC deposition curve characteristics (and taken over a period not less than four hours) must be used to assess the personal exposure of a worker to 'respirable' dust containing crystalline silica.

11.1.4 Historical Development of Sampling

The Konimeter, the Owens Jet Dust Sampler and the Greenberg-Smith impinger are particle count devices which remove dust from air by impingement onto a flat plate or into a liquid. These impinger devices all suffer from problems of changing the state of the original dust to an unpredictable degree, by breaking up aggregates, shattering large particles or losing small particles.

A number of other filtering sampling devices were also developed, which relied on dust being collected on a filter which was weighed before and after the sample was collected. While the early filter containing devices were relatively crude, current technology can provide sensitive and accurate information of airborne dust concentration in gravimetric terms.

There has been a gradual change in sampling instrumentation brought about by research into the health effects of silica. Previously, particle counts were conducted with no size selectivity until research on lung deposition defined the *respirable fraction*. Particle collection was then changed to gravimetrically measure only particles with an aerodynamic diameter less than five micrometers.

11.1.5 Modern Gravimetric Methods and Size Selection Criteria

Modern measurements of quartz-containing dusts are conducted by gravimetric means. Unfortunately, there are different methods in use internationally which can produce different estimates of the same atmospheric conditions.

11.1.5.1 British Medical Research Council respirable dust fraction

For pneumoconioses-producing dust, the BMRC defined 'respirable dust' as that reaching the alveolar region of the human lung, and developed the 'Johannesburg' criterion in 1959 which described the 'respirable fraction' of the dust cloud. This theoretical respirable fraction can be met by commercially available, precision built devices. The calibration instrument is the

Casella MRE113A, but for practical field measurements miniature cyclones were developed which generally satisfied the BMRC criteria. For cyclones, under-sampling of the fine particles and over-sampling of the larger particles occurs due to the process of inertial capture.

11.1.5.2 American Conference of Governmental Industrial Hygienists – respirable dust fraction

In 1968, the ACGIH included new Threshold Limit Values (TLV's) for crystalline silica which were based on respirable mass concentration as an alternative to TLV's that had been based on particle count concentrations. The proposal defined a respirable fraction which was developed by the US Atomic Energy Commission, but different from the Johannesburg criterion. The field sampling instrument was a '10 mm nylon cyclone' used at a flow rate of 1.7 litres per minute.

While hard rock and general industrial crystalline silica dust determinations are conducted according to the ACGIH criterion in the United States, coal mine dust sampling - as required by the Mine Safety and Health Administration (MSHA) - makes use of a 10 mm Dorr-Oliver cyclone operating at 2.0 L/min. This method multiplies the mass concentration by 1.38 (later this was changed to 1.40) to arrive at the equivalent concentration, as if taken by the UK's Casella instrument.

11.1.5.3 International Standards Organisation

In 1983, the International Standards Organisation (ISO) published definitions of size fractions for health-related sampling which included unmodified BMRC and ACGIH respirable dust fraction definitions, of which either could be chosen because past measurements using the two curves were found to be similar. A number of studies have revealed systematic and significant differences between sampling devices working to either ACGIH or to BMRC criteria. However, a conversion factor of 1.4 is reasonable for BMRC (Johannesburg) to ACGIH methods.

In 1990, discussion between ISO, ACGIH and the Comité Européen de Normalisation resulted in agreement by the Working Groups in relation to size fraction definitions. This was to be followed by adoption of another standard specifying how instrument performance should be tested in relation to the definition.

11.1.5.4 Australian Standards method for monitoring

Australian Standard AS 2985-1987 *Workplace Atmospheres - Method for Sampling and Gravimetric Determination of Respirable Dust* is the required method for the collection and gravimetric determination of respirable dust in Australia. This standard calls upon a sampling device conforming to the BMRC deposition curve as described in the document ISO/TR 7708-1983.

It is the intention of Standards Australia to rewrite AS 2985 when the ISO and ACGIH reach agreement on the definition of fraction sizes. As in the past, it is then expected that individual States will adopt the revised Standard for regulatory purposes.

11.1.5.5 Direct reading instruments

There are several commercially available instruments which use a variety of sensors to detect the presence and quantity of dust particles, and give a direct and immediate indication of the concentration on a digital or analog read-out (ACGIH, 1989). Direct reading instruments can be most useful for engineering dust control purposes or for educating management and employees of the need to control dust, and to demonstrate the impact of different work practices. Some sensors are based on the light scattering properties of dust while others are based on beta-attenuation methods. All the sensors share the problem of sensitivity to other variable properties of dust or to other airborne components of dust. Therefore, readings obtained can have gross systematic bias and/or random variability. Most of the instruments available are designed for use as static samplers.

11.1.6 Conversion Factors

Due to changes in sampling instrumentation over the last eighty years, a number of attempts have been made to make comparisons between the results obtained from different sampling devices. Examination across a spectrum of the original field and laboratory data (collected for the purpose of comparison) indicates that although various conversion factors can been calculated, there is a considerable spread of conversion factors for specific processes, locations, and across various industries. When conversion factors have been used, the total error of the final results will be increased, and will comprise both sampling and analytical errors.

11.2 Analytical Methods for Quartz Content of Dust Samples

This section describes some of the main features of various analytical methods that have been used for assessing the crystalline silica content of dust measurements.

11.2.1 Talvitie Method

This now outdated colorimetric method is unable to detect the presence of crystalline silica.

11.2.2 X-ray Diffractometry Method (XRD)

This method works on the principle of regular scattering of x-rays by the crystal structure of the silica materials. Slight differences in atomic packing between the various polymorphs result in XRD spectra specific to the various forms of crystalline silica, including microcrystalline variants and cristobalite (NHMRC, 1984). This method has a practical detection limit of 5-10 micrograms of quartz for either the direct on the filter or re-deposition method.

11.2.3 Infrared Spectroscopy Method (IR)

This method works on the principle of absorption of specific wavelength IR radiation by bonds in the silica tetrahedra (NHMRC, 1984). Infrared Spectroscopy is reasonably sensitive, especially when using Fourier Transform Infrared (FTIR) instruments, but suffers some interferences. It cannot detect the small amounts of cristobalite and tridymite that XRD can detect. This method is now routinely used by many laboratories because of its simplicity and the relatively inexpensive equipment required. On good samples, this method can achieve a practical detection limit of 10-15 micrograms of quartz.

11.3 Quartz Mineral Analytical Standards

A considerable number of analytical standards have been available and in use for some decades; some designations include X7488, DQ120, DQ12, Fyle, Min-u-Sil 5, Min-u-Sil 10, Min-u-sil 15. All of these materials have been extensively tested using IR and XRD methods by the British Cast Iron Research Association.

During 1980, a new analytical standard sample became available known as A9950 - derived from Sikron F600, which was proposed as the European Community (EC) standard. A9950 was soon adopted as the British analytical standard. Soon after, a sub-sample of A9950 was brought to Australia, rigorously subdivided, relabelled A9950 (Aust 1), and included as the analytical standard in the 1984 NHMRC Quartz Method.

Studies in the United Kingdom and the United States show that infrared and x-ray methods compare very well for most samples, when using A9950 as the analytical standard. There are some specific cases where interferences specific to the x-ray method force the utilisation of the infrared technique, and vice versa (Mangla, 1975).

11.3.1 Limits of Detection and Quantitation

The Limit of Detection (LOD) for silica is defined as the lowest concentration of crystalline silica that can be determined to be statistically different from a sample which contains no crystalline silica (that is, a 'blank') (Curry, 1968, Keith et al., 1983).

The Limit of Quantitation (LOQ) is defined as the level above which quantitative results may be obtained with a specific degree of confidence.

If a measured sample is found to be less than the LOD, it is reported as 'Not Detected'. A result between the LOD and LOQ generally lacks acceptable precision, while a result equal to or greater than the LOQ corresponds to an uncertainty of ± 30 per cent or less, at the 99 per cent confidence level. Therefore, concentrations measured at or near to the LOD have two problems. First, the uncertainty can equal or even exceed the reported value. Secondly, it is virtually impossible to confirm the presence of crystalline silica because of the lack of sufficient instrument response. Accordingly, quantitative interpretation and regulatory decisions should be limited to concentrations of crystalline silica at or above the LOQ.

It has been emphasised that the LOD and LOQ are not intrinsic constants of a particular method, however they depend upon the precision attainable by a laboratory when using that method, as well as the type and quantity of dust in the sample. In some cases, it may be necessary to choose an analytical method more suited to a particular industry or process, which is less sensitive to the associated interferences, and which consequently has a lower LOQ.

The NHMRC defines detection limits of infrared spectroscopy and x-ray diffractometry methods for quartz (NHMRC, 1984) :

"The detection limit of the methods under practical sampling and analytical conditions and in the absence of interfering substances is approximately:

a. 0.02 mg of quartz for IR 'Direct on Filter';
b. 0.01 mg of quartz for IR 'Direct on Re-deposited filter', IR 'Potassium Bromide Disc' and XRD.

Actual detection limits achieved for specific equipment and operating conditions can differ considerably from those stated above, and should be determined by each laboratory."

Using these LOD's, and the fact that miniature cyclones used as field collection devices are operated at a flow rate of 1.9 L/min, the actual LOD and LOQ can be calculated. When using these Limits of Detection, the LOQ ranges from 0.03 to 0.07 mg of crystalline silica on a membrane filter. For an eight hour sample, these figures translate to concentrations with a range of 0.04 to 0.07 mg/m^3 of crystalline silica. Due to practical difficulties in verifying personal work practices and sampling procedures in the field, it is often only possible or practical to conduct a maximum of a six hour sampling period. This yields LOQ's between 0.05 to 0.10 mg/m^3. When forced to use a four hour duration of sampling, the LOQ becomes correspondingly worse.

The LOQ is useful for defining the lower limit of the 'measurement range' of the method. On the other hand, an upper limit of approximately 0.6 mg of crystalline silica on a membrane filter normally applies, even though it can be higher under more ideal circumstances. This is due to analytical method non-linearity, related to matrix effects and interferences. It follows that for a six hour sample period, the 'measurement range' is from approximately 0.05 or 0.10 mg/m^3 of crystalline silica (depending upon analytical method), and up to 0.9 mg/m^3.

While not addressed in the National Health and Medical Research Council document, special sample preparation methods, and the use of modern infrared instruments such as the Fourier Transform Infrared Spectrophotometer (FTIR) can produce an LOD similar to that of XRD. All methods are subject to inaccuracies produced by method limitations, and factors such as mineral interferences, airborne particle size distribution, choice of mineral standard, mineral standard generation methods, filter homogeneity and suitability, variation of particle size, mass distribution and mineral make-up on the collection filters and matrix effects.

When samples have to be transported over long distances or difficult terrain, a further difficulty arises due to loss or contamination of sample, especially when the sample standard is numerically close to the LOD.

NIOSH has assigned a LOD of 0.005 mg of crystalline silica by X-ray diffraction, and a measurement range of 0.05 to 2.5 mg per cubic metre of crystalline silica for a seven hour sampling period (NOHSC, 1996). By definition, this implies an LOQ of 0.05 mg/m^3 of crystalline silica. Even though there are apparent inconsistencies between several of the NIOSH crystalline silica methods, the lower limit of the measurement range agrees with that as derived from the NHMRC figures.

Pickard and colleagues from the United Kingdom Health and Safety Executive (HSE), determined the LOD of the IR and XRD methods to be 0.005 and 0.003 mg of quartz respectively, and observed that for pure quartz, "... it is possible to detect one quarter of the Threshold Limit Value" (Pickard et al., 1985). While this is no doubt true for HSE methodology and equipment under ideal conditions, the paper did not show the level at which reliable measurements commenced, ie. the LOQ for the methods.

The NIOSH document on Occupational Exposure Standards (NOHSC, 1995) does not describe analytical methods but refers to the choice of sampling and analytical methods in relation to LOD and Occupational Exposure Standards in the NIOSH Manual of Analytical Methods (NIOSH, 1994). This states that "for OSHA compliance sampling, the analytical range should be sufficient to allow analysis of samples ranging from at least one-half to two times the standard for which the method is being developed (for a nominal sampling duration) ...".

This concept is based on the fact that for an employer to prove legal compliance to a regulatory standard, it is necessary to measure workers' exposures to an acceptable level of statistical certainty. Further, every worker cannot be sampled every day of his or her working life, and dust measurement and dust control strategies are generally based on sampling schemes, whereby a limited number of individual occupations or tasks are monitored.

While statistically rigorous and formal 'compliance' strategies have been developed, a simple and effective rationale used by occupational hygienists is to keep measured concentrations at or below one-half of the OES. Provided that the sampling strategy is sound, this helps to ensure that all, or nearly all workers, are not exposed to concentrations above the OES. However, it is not clear as to why the sensitivity of dust measurements cannot be increased by increasing the sampling duration.

11.4 Analytical Methods for Cristobalite and Tridymite

For some processes, there is a need to analyse the amount of cristobalite and tridymite in respirable dust. Limited work has been conducted on the analytical methods for these and there are problems in obtaining standardised materials. Additional errors have been found in the analytical method.

11.4.1 X-ray Diffractometry Method (XRD)

A number of laboratories are prepared to qualitatively and quantitatively analyse for cristobalite and tridymite by XRD. However theoretical predictions depend upon the experience and skill of the analyst, as well as the type of sample analysed.

11.4.2 Infrared Spectroscopy Method (IR)

The sensitivity response of IR to cristobalite is not as high as for quartz, so a larger sample is needed in order to obtain a reasonable measurement. While the use of modern Fourier Transform IR spectrophotometers can assist a little in this respect, this method otherwise gives no major advantage over the older IR instruments. For these reasons, analyses of cristobalite and tridymite are better conducted by using XRD.

11.5 Cristobalite and Tridymite Mineral Analytical Standards

A properly validated tridymite analytical standard is not thought to exist. One quality cristobalite is available from the United State's National Bureau of Standards and is known as *Standard Reference Material 1879-respirable cristobalite*. This material has been certified as a quantitative X-ray diffraction standard containing 98 per cent cristobalite.

It has been experimentally determined that a wide range of cristobalite structures exist in ceramic bodies, and these are different from synthetic cristobalite structures. This prohibits the use of both conventional and synthetic cristobalites as calibration substances or as quantitative X-ray diffraction standards, until this can be justified by calculation from a detailed knowledge of the crystal structures concerned. This suggests that even a highly monophasic sample of cristobalite may not be an appropriate calibration standard for cristobalite from a different source. This is because the intensity ratios of the cristobalite X-ray patterns are highly sensitive to crystallographic distortions, which in turn are functions of thermal pre-history, impurity levels and so on.

12.0 APPENDIX FIVE

DUST MEASUREMENT CONVERSIONS

APPENDIX 5. DUST MEASUREMENT CONVERSIONS

The following was provided by Dr David Grantham (Advisory Committee Member) to summarise the literature on the conversion of dust exposure measurements.

12.1 Background

Much difficulty has been experienced over the years in converting particle counts, or respirable surface into areas equivalent masses, whether they be to BMRC or old ACGIH gravimetric equivalents. There appears to be no clear, uncontested formulaic approach for converting one set of sampling results into equivalent results for a different sampler. The values obtained depend somewhat on the particle size distribution of the dust clouds used for comparisons, and even elutriator manufacture, and therefore the outcome will be confusing to say the least. No doubt, the final result could be further compromised if the original dust measurements for epidemiological measurements were all particle counts which have been converted to an equivalent ACGIH respirable mass. Further conversion to a different convention heaps errors on errors. If nothing else, this exercise has been a telling argument for adoption of a globally standardised sampling criterion from which the researchers of the 21st century will gain immeasurably.

12.2 Conversions

There are a few references reporting on converting the old ACGIH to BMRC equivalents. Most users were not interested in converting their own mass measurements into someone else's convention. That appears to be a need specific to the epidemiologist. However, with the prospect of standard harmonisation, the interest now is on making comparisons of either the BMRC or the old ACGIH to the new CEN-ISO-ACGIH (Soderholm) curve. Only one paper could be found covering comparisons of both the old ACGIH and the BMRC to the new 'agreed-upon' CEN-ISO-ACGIH convention.

The spread of results from empirical studies from comparisons of elutriators is wide. Also, one is never too sure in reading epidemiological studies whether the results referred to in individual studies in the literature are measured as ACGIH measurements with elutriators run at 1.7 L/min, or AGCIH elutriators run at 2 L/min but with correction factors applied to emulate BMRC type measurements. One can choose conversion factors from between 1.28, 1.4, or up to 2 depending on the reference.

There has been some tentativeness in making comparisons until the US moved to the new CEN-ISO-ACGIH curve. Both the US and the UK have now moved to this. There may be more extensive publications in the future, as those who hold collections of data measured to different conventions convert them all to the new CEN-ISO-ACGIH type measurements, where this is possible. The Technical Report on Silica (1996) –paragraph A2.67 indicated that the conversions were not available, although that was probably the situation when the Technical Report came out in 1993.

There are a few studies on the comparison of the old AGCGH to BMRC conversions, although these are certainly becoming of less interest. The situation is also confused by whether the US mining data (essentially all that exists of any quality) is all expressed in terms of the wretched "portal-to-portal" measurement or not. By implication, it suggests that BMRC measurements might not have been.

The work of Groves and colleagues is a limited side-by-side study on BMRC, new CEN-ISO-ACGIH and old ACGIH samplers (Groves et al., 1994). It was on respirable dust, and so presumably also applies to respirable quartz.

The ratios normalised to the new CEN-ISO-ACGIH sampler for 5 sets of measurements are

BMRC	CEN-ISO-ACGIH	Old ACGIH
1.5	1	0.66
1.6	1	0.95
1.39	1	0.95
1.72	1	0.88
1.57	1	0.76

Here the ratio of BMRC to old ACGIH type measurements ranges from 1.46 to 2.27 with a median value of 1.95. These figures are more extreme in their relative performance of the BMRC:old ACGIH than those reported previously (below) in the NOHSC Technical Report (A2.61) which was based on Knight and Moore (1987). However, the NOHSC report does say that the ratio can be up to 1.4:1.

Knight and Moore investigated a number of samplers (Knight et al., 1987). The NOHSC Technical Report in A2.61 states that the ACGIH respirable mass must be multiplied by a factor of 1.23 to convert it to an equivalent BMRC criterion. It is possible that this is incorrect, by a fair margin. This quoted correction factor (1/0.81) appears smaller than those found in newer research. However, a re-reading of the original paper from which the statement in A2.61 is derived - *"the ratio of the concentrations indicated at the two flow rates has been close to the expected ratio of 0.81"- page 126* - refers to the performance of the Hexhlet when run at flow rates to emulate either BMRC or ACGIH type depositions, not a comparison of BMRC cyclones or the MRE elutriator with purpose designed personal samplers running to meet the ACGIH criterion.

The real relation between BMRC and ACGIH in-field measurements is in fact, much closer to a ratio of 1.4 – 1.7:1, errors in which appear to be due to mechanical problems with ACGIH measuring elutriators (reproducibility, leaks, flow control etc). Conversion figures of about 1.16 – 1.4 were obtained only when they ran a BCIRA (British Cast Iron Research Association) cyclone at the ACGIH recommended flow rate, but American mines generally used American sampling equipment, (MSA, Sensidyne elutriators etc), because it was required by MSHA law. (I am not sure how this argument might go for particle counts to ACGIH convention equivalent mass conversions).

A re-calculation from Knight and Moore's work using the Hexhlet sampler as the basis and comparing ACGIH cyclones running at standard ACGIH specified sampling rates varies between 1.38 – 1.72:1 for laboratory based tests. Field based tests were of the same order. The ratios appear even slightly greater when comparing ACGIH performing elutriators with BCIRA cyclones.

More recently, Liden and Kenny note that the correction factor of 1.38 had to be applied to the 10mm cyclone to bring it to the CEN-ISO-ACGIH curve (Liden et al., 1993). Therefore, conversion to BMRC type convention would require multiplication by an even greater value (approximately 1.5).

The United Kingdom's HSE has altered the MEL for quartz from 0.4 mg/m^3 down to 0.3 mg/m^3 to accommodate a change from BMRC to CEN-ISO-ACGIH convention measurements (HSE, 1999a). This represents a ratio of BMRC: CEN-ISO-ACGIH of 1.33:1. This is generally a little more conservative than the Groves et al ratios above (1.39 to 1.72:1).

12.3 Summary

Conversion from old ACGIH to CEN-ISO-ACGIH seems to require a multiplication of the old ACGIH result by about 1.3, ranging from 1.38 (Liden and Kenny) to 1.21 (Groves et al).

Converting BMRC to the CEN-ISO-ACGIH curve seems to require a division of the original BMRC results by about 1.4. (Groves -1.55, Liden and Kenny - 1.1, HSE - 1.33).

Conversion of regular gravimetrically determined ACGIH measurements to a rough equivalent of BMRC would require multiplication of the ACGIH results by a factor of between 1.4 to 1.7 (average 1.6). This seems the most error prone conversion, but may be one which is required. For converting the BMRC to equivalent ACGIH measurements, if the latter are the predominant ones in the studies, then divide BMRC measurements by 1.6.

Although these conversions appear somewhat 'elastic' they seem the best that can be achieved at present.

GLOSSARY OF TERMS

ACGIH	American Conference of Governmental Industrial Hygienists
Acute effect	An effect that occurs immediately or shortly after a single, high level exposure.
Airborne Contaminant	An airborne contaminant is a potentially harmful substance that is either normally absent from air, or present in an unnaturally high concentration, and to which workers may be exposed in their working environment.
Alveoli	Thin-walled air sacs at the distal end of the conducting airways of the lungs, where gas exchange occurs between air and blood.
Asthma	Variable airflow obstruction/airflow limitation
Auto-immune Disease	Disorders including rheumatoid arthritis, scleroderma, lupus erythematosus and renal disease thought to result from an immune response of the body to its own tissues.
BMRC	British Medical Research Council
Breathing zone	A person's breathing zone has been (arbitrarily) defined by a hemisphere of 300 mm radius extending in front of the face and measured from the mid-point of an imaginary line joining the ears.
Bronchitis	cough and/or sputum production
Cancer	A malignant tumour of an organ or tissue arising from the uncontrolled division of cells, that can spread to other organs of the body either by direct growth or through transport channels (blood, lymph, etc). This is distinct from a benign tumour, which cannot usually spread.
Case-Control Study	A study that starts with the identification of persons with a condition of interest and a suitable comparison group of persons without that condition
Chronic Bronchitis	cough and/or sputum production occurring on most days for ≥ 3 months each year
Chronic effect	An effect that occurs after repeated or prolonged exposure. A chronic effect may occur some time after exposure has ceased.
Cohort	A designated group of persons which is followed or traced over a period of time
Cohort Study	Follow up or longitudinal study of a defined cohort
Construction work	All work performed in or in connection with the installation, erection, repair, cleaning, painting, renewal, renovation, dismantling, maintenance, ornamentation or demolition of buildings, structures, pipes, plant, machinery,

	parts, artefacts, appliances or tools, or parts thereof.
COAD/COPD	Chronic Obstructive Airways or Pulmonary Disease (ie. chronic persistent airflow obstruction or limitation)
Cross-sectional study	The study of the prevalence of a disease and other variables as they exist in a defined population at one point in time.
Dusts	Solid particles generated and dispersed into the air by handling, crushing and grinding of organic or inorganic materials such as rock, ore, metal, coal, wood or grain.
Emphysema	Dilation of the alveoli or air spaces of the lung distal to the terminal bronchioles, with the destruction of their walls.
EPA	Environmental Protection Authority (United States)
Epidemiology	The study of the relationships of various factors determining the distribution of disease in a human community.
ESEWG	Exposure Standards Expert Working Group
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FEV/FVC	A commonly used index of airflow obstruction
Fibrogenic dust	A dust (eg. crystalline silica or asbestos) which causes the formation of fibrotic (scar) tissue after its deposition in the gas-exchange region of the lung.
Fibrosis	The development of excess fibrous connective tissue in an organ.
FTIR	Fourier Transform Infrared Spectrophotometer
Hazard	The intrinsic ability of an agent or process to produce adverse effects on health.
HSE	Health and Safety Executive (UK)
HSSC	Hazardous Substance Sub Committee (NOHSC)
IARC	International Agency for Research on Cancer, a subsidary of the World Health Organisation
IL	Interleukin (an inflammatory cytokine)
ILO Classification	International Labour Organisation Classification

Inhalable Fraction	The amount of dust capable of entering and depositing in the upper respiratory tract (≤100 um in diameter).
Inspirable Fraction	This is an outdated term which has been replaced by the respirable fraction
IFN	Interferon (inflammatory cytokine)
Intratracheal	Within the trachea
IRS	Infra-red Spectroscopy
Limit of Detection (LOD)	The lowest concentration of substance eg. crystalline silica, that can be determined to be statistically different from a sample which contains none of that substance.
Limit of Quantitation (LOQ)	The level above which quantitative results may be obtained with a specific degree of confidence. Traditionally, the LOQ is assigned to be 10 standard deviations above the value of the blank.
mRNA	messenger ribonucleic acid
Material safety sheet	A document that describes the properties and risks of using a substance.
Micrometre (µm)	One thousandth of a millimetre.
Morbidity	Measured health outcomes (eg. hospital admissions) for a particular cause or disease (excluding death)
Mortality	Deaths from a certified cause or all causes
NHMRC	National Health and Medical Research Council (Australia)
NIOSH	National Institute for Occupational Safety and Health (United States)
NOHSC	National Occupational Health and Safety Commission (Australia)
No Observed Adverse Effect Level (NOAEL)	The level of exposure at which no adverse effect is observed.
NF-kappa B	Nuclear Factor kappa B (an inflammatory cytokine)
OEL	Occupational Exposure Level
OES	Occupational Exposure Standard
OSHA	Occupational Safety and Health Administration (United States)

Oxygen/free Radicals	A group of highly reactive oxygen atoms that act as a unit but do not commonly exist in the free state (also see ROS).
Parenchymal disease	A disease of the essential or specialised part of an organ (eg. alveoli) as distinguished from the supporting connective tissue.
PEL	Permissible Exposure Level
Personal sample	An atmospheric sample collected from within the breathing zone of an individual.
Personal sampling	A method whereby air is sampled from within employees' breathing zones to evaluate personal exposure to airborne contaminants.
Person-years	Sum of all years of follow up contributed by each person in a study population; used as a denominator in person-time incidence and mortality rates, eg. 1 person followed up for five years contributes a total of 5 person-years; 2 people each followed up for five years contribute 10 person-years.
PMF	Pulmonary Massive Fibrosis
PMR	Proportional Mortality Ratio: a ratio of mortality rates of a specified population, for a given cause of death, compared with all causes of death in that population.
Pneumoconiosis	Dust disease of the lung
py	Person-Year - 1 person at risk for 1 year
Reactive Oxygen Species (ROS)	A group of highly reactive oxygen atoms that act as a unit, but do not commonly exist in the free state (also see Oxygen/free Radicals).
REL	Recommended Exposure Limit
Respirable fraction	That fraction of dust which penetrates to the gas-exchanging parts of the lung.
Risk	The likelihood that a hazard will give rise to an adverse effect on health.
Silicates	Mineral compounds containing silica, eg. asbestos, talc, mica, feldspar, slate, sillimanite and various clays
Silicosis	Nodular fibrosis of the lung diagnosed clinically and epidemiologically by small rounded opacities on a plain chest x-ray, with profusions according to the ILO classification $\geq$ 1/0, with or without large opacities.
Silicotic	A certified case of Silicosis
SMR	Standardised Mortality Ratio, or the ratio of observed cases/expected cases

	using a comparative population.
SRR	Standardised Rate Ratio, or ratio of one rate relative to the other, using an internal reference, such as a baseline exposure category
Static sample	An air sample taken at a fixed location, commonly between one and two metres above floor level.
Tuberculosis	*Mycobacterium tuberculosis*
TLV	Threshold Limit Value
TGF	Transforming Growth Factor (inflammatory cytokine)
TNF	Tumour Necrosis Factor (inflammatory cytokine)
TWA	Time Weighted Average
XRD	X-ray Diffraction
WHO	World Health Organisation

Units

mg/m^3 = milligrams per cubic metre
g/mL = density of fluids in grams per millilitre
mppcf = million particles per cubic foot
ppcc = particles per cubic centimetre
ug/m^3 = micrograms per cubic metre
g/cm^3 = grams per cubic centimetre
L/min = a flow rate of litres per minute

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