

HSE Workplace Health Expert Committee (WHEC)

Silica and lung cancer



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This report, its contents, including any opinions and/or conclusions expressed, are those of the committee members alone and do not necessarily reflect HSE policy.



Foreword

The development of policy in HSE needs to be informed by the best available contemporary scientific evidence. In 2015, HSE formed the Workplace Health Expert Committee (WHEC) to provide independent expert advice to them on:

- New and emerging workplace health issues
- New and emerging evidence relating to existing workplace health issues
- The quality and relevance of the evidence base on workplace health issues

Questions about workplace health issues come to WHEC from many sources, which include HSE, trade unions, employers, interested individuals and members of WHEC. WHEC's responses to these questions are published online as reports to HSE, as position papers following investigation, or as a briefer response where the current evidence is insufficient to warrant further investigation. In cases where the evidence-base is limited WHEC will maintain a watching brief and undertake further investigation if new and sufficient evidence emerges.

In its formal considerations, WHEC aims to provide answers to the questions asked based on the available evidence. This will generally include review of the relevant scientific literature, identifying the sources of evidence relied on in coming to its conclusions, and the quality and limitations of these sources of evidence.

The purpose of WHEC reports is to analyse the relevant evidence to provide HSE with an informed opinion on which to base policy. Where there are gaps in the evidence, which mean that this is not possible, WHEC will identify these and, if appropriate, recommend how the gaps might be filled.

Executive Summary

WHEC was asked by HSE to consider “whether or not the development of silicosis is a necessary precursor event required for the induction of lung cancer in workers regularly exposed to respirable crystalline silica (RCS)”.

Several high quality cohort studies of workforces exposed to RCS in different occupational settings have shown an increased risk of lung cancer of the order of 20 to 30%. The risk of lung cancer in these studies shows consistent evidence of an exposure-response relationship with similar increases in risk at similar levels of cumulative exposure, making a causal association likely.

The risk of lung cancer has been consistently increased in those with silicosis. Few studies have compared the risk of lung cancer in those with and without radiographic evidence of silicosis. The two studies which have investigated this question in study populations comparably exposed to RCS with and without silicosis, have found a similar increase in risk in those without radiographic evidence of silicosis as in (1) the study population overall in the larger study and (2) those with silicosis in the second study. These studies suggest that radiographic silicosis is not an essential precursor of lung cancer in those exposed occupationally to RCS.



Introduction

Silica (silicon dioxide) constitutes some 60% of the earth's crust and is the main constituent of more than 95% of known rocks. It is therefore frequently encountered by those working in mining, quarrying and tunnelling as well as in the many other industries in which silica-containing materials, such as sand and quartz are used, e.g. foundries, pottery work and ceramics. Inhaled respirable crystalline silica (RCS) has long been recognised to cause a characteristic nodular scarring of the lung, silicosis, which, often accompanied by tuberculosis, is the cause of respiratory disability and premature death.

The current workplace exposure limit (WEL) in the UK of 0.1mg/m³ is intended to minimise the risk of developing silicosis in those encountering RCS in their work. In the context of the increasing evidence that inhaled RCS can cause lung cancer, HSE asked WHEC to consider "whether or not the development of silicosis is a necessary precursor event required for the induction of lung cancer in workers regularly exposed to respirable crystalline silica".

A causal relationship between an exposure and a disease (e.g. silica and lung cancer) is probable when:

- The risk of the disease is increased in the exposed as compared to the general population (increased risk ratio).
- The increased risk ratio is consistent in the majority of high quality studies of the question, for a given level of exposure, recognising that exposure levels may change over time or vary by setting.
- The increase in risk is unlikely to be explained by confounding.
- There is evidence of an exposure-response relationship.
- There is evidence that the exposure preceded the disease.
- There is supporting evidence where possible, of biological plausibility, e.g. evidence from toxicological studies *in vivo* or *in vitro*.
- Where available there is evidence that when the exposure is demonstrably removed or reduced the risk of disease decreases.

Cancers usually develop only after a long period, usually 20 or more years, from initial exposure to a cause. Over such a period people can be lost to investigation and information about exposure levels in the relevant period, if made, may no longer be accessible. For these reasons, in order to make confident inferences of cause and effect, it is important to rely on strong epidemiological studies. In general these will be cohort studies, with (i) follow up of a high proportion of the cohort for a long enough period for long latency effects, such as cancer, to have developed, (ii) sufficient numbers and power to detect an effect in relation to a suitable comparator population and (iii) reliable estimates of exposure levels of sufficiently high quality, ideally based on actual measurements to estimate the risk of disease in relation to varying levels of exposure (exposure-response relationship). In addition (iv) there will be sufficient information to allow for potential

confounders, e.g. cigarette smoking and asbestos exposure, in investigating the relationship of silica and lung cancer.

Evidence for the carcinogenicity of inhaled RCS has been reported in recent decades. In 1996 an IARC review concluded that crystalline silica in the form of quartz and cristobolite was a definite pulmonary carcinogen in man. The evidence for carcinogenicity was considered strongest in cases of silicosis. Since then several further informative studies of the carcinogenicity of crystalline silica have been published. These have, in general, confirmed the association of inhaled crystalline silica with lung cancer, the majority providing evidence for an exposure-response relationship. The risk in general has been found to be higher in cases of silicosis but few cohort studies have been able to estimate risks separately for those with and without silicosis.

1 EVIDENCE THAT INHALED RESPIRABLE CRYSTALLINE SILICA (RCS) IS A CAUSE OF LUNG CANCER.

This section reviews the evidence from high quality studies of the relationship of silica and lung cancer and concludes, primarily on the basis of the consistency of exposure-response relationships, that the association is likely to be causal.

Several high quality cohort studies in working populations exposed to RCS have been reported, the majority showing an increased risk of lung cancer. The most informative of these studies are:

(i) Diatomaceous earth industry.

Checkoway H *et al*, 1990.

Checkoway H *et al*, 1993.

Checkoway H *et al*, 1996.

Checkoway H *et al*, 1997.

Rice FL *et al*, 2001.

Gallagher LG *et al*, 2015.

(ii) Industrial sand workers.

Hughes JM *et al*, 2001.

McDonald AD *et al*, 2001.

Steenland K *et al*, 2001.

McDonald JM *et al*, 2005.

(iii) Pottery workers.

Cherry NM *et al*, 1998.

(iv) Granite workers.

Attfield MD, Costello J. 2004.

(v) Miners

McDonald JC *et al*, 1978.

Steenland K, Brown D. 1995.
An update of the McDonald study.

Liu Y, Steenland K, Rong Yi *et al*, 2013.

Miller B, MacCalman L. 2010.

The evidence that RCS causes lung cancer is considered strong because each is a well-designed cohort study with registration of the population at risk and follow-up of a high proportion of the cohort 20 years or more from initial exposure, with exposure estimates, often based on direct measurements and comparison of outcome with appropriate comparator populations. Most studies adjusted for confounding by relevant occupational factors, such as asbestos and radon, although adjustment for smoking was not invariable (Table 4, see page 10).

(i) Diatomaceous earth industry workers

The series of studies reported by Checkoway and colleagues on the mortality of 2342 diatomaceous earth industry workers, employed for at least one year between 1942-87 and exposed to RCS, predominantly cristobolite, show a consistently increased risk of lung cancer and of non-malignant respiratory disease (NMRD). In the 7 year extended mortality report published in 1997, the Standardised Mortality Ratio (SMR) for NMRD was 2.01 (95% CI 1.56-2.55) and for lung cancer was 1.29 (95% CI 1.01-1.61). Allowing for a 15 year latency, the risks for both NMRD and lung cancer showed a gradient of increasing risk with increasing exposure, with the rate ratio in the highest exposure category (>18.3 mg/m³yr) for NMRD of 5.35 (95% CI 2.23-12.8) and for lung cancer of 2.15 (95% CI 1.08-4.28).

Table 1: Risk of lung cancer in diatomaceous earth workers (from Gallagher, 2015)

	First follow up 1942-1992		Extended follow up 1993-2011		Combined follow up 1942-2011	
	SMR	95% CI	SMR	95% CI	SMR	95% CI
Lung cancer	1.29	1.01-1.61	0.66	0.46-0.92	1.03	0.85-1.23
Pneumoconiosis	3.96	2.63-5.72	1.12	0.63-1.84	2.16	1.56-2.91

In their conclusions the authors stated that for lung cancer “excess risk was predominantly concentrated in the highest cumulative exposure stratum of either respirable dust or respirable silica”.

In a more recent report, which extended the period of follow-up from 1993 to 2011, Gallagher et al, (2015), found that during this later period the risks of developing lung cancer was not elevated and that of pneumoconiosis only slightly and not significantly. See Table 1.

An interpretation of these findings is that the increased risk of lung cancer primarily occurred in those who experience higher levels of cumulative exposure and that the reduced risk in the second period reflected a reduction in exposure to RCS in the relevant period of exposure. Consistent with this interpretation was evidence of a reduction in the risk of pneumoconiosis in the second period. Also in both periods there was evidence of an increasing gradient of risk of lung cancer and non-malignant respiratory disease with exposure to RCS, with a hazard ratio for lung cancer of 1.75 in the first period and of 1.74 in the second period in the highest category of exposure ($>5.6\text{mg/yr/m}^3$) – that is to say, for comparable levels of high exposure to silica, comparable increases in risk of lung cancer were found.

(ii) Industrial sand workers

The studies of the N. American industrial sand workers included 4626 persons in the Steenland study and 2670 in the Hughes and McDonald population. See Table 2. Both studies found an increased risk of lung cancer with evidence for a gradient of increasing risk with increasing cumulative exposure to silica, although the categories of cumulative exposure differed between these two studies.

(iii) Pottery workers

The study of pottery workers showed an increased mortality rate from lung cancer relative to that in the local population. The SMR for lung cancer in the Stoke pottery population of 5115 men was 1.28 (95% CI 0.99-1.62). Mean concentration of exposure (but not cumulative exposure or duration of exposure) was related to the risk of lung cancer.

(iv) Granite workers

In the study of 5414 Vermont granite workers, employed between 1950 and 1982, cumulative exposure to silica was related to the risk of pneumoconiosis, TB, lung cancer and kidney cancer (Attfield and Costello, 2004). The SMR

Table 2: Risk of lung cancer in industrial sand workers: exposure-response relationships

	Steenland (2001)	Hughes/ McDonald (2001)	McDonald (2005) updated
Lung cancer			
SMR	1.6	1.39	1.47
SMR v cumulative exposure (lagged 15 years)			
Low 1	1.0	1.0	1.0
2	1.35	0.84	0.94
3	1.63	2.02	2.24
High 4	2.0	2.07	2.66

Table 3: Risk of lung cancer in British coal miners (Miller and MacCalman, 2010)

Period	SMR	95% CI
1959 – 1974	0.78	0.67 – 0.91
1975 – 1989	0.95	0.86 – 1.05
1990 – 2005	1.16	1.05 – 1.28
1959 – 2005	0.99	0.93 – 1.05

for lung cancer for shed workers was 1.3, as compared to 0.72 for quarry workers. The highest lung cancer SMR of 1.7 was found in shed workers with more than 30 years exposure and more than 40 years from first exposure. Lung cancer SMR 15 or more years from first exposure showed a gradient of increased risk with increasing cumulative exposure, (from 0.77 at 0-0.25 mg/m³yr to 1.7 at 3.0-6.0 mg/m³yr), reducing at the highest level of cumulative exposure (1.16 at ≥ 6 mg/m³yr). The authors estimated from these results that exposure to RCS at 0.05mg/m³ from age 20 to 64 years was associated with a lifetime excess risk of lung cancer for white males of 27/1000.

(v) Miners.

Several studies of underground miners have been reported. An important consideration in attributing lung cancer to inhaled RCS in these cohorts has been to take account of, or exclude, populations exposed to other causes of lung cancer in their working environment, such as arsenic and ionising radiation.

The SMR from lung cancer in British coal miners (Miller and MacCalman) exposed to quartz varied by era (See Table 3).

Thus, in the earlier periods, there was no elevation in risk of lung cancer overall. However, mortality rates in workers often tend to be lower than the general population because of 'healthy worker' selection bias. The risk of lung cancer also showed a significant relationship to the cumulative level of quartz exposure lagged 15 years, i.e. evidence of an exposure-response relationship.

Gold has been mined in South Dakota since 1875.

McDonald and colleagues investigated the causes of death of 657 of the 660 men who had died from the population of 1321 recorded as having worked more than 21 years in

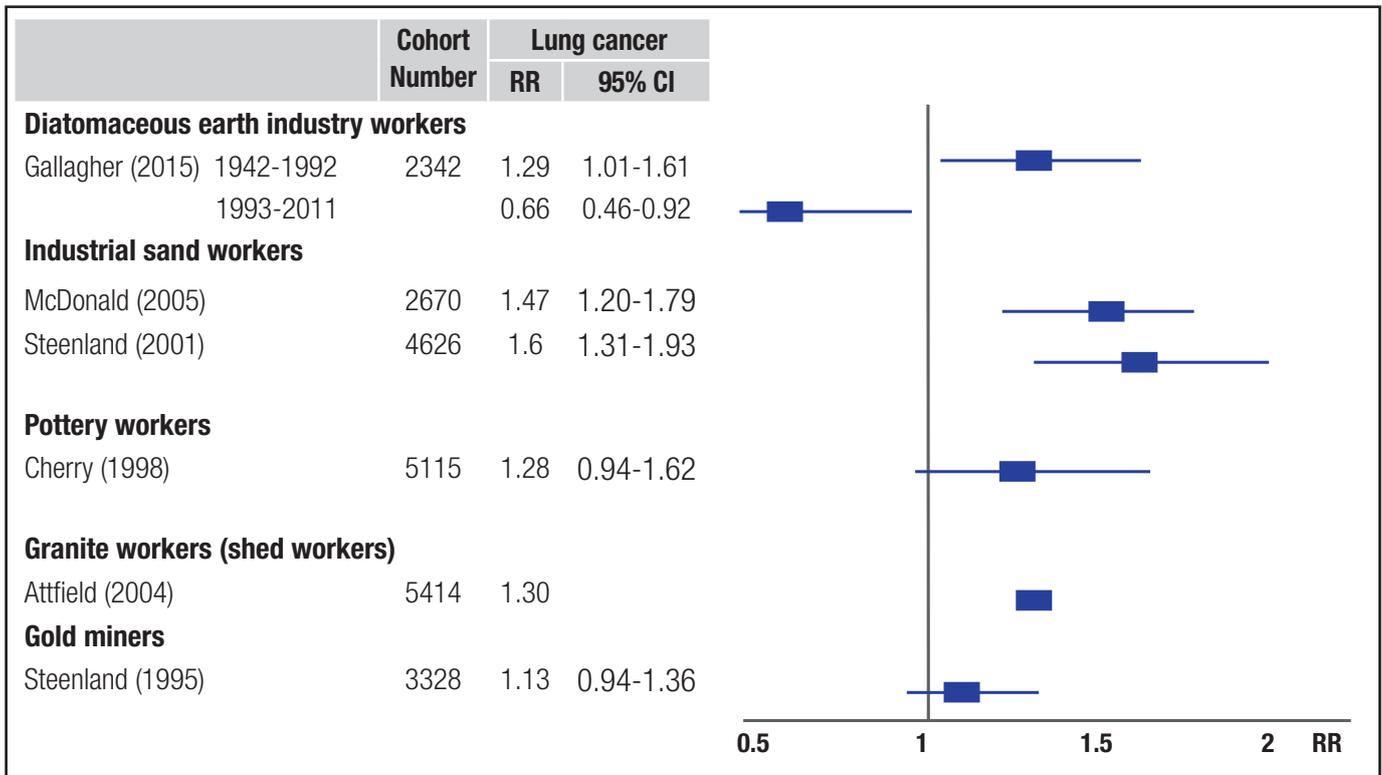
the mine. A clear excess of deaths was found from silicosis, TB and silico-tuberculosis, but not from lung cancer. This study is of interest as being a well-designed study, with a population sufficiently exposed to RCS to cause an excess of pneumoconiosis and TB, but without an excess of lung cancer or evidence of an exposure-response relationship for lung cancer. It seems unlikely that the absence of an increased risk of lung cancer is attributable to competing causes of death, given that the interval from first exposure to death was on average 35 years, ranging from 22 to 51 years.

Steenland and Brown updated the findings of the McDonald study, increasing the criteria for inclusion from working for 21 years to having worked for 1 year or more and following up the population for a further 14 years. Their study population was 3,328 gold miners who had worked underground for at least one year between 1940 and 1965, with a total of 1551 deaths and 115 lung cancer deaths. They also observed an increased SMR of 2.61 (95% CI 2.11-3.20) for silicosis and of 3.52 (95% CI 2.47-4.87) for tuberculosis, with evidence for an exposure-response relationship for these diseases. The lung cancer SMR was 1.13 (95% CI 0.94 – 1.36) against US population and 1.25 (95% CI 1.03 – 1.55) against the county population, without evidence of an exposure-response relationship. This remains one of few well studied cohorts in which there is evidence for sufficient exposure to silica to cause silicosis and to increase the risk of tuberculosis without evidence of a clearly increased risk of lung cancer or of an exposure-response relationship between lung cancer risk and estimated silica exposure.

Table 4 Data for most recent studies of occupational cohorts exposed to RCS

Author/year	Type of industry	Cohort description	Exposure assessment	Primary outcome	Measure of risk	Lung cancer / total deaths	Adjustment for confounders	Exposure
Checkoway 1997	Diatomaceous earth industry	2,342 white males employed > 1yr 1942 - 1987	Exposure measurements 1948 – 1962 1962 – 1988 + work history	Lung cancer	SMR (HR for exposure-response)	77 / 749	Smoking, Asbestos	Gradient
Gallagher 2015	Diatomaceous earth industry	1993 - 2011		Lung cancer		113 / 1,242	Smoking, Asbestos	Gradient
Steenland 2001	Industrial sand workers	4,626 workers follow-up 1960 - 1996	4,269 hygiene samples 1974-1995	Lung cancer	SMR	109 / 1,073	Smoking limited data from co records 1978-1989	Gradient
McDonald 2005	Industrial sand workers	2,670 workers employed >3yrs 1940 – 1979 follow-up to 2000	Co records of silica exposure + use of RPE	Lung cancer	SMR	112 / 1,225	Smoking	Gradient
Cherry 1998	Pottery, refractory, sandstone industries	5,115 men born 1916 - 1945	Airborne dust measurements	Lung cancer	SMR	68 / 470	Smoking from medical records	Gradient with average not cumulative exposure
Steenland 1995	Gold miners	3,328 men worked underground > 1yr 1940 – 1965 follow-up to 1990	Measured dust levels	Lung cancer	SMR	115 / 1,551	Smoking estimated from sample	No gradient v exposure measures
Liu 2003	Metal workers + pottery workers	34,018 workers 1960- 2003 34.5yr follow-up	Historical data on dust conc + work	Lung cancer	HR	546 / 11,377	Smoking history (pack years) Excluded tin and copper miners (Arsenic exposed) from study	Gradient v cumulative exposure

Fig. 1 Estimates of lung cancer mortality in different occupational cohorts exposed to RCS



Meta analyses of studies of exposure to respirable crystalline silica and lung cancer

Several studies have reported pooled or meta-analyses of the available individual studies to provide an overall summary measure of risk and investigate any heterogeneity in the exposure-response relationships. Pelucchi *et al*, (2006) reviewed the epidemiological literature relating to crystalline silica exposure and lung cancer risk since the publication of the IARC Monograph (1996-2005). They included 28 cohort studies, 15 case-control studies and two proportionate mortality ratio studies. They carried out a series of meta-analyses by study type, separately for studies of silicotics and studies where the status of subjects in relation to silicosis was undefined. The pooled relative risk from all cohort studies was 1.34, (95% CI 1.25-1.45). In cohort studies of silicotics the relative risk was 1.69, (95% CI 1.32-2.16), and in other studies the relative risk was 1.25, (95% CI 1.18-1.33); in case-control studies the odds ratio was 1.41, (95% CI 1.18-1.67). The authors found little evidence of consistent differences in risk by occupational setting (mines, sand workers etc).

Steenland *et al*, (2001) undertook a pooled analysis of ten cohorts in whom there was quantitative data on cumulative

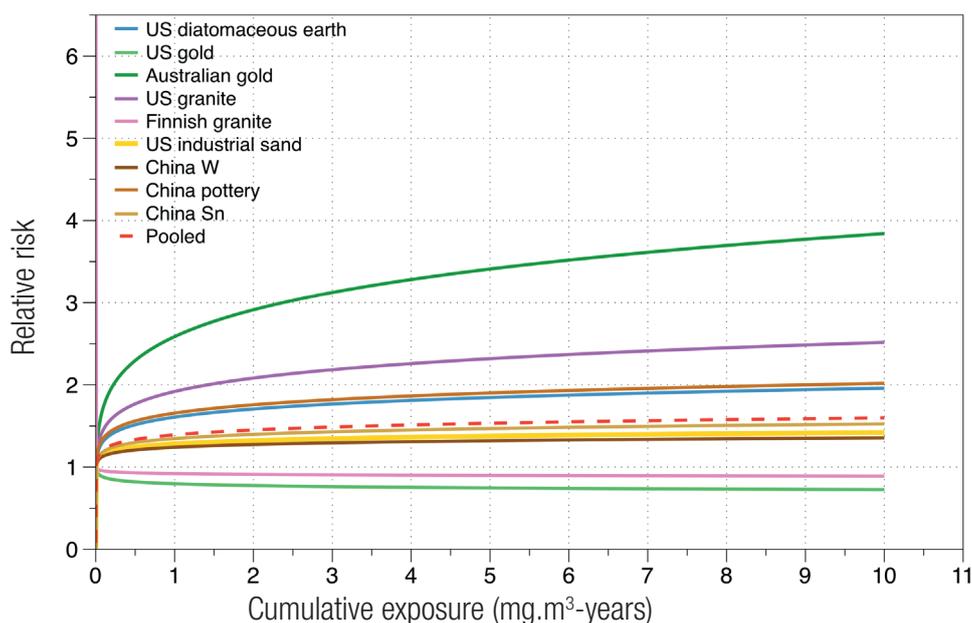
exposures to RCS (four US studies, three from China, one from South Africa and one from Australia). They included 65,980 workers of whom 1072 had died from lung cancer. They found that log-transformed cumulative exposure with a 15-year lag was the best predictor of lung cancer risk ($p=0.0001$), with the equation in the form:

$$RR = 1 + \beta X$$

Where β was the slope of the relationship and X the cumulative exposure in $\text{mg}/\text{m}^3\text{-days}$.

The study was later reanalysed by Steenland as part of a quality assurance exercise linked to a review undertaken by the US Occupational Safety and Health Administration in support of setting a standard for crystalline silica, which resulted in some minor changes to the risk models (www.osha.gov/silica/). Figure 2 shows the regression lines for nine of the studies¹ and the pooled result (red dotted line). There is considerable heterogeneity across studies, although less when log-transformed cumulative exposure was used in the analysis rather than average or cumulative exposure. There was no indication that the risks were importantly different in the one study where workers were mainly exposed to cristobalite (US diatomaceous earth

Figure 2: Exposure-response relationships for individual studies included in the Steenland *et al* pooled analysis of lung cancer as presented in the OSHA risk assessment



¹ The South African gold miner cohort produced a very high risk estimate across the range of cumulative exposures evaluated, which the authors suggest could be due to radon exposure in the mines. These data are excluded from the graph, but were included in the pooled analysis. In this study the modelled RR at $4.5\text{mg}/\text{m}^3\text{-yr}$ is 6.

workers) rather than alpha-quartz, the presumed exposure in the remaining studies. However, the authors suggest that other physical difference between the dusts, such as the freshness of the particle cleavage surfaces and the presence of coating on the silica surface could explain some of the differences between studies. In summary evidence was found of an exposure-response relationship between RCS and lung cancer, although with several potential factors modifying its exact form.

Thus the model implied by Steenland's data is compatible with a possible increased risk of lung cancer below the current Workplace Exposure Limit (WEL).

It is notable that the rate of increase in relative risk decreases as cumulative exposure increases, which Steenland and his colleagues suggest might be explained by several factors, including saturation of the biological processes, poor estimation of exposure at higher levels, the healthy worker survivor effect or limitation of the number of people in the working population who are susceptible to the risk from silica exposure.

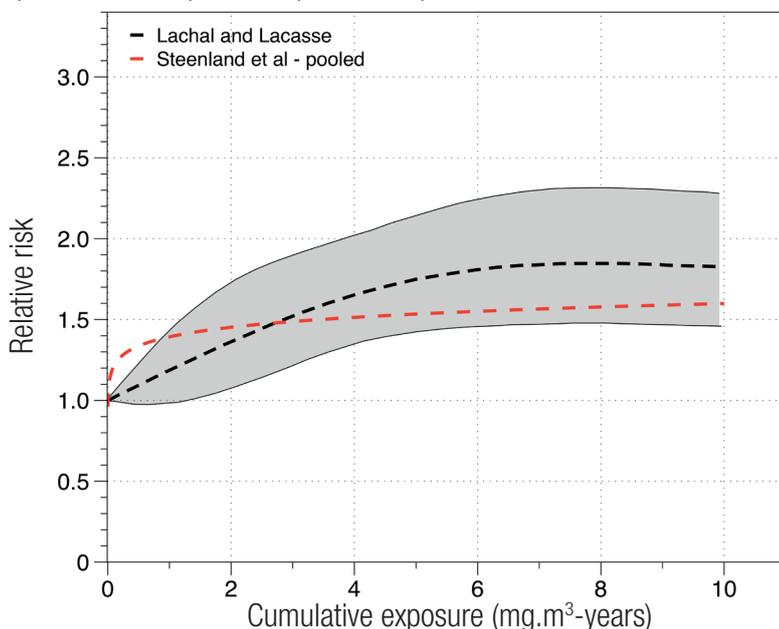
Steenland *et al* discussed a number of possible sources of bias and confounding in their analysis, in particular the absence of smoking data in several studies and co-exposure of workers to other carcinogens, but they

concluded that none of these could explain the observed exposure-response relationship.

Lacasse *et al*, (2009) has provided a more recent meta-analysis of studies on lung cancer and RCS in the epidemiological literature in the period 1966-2007. They carefully selected studies that best aimed to minimise potential confounding from co-exposure to other occupational carcinogens, e.g. radon and asbestos,. Nine studies were included in the meta-analysis; three of these studies were common, at least in some way, to cohorts in Steenland *et al*. A model (spline of order 3) was fitted to the data to provide for the possibility of a non-linear exposure-response. The analysis identified an increasing risk of lung cancer with increasing cumulative exposure to silica, although with heterogeneity across the studies. Two studies were clear outliers – a study of all Finns born between 1906 and 1945 who participated in the 1970 national census, and a cohort of industrial sand workers in the USA, both of which had different design from the others. The remaining seven studies were more homogeneous, although restricting the meta-analysis to these produced an exposure-response curve that was similar to that from the analysis including all studies.

This paper was subsequently criticised by Morfeld (2009), in particular on the grounds that the original analysis did not restrict the regression line to pass through a RR of 1 at zero

Figure 3: Exposure-response relationship with its 95% confidence limit (no lag time): spline fitting with no intercept, compared with the pooled exposure-response curve from Steenland *et al* (15 yr lag)



exposure. In response, Lakhal and Lacasse (2009) provided an additional analysis where the spline curve was fitted without an intercept, and this is shown in Figure 3 (with confidence intervals as the shaded area) together with the regression curve for the pooled analysis by Steenland *et al.*

As in the Steenland *et al.* analysis, Lakhal and Lacasse (2009) found that the exposure response flattened at higher cumulative exposure. Both analyses show statistically significant increased risks for cumulative exposures above around 2 mg/m³-years, which is equivalent to an average exposure over a working lifetime of 0.04 mg/m³.

Thus both reports, while not providing an exact match, indicate an exposure-response relationship between RCS and lung cancer.

2 IS THE INCREASED RISK OF LUNG CANCER A RISK OF SILICOSIS OR OF EXPOSURE TO SILICA ALONE?

This section reviews the limited number of studies which have investigated the risk of lung cancer in those with and without silicosis. It concludes that the limited available evidence suggests that silicosis, as defined by abnormalities on a chest radiograph, is not a necessary precursor for the development of lung cancer.

Several studies have reported an increased risk of lung cancer in cases of silicosis. This may reflect:

- Silicosis as a fibrotic reaction which predisposes to the development of lung cancer. A similar argument was advanced (e.g. Hughes and Weill, 1991) for the increased risk of lung cancer in asbestos workers being the consequence of asbestosis.
- Cases of silicosis have experienced the highest levels of exposure to inhaled silica and are therefore at the highest risk of lung cancer.

Several of the studies showing an increased risk of lung cancer in cases of silicosis have been based on cases ascertained through compensation claims or hospital attendance. Cases coming to light in these ways are unlikely to be representative of cases of silicosis in general: in particular those applying for compensation or attending hospital are more likely to have respiratory symptoms and impaired lung function, which may be, at least in part, attributable to other causes, such as cigarette smoking. For this reason studies such as Amandus *et al*, (1991, 1995) based on cases of silicosis identified through regular health

surveillance are likely to be more informative than studies such as Infante-Rivard *et al*, 1989 or Marinaccio *et al*, 2006, both of which were based on compensated cases of silicosis.

The 2 studies of Amandus and colleagues report an increased risk of lung cancer in 760 males, of whom 550 had died with silicosis diagnosed between 1930 and 1983, who had been subject to regular surveillance by the State of Carolina's medical examination for dusty trades. The lung cancer SMR in this white male group was 2.6 (95% CI 1.8-3.6) in comparison to US white males, which was not accounted for by cigarette smoking or exposure to other known occupational carcinogens. In their second study Amandus and colleagues reanalysed the death rates in a subgroup of 306 of the population for whom technically acceptable chest radiographs were available for reading. The SMR for lung cancer was 1.7 (95% CI 0.8-3.1) in this group, 2.5 (95% CI 1.1-4.9) in the 143 subjects with simple silicosis and 1.0 (95% CI 0.1-3.5) for the 96 with ILO category 0. There were no cases of lung cancer in 67 men with progressive massive fibrosis (PMF).

Checkoway *et al* (1990) investigated 1809 men of the 2342 in their cohort with available and readable chest radiographs. The SMR for lung cancer was 1.19 (95% CI 0.87-1.57) in those without silicosis (48 deaths) and 1.57 (95% CI 0.43-4.03) in those with silicosis (4 deaths). The SMR's at the highest level of cumulative exposure were 2.40 (95% CI 1.24-4.2) in those without silicosis (12 deaths) and 2.94 (95% CI 0.8-7.55) in those with silicosis (4 deaths).

Liu *et al* (2013) reported lung cancer mortality in 34,018 pottery workers and metal miners excluding copper miners,

Table 5: Risk of lung cancer overall and in those without silicosis: exposure-response relationships (Liu 2013)

Cumulative silica exposure mg/m ³ .yr	Hazard ratios (25yr. lag)					
	n	Overall	(95% CI)	n	Without silicosis	(95% CI)
< 0.01		1			1	
0.01 – 1.12	8765	1.26	0.98-1.60	8325	1.12	0.86-1.46
1.12 – 2.91	4179	1.54	1.16-2.05	3478	1.41	1.03-1.93
2.91 – 6.22	4659	1.68	1.26-2.24	3140	1.58	1.41-2.19
> 6.22	3907	1.70	1.23-2.34	1970	1.70	1.15-2.52

because of potential arsenic exposure; 5297 had died of silicosis and 546 of lung cancer. See Table 5. They found an exposure-response relationship between lung cancer and cumulative exposure to RCS overall and in cases without silicosis.

The results of the Checkoway study and particularly the larger Liu study suggest that the increased risk of lung cancer in silicosis may be more a reflection of exposure to high levels of silica, rather than of silicosis per se. However, the number of studies which have been able to explore this question and the numbers available for study remain too low as to yet come to a definite conclusion.

3. MODE OF ACTION FOR CRYSTALLINE SILICA CARCINOGENICITY

This section reviews the toxicological evidence in relation to silica and lung cancer. This suggests that from animal studies the most likely mechanism is that genotoxicity is secondary to silica-induced inflammation. The relevance of these studies to humans is unclear.

It is important for the purposes of hazard and risk assessment to understand the mechanism or Mode of Action (MoA), by which RCS may induce lung cancer. The question which HSE has asked WHEC is whether silicosis is a prerequisite for the development of lung cancer or can RCS cause cancer in the absence of silicosis. A major problem with disentangling the possible mechanisms for both silicosis and RCS associated lung cancer is the crucial role played by alveolar macrophages and neutrophils in both diseases (Hamilton *et al.*, 2008).

In 1997, the IARC Monograph meeting on silica (IARC, 1997) concluded that inflammation was the most likely mechanism responsible for the induction of lung cancer associated with exposure to RCS, implying a secondary genotoxic effect. However, they noted that reactive oxygen species (ROS) can be directly generated by RCS polymorphs themselves, which could be taken up by target epithelial cells, and that a direct effect on lung epithelial cells could therefore not be excluded (Schins, 2002; Fubini and Hubbard, 2003 and Knaapen *et al.*, 2004).

Since the IARC 1997 evaluation, two important reviews have critically considered the MOA of RCS and lung cancer: these are IARC 2012 and Borm *et al.*, 2011. Both drew on a number of *in vitro* and *in vivo* studies which had been published since the 1997 IARC evaluation and which shed light on the MOA of RCS. Caution must be exercised in the interpretation of much of this *in vitro* and *in vivo* data as our primary concern is with responses of the human lung: there are, in the case of *in vivo* investigations, important inter-species differences in responses of the lung between experimental models (rats and mice) and humans both qualitatively and quantitatively, which need to be considered in any extrapolation to humans. A further complication is that a wide variety of RCS materials have been used in

these studies from the well-defined DQ12 and MinUsil (with and without modifications) through to real life quartz-containing particles.

Helpfully, in their review, Borm *et al.* (2011) provide a contextual background and definitions. They noted that determining a mechanism is important as it can be argued that a “secondary” genotoxicity MOA implies a threshold for a triggering biological effect with important implication for risk assessment (Kirsch-Volders *et al.*, 2003).

IARC (2012) in its most recent synthesis of the MOA data has proposed that there are three mechanisms for the carcinogenicity of RCS seen in rats. The first is that exposure to RCS impairs alveolar-macrophage-mediated particle clearance (as seen with inert respirable particulates – see ECETOC (2013) TR-No.122 Poorly Soluble Particles/ Lung Overload). This increases the persistence of silica in the lungs resulting in macrophage activation and the sustained release of chemokines and cytokines. This persistent inflammatory response in rats is characterised by an increase in neutrophils which generate oxidants (including ROS) which can induce genotoxicity, injury and proliferation of lung epithelial cells leading to the development of lung cancer. In their second proposed mechanism, RCS particles in the lung generate free radicals which deplete antioxidants in the lung-lining fluid and induce epithelial cell injury followed by epithelial cell proliferation. Thirdly, RCS particles are directly taken up by lung epithelial cells followed by intracellular generation of free radicals that directly induce genotoxicity. The IARC 2012 Working Group (WG), considered the first of these mechanisms to be “as the most prominent” based on the rat inhalation or intratracheal instillation experimental rat data although “the other mechanisms cannot be excluded”. It then noted, however, that it is unknown which, if any, of these mechanisms occur in humans exposed to RCS.

In a more comprehensive review, including, taking into account dose thresholds for both inflammation and genotoxicity, Borm *et al.*, 2011 came to a very similar conclusion regarding the most likely MOA for the carcinogenicity of RCS and proposed that the experimental evidence, including dose thresholds, “supported the contention that the most likely mechanisms for quartz

genotoxicity in vivo under plausible exposures is a secondary, inflammation driven one”.

It should be noted that the rat has a particularly exaggerated reaction in its inflammatory-associated responses to poorly-soluble inhaled respiratory particulates and seems to be unique in its ability to develop lung tumours as a consequence of sustained inflammation as compared to other similarly exposed experimental species (mouse and hamster) (ECETOC.,2013). Thus the relevance of these findings to the mechanism of action of silica in humans remains conjectural.

4. CONCLUSIONS

WHEC has concluded that, on the evidence currently available, silica is a cause of lung cancer and that silicosis, defined by nodules visible on the chest radiograph, is probably not a necessary precursor.

Cohort studies of working populations exposed to RCS, in the majority of cases, show an increased risk of lung cancer (Figure 1, see page 11). The overall increase in risk is of the order of 20 to 30%, a level that might be explained by confounding by other causes of lung cancer, including cigarette smoking, asbestos and, in miners, arsenic and radon, although the majority of studies have endeavoured to take such factors into account. The particular strength of the cohort studies reviewed in indicating causation is that with the exception of the 2 studies of the S. Dakota gold miners, they all showed a clear gradient of increasing risk of lung cancer with increasing level of exposure to RCS, in many cases based on contemporary measurements of airborne RCS. This consistency of evidence for an exposure-response relationship in the different studies undertaken on different working populations is the most convincing evidence for inhaled RCS as a cause of lung cancer.

The meta-analyses undertaken of the studies investigating the association between lung cancer and RCS come to similar conclusions, with a pooled relative risk in the Pelucchi report from all cohort studies of 1.34 (95% CI 1.25-1.45), with a relative risk of 1.69 (95% CI 1.32-2.16) in silicotics and of 1.25 (95% CI 1.18-1.33) in other studies. The meta-analyses of Steenland and of Lacasse both provide evidence of an exposure-response relationship, flattening at higher cumulative levels of exposure.

In general, the risk of lung cancer in cases of silicosis has been found to be higher than in working populations exposed to RCS as a whole. It is not clear whether this is because silicosis, or the associated inflammatory reaction, is a necessary precursor to the development of cancer, or whether it is a reflection of higher levels of exposure to silica experienced by cases of silicosis.

Two of the cohort studies, Checkoway (1990), Lui (2013), reviewed have investigated this question, both finding evidence of an increased risk of lung cancer in cases without silicosis at higher levels of exposure. Of the two, the Lui study is probably the more reliable because of the considerably larger number of cases of lung cancer both in cases with and without silicosis.

The results of toxicological studies suggest that the “most likely mechanisms for quartz genotoxicity is a secondary inflammatory one”. This is not necessarily at variance with the results of studies, albeit limited in number, in human working populations showing an increased risk in those without silicosis. Silicosis is identified by the presence of widespread nodules on a chest radiograph. The chest radiograph is a relatively insensitive index of intrapulmonary response to silica retained in the lungs. Other imaging modalities, such as CT, are more sensitive, but less sensitive than direct observation of the lung, usually only possible at post mortem. In a study of the relationship between silicosis diagnosed during life on chest radiograph and on pathological changes in the lung at post mortem, Hnizdo et al found the diagnostic sensitivity of chest radiograph was low (<0.4) i.e. a high false negative rate and the diagnostic specificity was high (>0.95), i.e. a low false positive rate. RCS retained in the lungs is likely to stimulate inflammatory changes in the lung, not visible on chest radiograph or lung CT, which toxicological studies suggest may act as the precursor to genotoxic changes in respiratory epithelial cells underlying carcinogenicity.

The evidence reviewed in this paper indicates that RCS is a cause of lung cancer, suggests that lung cancer can occur in the absence of radiologically evident silicosis but, as yet, the evidence is insufficient to distinguish in humans whether the cancer is secondary to the inflammatory reaction to silica retained in the lungs or from a direct genotoxic effect of silica.

Taken overall, current evidence is not consistent with silicosis (apparent on the chest radiograph) being a necessary precursor of lung cancer in workers regularly exposed to respirable crystalline silica.

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Glossary

Types of study

Case-control study: a study which compares people who have a given disease (cases) with people who do not have that disease (controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an **Odds Ratio**, a form of **Relative Risk**.

Cohort study: A study which follows those with an exposure of interest (usually over a period of years), and compares their incidence of diseases or mortality with a second group, who are unexposed or exposed at a lower level. Is the incidence rate higher in the exposed workers than in the unexposed/less exposed group? Sometimes the cohort is followed forwards in time ('prospective' cohort study), but sometimes the experience of the cohort is reconstructed from historic records ('retrospective' or 'historic' cohort study). The ratio of risk in the exposed relative to the unexposed can be expressed in various ways, such as **Relative Risk** or **Standardised Mortality Ratio**.

Nested case-control study: a special form of case-control study in which the cases and controls all come from within a well-defined cohort.

Measures of association

Relative Risk (RR): a measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicated a positive association between exposure and disease.* (This may be causal, or have other explanations, such as bias, chance or **confounding**).

Odds Ratio (OR): a measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure in those without disease, expressed as a ratio. For rare exposures, odds and risks are numerically very similar, so

the OR can be thought of as a **Relative Risk**. *A value greater than 1.0 indicates a positive association between exposure and disease.* (This may be causal, or have other explanations, such as bias, chance or **confounding**).

Standardised Mortality Ratio (SMR): a measure of the strength or association between exposure and mortality; a form of **Relative Risk (RR)** in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard).

By convention, the figure is usually multiplied by 100. Thus, an SMR of 200 corresponds to a RR of 2.0. For ease of understanding in this report SMRs are quoted as if RRs, and are not multiplied by 100. Thus *a value greater than 1.0 indicates a positive association between exposure and disease.* (This may be causal, or have other explanations, such as bias, chance or **confounding**).

Other statistical terms and concepts

Confidence interval (CI): The **Relative Risk** reported in a study is only an *estimate* of the true value in the population; another study, involving a different sample of people, may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95% CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). *Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values.*

Confounding: arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease, that occurs to a different extent in the groups being compared.

For example, smoking is a cause of lung cancer and tends to be more common in blue-collar jobs. An apparent

association between work in the job and lung cancer could arise because of differences in smoking habit, rather than a noxious work agent. Studies often try to mitigate the effects of ('control for') confounding in various ways: such as restriction (e.g. only studying smokers); matching (analysing groups with similar smoking habits); stratification (considering the findings separately for smokers and non-smokers); and mathematical modelling (statistical adjustment).

What is WHEC?

The Workplace Health Expert Committee (WHEC) provides independent expert opinion to HSE by identifying and assessing new and emerging issues in workplace health. Working under an independent Chair, WHEC gives HSE access to independent, authoritative, impartial and timely expertise on workplace health.

<http://webcommunities.hse.gov.uk/connect.ti/WHEC/grouphome>