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Research into Malignant and Non-malignant Respiratory Disease Prescriptions: Report for Silica and Lung Cancer

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1 Introduction

Silica and lung cancer is the second of 6 high-priority occupational exposure-disease combinations that were identified with IIAC as being of highest priority for more detailed investigation (see Report of Phase 1 of this project).

This document contains a commentary on the extracted data for relevant occupational epidemiological studies and is meant to be read in conjunction with the associated spreadsheets containing the data extraction from these studies (Appendix 1). The data contain those studies reported in the most recent IARC Monograph (IARC Working Group, 2012), together with those identified from literature searches by the IOM research team of more recent publications. A particular issue to be resolved is the strength of evidence for associations in the absence of silicosis (a sign of heavy silica exposure).

2 Methods

Searches of Web of Science and NLM PubMed databases were undertaken in September/November 2022 using the following search string: exposure AND silica AND (lung AND cancer).

Bibliographies of the studies included in the silica and lung cancer reviews found in our earlier literature searches (see below) were searched to identify any additional individual studies that should be screened for inclusion in the tables of evidence.

3 Results

The results are set out using the same categories as that of the IARC Monograph. Note that studies of silicotics were excluded.

3.1 Diatomaceous earth workers

From the IARC Monograph:

> *"Work in the diatomaceous earth industry is associated mainly with exposure to cristobalite rather than quartz, and, in the USA, is generally free of other potential confounding exposures apart from exposure to asbestos in a minority of locations. The first study of diatomaceous earth workers revealed significant positive trends in lung cancer risk with both cumulative exposure to crystalline silica (semiquantitative) and duration of employment (Checkoway et al., 1993)."*

The SMR for non-malignant respiratory diseases, excluding infectious diseases and pneumonia was 2.59 (95% CI: 1.96 to 3.36, n = 56).

From the IARC Monograph:

> *"Owing to concerns with confounding from asbestos, estimates of asbestos exposure were developed (Checkoway et al., 1996). Among those with no asbestos exposure, the lung cancer SMRs for the two higher crystalline silica exposure groups were twice the magnitude of those for the two lowest groups although these were not significantly elevated. Rate ratios, with and without adjustment for asbestos exposure were very similar (within 2%), indicating that confounding due to asbestos was not an issue."*

Internal analysis after adjustment for asbestos exposure yielded rate ratios for categories of exposure to crystalline silica: 1.00 (reference), 1.37, 1.80 and 1.79.

From the IARC Monograph:

> *"(Checkoway et al., 1997) provided findings from one of the two plants previously investigated but including 7 more years of follow-up as well as newly developed quantitative respiratory crystalline silica exposures. The lung cancer relative risks (RR) for the highest unlagged or 15-year exposure category were both significantly elevated."… "Trends for both unlagged and lagged exposure-response were of borderline significance."*

The RR for respirable crystalline silica was for the highest exposure stratum ($\geq$ 5.0 mg/m^3) 5.35 (2.23 to 12.8) for 15-year lag and 4.79 (2.01 to 11.9) for 0 lag. The SMR for respiratory disease except pneumonia and infections was 2.01 (1.56 to 2.55).

From the IARC Monograph:

> *"(Rice et al., 2001) used the same cohort to examine risk, assessing the relationship between lung cancer mortality and respirable crystalline silica using a variety of models. All except one model demonstrated statistical significance, and the trends of predicted rate ratios with cumulative crystalline silica exposure were generally similar across models."*

Cumulative exposure to dust and years of mining was strongly associated with risk of lung cancer, until silicosis was included in the model, which results in disappearance of the exposure effects, a result that is not surprising giving the role of silica in causing silicosis.

From the IARC Monograph:

> *"A small cohort study among Icelandic diatomaceous earth workers (Rafnsson & Gunnarsdóttir, 1997) provided findings that supported an effect of crystalline silica on lung cancer risk SIR 2.34 (0.48 to 6.85) for those who had worked 5 or more years. Smoking habits among the workers were reported to be similar to the general population."*

No cases of silicosis had been found in the employees at the diatomite plant.
(Gallagher et al., 2015) updated the follow-up of (Checkoway et al., 1997) by 19 years. The cohort included 2,342 white men who were employed for at least 1 year at a diatomaceous earth plant beginning in 1942. Detailed work history and quantitative air monitoring measurements estimated exposure intensity. Cox proportional hazards modelling estimated HRs and 95% CI. SMRs were also calculated. Elevated mortality was observed by quartile of cumulative crystalline silica exposure for lung cancer (HR = 2.03, 1.07 to 3.85, highest quartile, unlagged) although trends were not statistically significant. Associations were attenuated when adjusted for smoking and asbestos exposure. An increase for lung cancer was confined to the earlier follow-up SMR 1.29 (1.01 to 1.61).

3.2 Ore miners

From the IARC Monograph:

> *"(Steenland & Brown, 1995) updated a cohort of US gold miners previously studied (McDonald et al., 1978). Using quantitative estimates of cumulative exposure based on particle counts, no obvious evidence of exposure-response with lung cancer mortality was observed, nor were any of the exposure category SMRs elevated." "In contrast"…"silicosis mortality was elevated and exhibited an exposure-response relationship with crystalline silica."*

The SMR for lung cancer based on US rates was 1.13 (0.94 to 1.36, n = 115) and based on county rates was 1.27 (1.02 to 1.55) for person-time with more than 30 years potential latency. The authors stated that lung cancer mortality did not show a positive exposure-response trend with estimated cumulative dust exposure.

From the IARC Monograph:

> *"Gold miners were investigated in a South African cohort study (Hnizdo & Sluis-Cremer, 1991) and in case-control studies nested within that cohort study and within another South African gold miner cohort (Reid & Sluis-Cremer, 1996). In the cohort study, lung cancer mortality was related to cumulative dust exposure when modelled as a continuous variable (respirable-surface-area-years) adjusting for smoking, as well demonstrating a monotonic increase with categories of cumulative exposures. There was also some indication of exposure-response in both case-control studies, and lung cancer mortality was elevated in the highest exposure group after adjusting for smoking in the (Hnizdo et al., 1997) study."*

The IARC Working Group noted that in this study, exposure to uranium did not confound the results, but that there was potential confounding from radon, and that the South African cohorts might overlap. In the (Hnizdo & Sluis-Cremer, 1991) study there was no association with the presence of silicosis of the lung OR 0.9 (0.5 to 1.6). In the later study (Hnizdo et al., 1997) lung cancer risk was influenced by the risk of silicosis. The authors of this study offered three interpretations for their findings: (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 their own are important in the pathogenesis of lung cancer; and (3) high levels of silica dust exposure may be a surrogate for exposure to radon daughters.

From the IARC Monograph:

> *"(McLaughlin et al., 1992) undertook a nested case-control study of lung cancer among the members of a prior cohort study by (Chen et al., 1992). The study included workers from iron, copper, tungsten, and tin mines, and used quantitative estimates of crystalline silica dust and certain confounder exposures. Only tin miners showed a clear and substantial exposure-response relationship with quantitative measures of crystalline silica*
> *cumulative exposure."*

The study authors reported that the positive association between lung cancer and silicosis observed among copper-iron and tin miners may at least partly reflect ascertainment bias[1]. On the other hand, some deaths among silicotic patients may be more likely attributed to silicosis, with under-reporting of accompanying lung cancer (McLaughlin et al., 1992).

From the IARC Monograph:

> *"The tin miners underwent further follow-up in a cohort study (Chen et al., 2006) and a nested case-control study (Chen & Chen, 2002). Although the cohort study findings provided some overall indication of elevated lung cancer exposure-response mortality with cumulative dust exposure, the findings were much less clear when presented by mine and silicosis status. In the nested case-control study, there was evidence of exposure-response with cumulative total dust exposures. There was also evidence of a relationship between lung cancer mortality and cumulative arsenic exposure, but the high correlation between arsenic and crystalline silica levels prevented mutual adjustment, and left the etological factor unclear."*

From the IARC Monograph:

> *"The same conclusions, more generally expressed, were reported in a simple ever/never exposed approach by (Cocco et al., 2001), and were confirmed by (Chen et al., 2007) adjusting for smoking and other factors. Here no relationship for lung cancer mortality with cumulative crystalline silica was noted for the tungsten mines, nor was there any evidence for the iron and copper mines, adjusting for radon."*

The IARC Working Group noted that crystalline silica exposures were very low in the iron and copper mines.

From the IARC Monograph:

> *"For the tin mines, no adjustment for arsenic could be made because of its collinearity with crystalline silica exposure, but in the overall group, adjusting for smoking, arsenic, polyaromatic hydrocarbons, and radon, no exposure-response for cumulative crystalline silica exposure emerged either by quintile or through the use of a continuous predictor."*

Risk did not vary after excluding subjects with silicosis or adjusting the risk estimates by radiological staging of silicosis (Cocco et al., 2001).

A cohort study was carried out in 8,321 iron ore miners with low exposure to radon, employed 1923 to 1998 and followed up for lung cancer 1958 to 2000. Miners had increased risk of lung cancer SIR 1.48 (1.22 to 1.78, 112 cases). The increased risk could not be explained by exposure to radon or diesel exhaust, but was associated with exposure to silica: SIR 0.96 (0.53 to 1.62), 1.45 (1.10 to 1.87), 1.99 (1.31 to 2.90) and 1.77 (0.92 to 3.10) in groups with exposure to 0, 0-2, 2-5 and > 5 mg.years/m^3, respectively (Bergdahl et al., 2010).

(Chen et al., 2012) studied 74,040 workers who worked at 29 metal miners and pottery factories in China for 1 year or more between 1960 and 1974 with follow-up to 2003. This study was an update of (Chen et al., 1992). Cumulative silica dust exposure was estimated for each worker by linking work history to a job-exposure matrix. SMRs for underlying causes of death based on Chinese national mortality rates and HRs for selected causes of death associated with cumulative silica dust exposure (mg/m^3.years) were estimated. The HR for exposure versus no exposure were 1.45 (1.19 to 1.75) for low (0.01-1.23 mg/m^3.y), 1.53 (1.27F to 1.84) for medium (1.24 to 4.46 mg/m^3.y) and 1.46 (1.19 to 1.78) for high (>4.46 mg/m^3.y) cumulative silica exposure. The SMR for lung cancer was not raised for any time period examined during follow-up.

Cancer incidence was evaluated among 31,067 Minnesota taconite mining workers employed for more than 12 months (Allen et al., 2014). The SMR for lung cancer was 1.16 (1.09 to 1.24). Standardised rate ratios adjusted for age, calendar period and sex did not show a trend with duration of employment.

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[1] *Ascertainment bias arises when data for a study or an analysis are collected (or surveyed, screened, or recorded) such that some members of the target population are less likely to be included in the final results than others.*

3.3 Coal miners

Underlying cause of death for 9,033 underground miners from 31 US mines enrolled between 1969 and 1971 was examined using life table analysis. Cox proportional hazards models were fitted to evaluate the exposure-response relationships between cumulative exposure to coal mine dust and respirable silica and mortality from lung cancer. Excess mortality for the whole cohort was observed for lung cancer SMR 1.08 (1.00 to 1.18). No significant association was observed for respirable silica HR 1.05 (0.90 to 1.23) (Graber et al., 2014).

3.4 Ceramics Industry Workers

From the IARC Monograph:

> *"A case-control study of Chinese pottery workers showed evidence of elevated risk for lung cancer with exposure to crystalline silica dust, although no obvious exposure-response was seen in the three higher exposure categories (McLaughlin et al., 1992). This study was nested within the cohort analysis by (Chen et al., 1992). Although reported exposure to asbestos was minimal, the workers exposed to polyaromatic hydrocarbons, and in a separate analysis there were non-significant elevations in lung cancer risk with increasing cumulative exposure to polyaromatic hydrocarbons (PAHs). This was confirmed in the follow-up analysis by (Chen et al., 2007) that found that the pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs in the analysis led to the crystalline silica exposure relative risk of 1.1 (1.02 to 1.12) dropping to 1.0 (0.96 to 1.09)."…. "The correlation between the crystalline silica and PAH exposures was reported as 0.56".*

The authors of this paper concluded that their analysis does not provide any evidence to show that exposure to silica caused lung cancer in the absence of confounding factors.

From the IARC Monograph:

> *"The OR ratio for cumulative exposure per 1000 μg/m^3.y adjusted for ever versus never smoked was 1.37 (1.24 to 1.53). (Cherry et al., 2013) extended the follow-up of this cohort to 2008. The SMR for lung cancer was lower for 1985 to 2008 and non-significant for lung cancer against rates for Stoke-on-Trent in that period SMR 1.07 (0.92 to 1.25). Exposure concentration was related to lung cancer in smokers for early not later deaths with mean silica concentration > 200 μg/m^3 among deaths to 1992 (HR 2.80, 1.21 to 6.50)."*

From the IARC Monograph:

> *"(Ulm et al., 1999) looked at workers in the German ceramics industry, as well as the stone and quarrying industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. No relationship of lung cancer mortality risk with cumulative exposure, average intensity, nor peak exposures was seen in the ceramic workers subset nor overall."*

(Mundt et al., 2011) updated an earlier analysis by (Birk et al., 2009) of a cohort of workers employed by more than 100 porcelain manufacturing plants in the western states of Germany and participating in an industry-wide preventive medical screening program for silicosis between 1985 and 1987. The analytical cohort contained 17,644 workers followed for mortality to 2005. Lung cancer mortality (n = 74) was not associated with cumulative crystalline silica exposure in adjusted Cox proportional hazards models, using either a lower or a higher exposure classification scheme.

3.5 Quarry workers

From the IARC Monograph:

> *"In an extension of the Vermont granite workers study by (Costello & Graham, 1988), (Attfield & Costello, 2004) both lengthened the follow-up from 1982 to 1994, and developed and analysed quantitative crystalline silica dust exposures. The exposures were noteworthy for being developed from environmental surveys*

undertaken throughout the period of the study. However, information on smoking and silicosis status was lacking, although confounding from other workplace exposures was likely to have been minimal or non-existent. The results showed a clear trend of increasing risk with increasing cumulative respirable crystalline silica exposure until the penultimate exposure group."

The relevant table from the paper showing the trends is pasted below.

TABLE IV. Mortality Statistics for Malignancy of Trachea, Bronchus, and Lung by Respirable Free Silica Exposure Group*

	SMR for each cumulative exposure level (mg-yr/m³)								
Exposure level	0-	0.25-	0.5-	1.0-	1.5-	2.0-	3.0-	6.0-	All
Observed deaths	29	15	28	22	22	26	29	30	201
Expected deaths	37.8	16.8	20.8	17.3	16.5	17.6	17.1	25.8	179.2
SMR	0.77	0.98	1.26	1.25	1.33	1.47[a]	1.70[b]	1.16	1.17[a]
SRR	1.00	0.91	1.28	1.32	1.32	1.38[a]	1.76[a]	0.86	1.30[b]

*Time since first exposure = 15 years or more.
[a]One-sided $P < 0.05$.
[b]One-sided $P < 0.01$.

From the IARC Monograph:

"(Graham et al., 2004) undertook a parallel analysis of the same data as (Attfield & Costello, 2004), but did not use quantitative exposures, and adopted essentially the same analytical approach as in their 1988 study. They concluded that there was no evidence that crystalline silica dust exposure was a risk factor for lung cancer, their main argument being that lung cancer risks were similar by duration and tenure between workers hired pre-1940 and post-1940 – periods before and following the imposition of dust controls when the crystalline silica dust levels were very different."

The SMR for lung cancer for quarry workers was 0.74 (0.50 to 1.06). The SMRs increased with increasing duration of tenure < 10 years 0.84 (0.57 to 1.20), 10-29 years 1.38 (1.08 to 1.73), and 30+ years 1.57 (1.15 to 1.52) (p < 0.01) without latency consideration.

From the IARC Monograph:

"As noted above, (Ulm et al., 1999) looked at workers in the German stone and quarrying industry (includes some sand and gravel workers), as well as the ceramics industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. Neither cumulative exposure, average intensity, nor peak exposure showed a relationship with lung cancer risk in the stone and quarry worker subset, nor overall."

The authors reported that exclusion of subjects with silicosis might have led to dilution with respect to the level of exposure and therefore reduced the power to detect a small risk.

From the IARC Monograph:

"Another study of German stone and quarry workers found an excess of lung cancer (SMR, 2.40), but no relationship between lung cancer mortality and crystalline silica exposure."

From the IARC Monograph:

"Among studies that did not use quantitative estimates of crystalline silica exposure, that by (Koskela et al., 1994) is of interest because it reported that the workers had little exposure to possible confounding exposures. The risk of lung cancer was significantly elevated among those with longer duration of exposure and longer latency (p < 0.05)."

The rate ratios ranged from 1.6 to 3.8 for different latency periods.

From the IARC Monograph:

"(Guénel et al., 1989) also found an excess of lung cancer among stone workers after adjustment for smoking, but it was not the case in a study of slate workers by (Mehnert et al., 1990)."

Note that the (Guénel et al., 1989) did not contain a relative risk for lung cancer.

3.6 Sand and Gravel workers

From the IARC Monograph:

"Confounding from other workplace exposures is minimal in sand and gravel operations. There are three main studies of sand and gravel workers, two in North America and one in the United Kingdom. The North American studies appear to arise from the same population of workers although there is no published information on their overlap, if any. Using the basic information from the (McDonald et al., 2001) cohort study of nine North American sand and gravel workers, (Hughes et al., 2001) reported significant exposure-response of lung cancer with quantitative estimates of cumulative respirable crystalline silica exposures and other related indices."

"(McDonald et al., 2005) examined a slightly smaller subset of the cohort described by (McDonald et al., 2001) based on an extended update at eight of the nine plants, and also undertook a nested case-control study. Risk of lung cancer increased monotonically with unlagged cumulative exposure (p = 0.011), but 15-year lagged cumulative exposures provided a slightly better fit (p = 0.006). These findings were basically similar to those obtained by (Hughes et al., 2001) using the larger cohort and shorter follow-up time. (McDonald et al., 2005) reported that average exposure intensity, but not years employed, showed a relationship with lung cancer (p = 0.015)."

The relevant trend results from (McDonald et al., 2005) were as follows:

Table 2. Original and updated odds ratios, based on silicosis cases and controls,[a] by cumulative silica exposure category

No lagging			Lagged 15 years		
Cumulative exposure category ($\mu g\ m^{-3}$ years)	Odds ratios[b,c] Updated	Odds ratios[b,c] Original	Cumulative exposure category ($\mu g\ m^{-3}$ years)	Odds ratios[b,d] Updated	Odds ratios[b,d] Original
≤1500	1.00 (6)	1.00 (7)	≤700	1.00 (7)	1.00 (7)
>1500, ≤5000	0.95 (5)	1.27 (7)	>700, ≤1800	2.20 (5)	2.54 (7)
>5000, ≤9000	3.08 (10)	2.62 (7)	>1800, ≤5100	4.34 (7)	4.55 (8)
>9000	1.90 (8)	2.13 (8)	>5100	5.45 (10)	5.16 (8)
Total	— (29)	— (29)	Total	— (29)	— (29)

[a]Only cases and controls for which both case and control had job history.
[b]Relative to lowest exposure category; number of silicosis cases in parenthesis.
[c]Adjusted for matching and three categories of smoking (never, ever and unknown).
[d]Significant trend one-tailed $P = 0.017$.

The results are consistent with showing a more than doubled RR for exposures > 700 μg/m^3 with a 15 year lag.

From the IARC Monograph:

"(Steenland & Sanderson, 2001) studied workers in 19 sand and gravel companies in the same trade organization as the nine included in the (McDonald et al., 2001) study. They, too employed quantitative estimates of exposure derived from company records, and found indications of a relationship with lung cancer mortality, most strongly in the subset that had worked 6 or more months in the industry (p < 0.06). Further analysis using a nested case-control approach found marginal evidence of exposure-response using quartiles of cumulative exposure (p = 0.04), but stronger evidence for average intensity (p = 0.003)."

The SMR for lung cancer was 1.60 (1.41 to 1.93) when analysis utilised underlying cause of death and 1.52 (1.26 to 1.83) when also utilising associated causes of death.

From the IARC Monograph:

> *"The mortality experience of crystalline silica sand workers in the United Kingdom was evaluated by (Brown & Rushton, 2005). No overall excess of lung cancer was found (although there was a large, and highly significant, variation in lung cancer SMRs between quarries; range: 0.27-1.61, both extremes p<0.01. Relative risk rose with cumulative respirable crystalline silica dust exposure in the first two quartiles, but fell below 1.0 in the highest quartile, resulting in no trend being detected."*

The lung cancer SMR was 1.62 (1.14 to 2.24).

3.7 Foundry Workers

Workers employed from 12 months or more before 2005 from 10 iron foundries in Sweden were included in a cohort (Andersson et al., 2009; Westberg et al., 2013). Exposures were assessed using historical exposures measurements and assigned to workers. The highest OR identified in the nested case-control study was 1.17 (0.53 to 2.55) in the medium exposure group (Andersson et al., 2009). Smoking data were not available for the original cohort, so a survey was carried out to estimate smoking patterns. SIRs were calculated for external comparisons and HRs for internal comparisons. The SIR for lung cancer was 1.61 (1.20 to 2.12). Lung cancer incidence by cumulative exposure and latency is presented in the table below. A doubling of risk is present only in the lowest exposure group (<1 mg/m^3 years) (Westberg et al., 2013).

Table 4 Lung cancer incidence amongst iron foundry workers by latency time and cumulative quartz exposure (mg m^{-3} years), Sweden 1958–2004

Latency	Exposure	Obs[a]	Exp[b]	SIR[c]	95 % CI[d]
0–19	<1	7	6.70	1.05	0.45–2.15
	1–2	0	1.01		
	2+	0	0.04		
20+	<1	25	12.22	2.05	1.32–3.02
	1–2	17	9.89	1.72	1.00–2.75
	2+	3	2.38	1.26	0.26–3.69

[a] Observed number of cases
[b] Expected number of cases
[c] Standardised incidence ratio
[d] 95 % confidence interval for the SIR

3.8 Other Industries

From the IARC Monograph:

> *"Two studies having quantitative exposures to crystalline silica remain, although both industries are known to be associated with exposure to other known or suspected lung carcinogens. The first, by (Watkins et al., 2002) was a small case-control study focused on asphalt fumes and crystalline silica exposure. Crystalline silica exposures were low compared to most other studies, and there were no significant lung cancer elevations or trends with exposure."*

Respirable silica RRs were not significantly raised and ranged from 0.70 to 1.53 compared to those with zero exposure.

From the IARC Monograph:

> *"The second study was a nested case-control analysis of Chinese iron and steel workers (Xu et al., 1996). A significant trend with cumulative total dust exposure was reported but not for cumulative crystalline silica dust exposure, although relative risk for the highest crystalline silica-exposed group was elevated. The findings were adjusted for smoking, but not benzo[a]pyrene exposure, for which the relative risks demonstrated a clear and significant trend with cumulative exposure level."*

There were problems interpreting both of these studies due to likely confounding with other occupational lung carcinogens.

A case-cohort study nested within a cohort of 267,400 women textile workers in Shanghai, China was carried out (Checkoway et al., 2011). Work assignments and exposure histories of 628 incident lung cancer cases diagnosed during 1989-1998 were compared with those of a reference subcohort of 3,188 workers. Exposures were reconstructed with a job-exposure matrix developed specifically for textile factories. Cox proportional hazards modelling was applied to estimate age/smoking-adjusted hazard ratios and risk gradients. An increased risk, although statistically imprecise was noted for silica exposure, adjusted HR 3.5 (1.0 to 13).

Mortality was assessed in 7,052 Vermont granite workers employed between 1947 and 1998 (Vacek et al., 2011). Exposures were estimated using a job-exposure matrix. Mortality was followed-up to 2004 and SMRs were computed. Associations with silica exposure were assessed by a nested case-control analysis using logistic regression. The SMR for lung cancer was 1.37 (1.23 to 1.52). No significant associations with cumulative exposure to respirable free silica were observed for lung cancer OR 0.99 (0.94 to 1.03).

The mortality of 2,650 employees in the mining and mill production of roofing granules at four US plants was examined between 1945 and 2004 (Olsen et al., 2012). Workers were employed for at least 1 year by 2000. Work history and vital status were followed to 2004. Cumulative crystalline silica exposure was calculated as the sum of the product of time spent and the average exposure for each plant-, department-, job- and calendar-year combination. There was a total of 77 lung cancer deaths (SMR 1.11, 0.88 to 1.39). With a 15 year lag, the SMR became 1.08 (0.84 to 1.38). Lagging exposures by 15 years, the RRs for males were (compared to baseline of 0-0.1 mg/m^3.y) were 1.83 (1.02 to 3.27) for low (0.1-<0.5), 1.83 (0.78 to 4.31) for medium (0.5-<1.0) and 1.05 (0.34 to 3.29) for high ($\geq$1.0) respectively. The p-value for trend was 0.9.

3.9 Semi-quantitative exposure and expert opinion studies

From the IARC Monograph:

> *"The studies that follow used quantitative exposure measurements for individuals but ultimately converted them to exposure scores or categories in the epidemiological analysis. (Hessel et al., 1986) undertook a case-control study of lung cancer and cumulative crystalline silica exposure in South African gold miners after coding the dust measurements to four discrete levels (0, 3, 6, 12). No exposure-response was detected. Neither was any evidence of exposure-response detected in the later necropsy study of South African gold miners (Hessel et al., 1990) that used the same approach to code the exposure data."*

The OR for radiological silicosis was 1.08 in (Hessel et al., 1986). In (Hessel et al., 1990) no association was found between lung cancer and the presence or severity of silicosis at any lung site.

From the IARC Monograph:

> *"(de Klerk & Musk, 1998) undertook a nested case-control analysis of lung cancer within a cohort study of gold miners and showed exposure-response for cumulative exposure (exposure score years) but not for any other index of exposure. The analyses adjusted for smoking, bronchitis, and nickel exposures, and took account of asbestos exposure."*

The RR for log(exposure-score year) was 1.20 (0.92 to 1.56).

From the IARC Monograph:

> *"The study by (Kauppinen et al., 2003) on road pavers found a relative risk for lung cancer of 2.26 in the highest exposure group, but there was no evidence of a linear trend of risk with level of exposure. No adjustment was made for concomitant exposure to PAHs, diesel exhaust, and asbestos, nor smoking."*

Co-exposure to other lung carcinogens makes interpretation of the study difficult in relation to risk from silica exposure.

From the IARC Monograph:

> *"(Moulin et al., 2000) conducted a nested case-control study to examine lung cancer among workers producing stainless steel and metallic alloys. Their results on 54 cases and 162 controls, adjusted for smoking but not for other confounders, indicated a marginally significant evidence of a trend with increasing crystalline silica exposure as well as with PAH exposure."*

The SMR for lung cancer was 1.19 (0.88 to 1.55, 54 deaths).

From the IARC Monograph:

> *"Two population-based studies that involved substantial expert opinion in assigning dust levels in developing quantitative crystalline silica exposures (Brüske-Hohlfeld et al., 2000) and (Pukkala et al., 2005) showed an increasing risk of lung cancer with increasing crystalline silica exposure after adjusting for smoking, and in the latter study, also for social class and exposure to asbestos."*

From (Brüske-Hohlfeld et al., 2000), the OR for crystalline silica adjusted for smoking and asbestos exposure was 1.41 (1.22 to 1.62), but there were other lung carcinogens present. From (Pukkala et al., 2005), the risk ratios ranged between 1.36 and 1.50 for lung cancer for occupations with the highest estimated cumulative silica exposure ($\geq$10 mg/m^3.years), allowing a lag time of 20 years.

The combined effect of silica dust exposure and cigarette smoking on total and cause-specific mortality in iron miners was examined in a cohort study in China (Lai et al., 2018). A total of 7,665 workers from a single mine were studies with a median follow-up of 42.8 years. Significantly elevated lung cancer mortality was observed among silica-exposed workers. Versus unexposed workers, the HRs (adjusted for gender, year of hire, age of hire and smoking intensity) for low (0.49 mg/m^3.y or below) medium (0.49 to 0.84 mg/m^3.y), and high exposure (0.84 mg/m^3.y or above) were 1.67 (1.13 to 2.47), 1.66 (1.19 to 2.32) and 1.67 (1.22 to 2.30) respectively. The p-value for the trend was 0.001.

3.10 Population-based studies

The relationship between racial disparities in occupational risk and lung cancer diagnosis following exposure to asbestos, silica and other workplace chemicals, fumes or dusts was examined in the National Lung Screening Trial in the US (Juon et al., 2021). Descriptive analyses and multivariable logistic regression models were performed. Against a baseline of no silica exposure in former smokers, the adjusted OR for silica exposure in former smokers was 1.34 (1.03 to 1.74) and the OR for silica exposure in current smokers was 2.35 (1.89 to 2.91). The models were adjusted for age, gender, family history of lung cancer, BMI, smoking status, and pack-years of smoking. The authors commented that silica exposure may have a multiplicative effect on lung cancer risk.

A study among men aged 55-69 (n = 58,279) from the Netherlands Cohort Study which included self-reported lifetime job histories was carried out (Preller et al., 2010). Job titles were linked to the occupational groups of the external Finnish Job Exposure Matrix (FINJEM), including probability and level of silica exposure, each for specific time periods. 1,667 incident lung cancer cases with known silica exposure status (210 exposed) were available after 11.3 years of follow-up. Risks were estimated based on a case-cohort design, using Cox proportional hazards models. Adjusting for smoking and other confounders, elevated risks were observed for exposure duration RR 1.65 (1.14 to 2.41 for 26-51 years vs no exposure) and cumulative exposure RR 1.47 (0.93 to 2.33) for $\geq$3 vs < 3 mg/m^3.years. Associations with average levels of exposure were weaker. Associations were stronger for occupations with an exposure probability of

≥90%. Adjustment for asbestos exposure slightly increased the risk. From Table 1 of the paper, occupation with high exposure were: Miners, shot firers excl Miners and quarrymen nec; Metal smelting furnace men; Moulders; Bricklayers, plasterers and tile setters; Reinforced concrete layers, stonemasons etc; Assisting building workers; Potters; Occupations related to glass, ceramic and fine earthenware nec; Stone cutters; Concrete mixer operators and cast concrete production workers; and Concrete shutterers and finishers.

A re-analysis of an earlier population-based case-control study (Richiardi et al., 2004) was conducted between 1990 and 1992 in two areas of Italy (Corbin et al., 2012). Cases (956 men; 176 women) were all individuals diagnosed with incident lung cancer aged less than 75. Controls (1,253 men; 300 women) were randomly selected from local population registries and frequency matched with cases by gender, study area and five-year age group. Information was collected on basic demographics details, active and passive smoking and lifetime occupational history. The focus was on asbestos, chromium and silica. Exposure to these was assessed via a General Population Job-Exposure Matrix DOM-JEM, which assigns an ordinal score of 0 = no exposure, 1 = low exposure and 2 = high exposure) to each occupation code. The OR of lung cancer for ever low exposure to silica, adjusted for age, area and cigarette smoking status, was 1.19 (0.97 to 1.46) and for ever high exposure 1.58 (0.92 to 2.71).

Detailed information on lifestyle and full occupational histories of 1,208 male lung cancer incident cases and 1,069 age-matched community controls in Hong Kong were obtained through interviews during 2006-2006 (Tse et al., 2012). After adjustment for smoking and other potential confounding factors, significant odds ratios were found for construction workers OR 1.37 (1.00 to 1.89), bricklayers carpenters and other construction workers OR 1.49 (1.07 to 2.06) and for occupational exposure to silica dust OR 1.75 (1.16 to 2.62).

A hospital-based case-control study was carried out in North-Eastern France with high lung cancer rates and a part history of mining and steel industry (Wild et al., 2012). Cases were males age 40-70 with a confirmed lung cancer diagnosis. Controls were stratified by broad age-classes, district and socioeconomic classes. Detailed occupational and personal risk factors were obtained in face-to-face interviews. Adjusted on the stratification variables, smoking and non-occupational confounding variables if significant (as well as for diesel exhaust, PAHs and asbestos), the ORs for lung cancer by quartile of cumulative silica exposure compared to non-exposed were 0.88 (0.48 to 1.60), 1.16 (0.64 to 2.13), 1.36 (0.76 to 2.44), and 1.76 (0.96 to 3.21) for increasing exposure.

Two case-control studies were conducted in Montreal, Canada (Lacourt et al., 2015). They included 1,593 lung cancer cases and 1,427 controls, of whom 1,304 cases and 1081 had been blue collar workers. Detailed lifetime job histories were obtained and translated into histories of exposures to chemical agents. The OR for all construction workers was 1.11 (0.90 to 1.38). The OR for exposure to silica was non-significantly raised: ever exposed OR 1.2 (0.9 to 1.5); ever substantially exposed 1.7 (1.0 to 3.0). The ORs were adjusted for age, median family income for census tract, comprehensive smoking index, respondent status, education level, ethnicity and study. An earlier analysis was published by (Vida et al., 2010).

A nationwide population-based case-control study of lung cancer and silica exposure and tobacco smoking has been conducted between 1994 and 1997 in Canada (Kachuri et al., 2014). Self-reported questionnaires were used to obtain lifetime occupational histories and information on other risk factors. Occupational hygienists assigned silica exposure to jobs based on concentration, frequency and reliability. Models included adjustments for cigarette smoking, lifetime residential second-hand smoke and occupational exposure to diesel and gasoline engine emissions. Relative to the unexposed, increasing duration of silica exposure was associated with a significant trend in lung cancer risk OR ≥ 30 years 1.67 (1.21 to 2.24), p-trend = 0.002. The highest tertile of cumulative silica exposure was associated with lung cancer OR = 1.81 (1.34 to 2.42), p-trend = 0.004, relative to the lowest.

A pooled analysis of 14 lung cancer case-control studies from across Europe and Canada with detailed smoking and occupational histories was carried out (Ge et al., 2020). A quantitative job exposure matrix was used to estimate silica exposure by occupation, time period and region. Lung cancer RRs ranged from 1.15 (1.04 to 1.27) to 1.45 (1.31 to 1.60) for groups with the lowest and highest cumulative exposures. Increasing cumulative silica exposure was associated (p-trend < 0.01) with increasing lung cancer risks in non-silicotics and in current, former and never smokers. Increasing exposure was also associated (p-trend < 0.01) with increasing risks of lung adenocarcinoma, squamous cell carcinoma and small cell carcinoma. Supermultiplicative interaction of silica and smoking was observed on overall lung cancer risks; superadditive effects were observed of risks of lung cancer and all three included subtypes.

The numerical results for the cohort and case-control studies as well as the various meta-analyses that have been carried out are in Appendix 2.

4 Synthesis and Discussion

The current prescription for Lung cancer from silica exposure is in Appendix 3. It is clear that a number of exposure circumstances where there is high occupational exposure to silica dust are covered (and are represented by many of the studies contained in this report). However, prescription is only where there is accompanying silicosis (to indicate high cumulative exposure to silica dust). A 1992 IIAC report concludes that there was insufficient evidence to justify the prescription of lung cancer in relation to silica exposure in the absence of silicosis, but that further research be undertaken to examine lung cancer risks in the absence of silicosis[2]

It is worth noting that IIAC position paper 41 considered lung cancer in coal miners with silicosis and concluded that a case exists for recognising PD D11 in coalminers with primary lung cancer if (i) a diagnosis of silicosis can be sustained and if (ii) it can be shown that their work has involved "tunnelling in, or quarrying sandstone or granite".

Nine reviews of silica and lung cancer were identified in the Phase 1 report.

A review by Cox suggested that a number of epidemiological studies had reported elevated lung cancer risks among patients with silicosis, but that others found no such association. They also reported that a recent meta-analysis concluded that the association disappears when confounders such as smoking or occupational coexposures are correctly adjusted for (Cox, 2011).

The recent meta-analysis referred to by (Cox, 2011) was carried out by (Erren et al., 2011) and it updated an earlier meta-analysis. They found a doubled RR of lung cancer in silicotics RR = 2.1 (2.0 to 2.3). In non-silicotics, they reported that smoking adjustment suggested marginally elevated risks RR 1.2 (1.0 to 1.4) in the presence of significant heterogeneity (such as due to industry sector). They concluded that question remains regarding lung cancer caused by silica and non-silicotics.

A review was published in the same year by (Gamble, 2011). In his opening remarks he commented that the 1996 IARC working group concluded that there was sufficient evidence for the carcinogenicity of quartz and cristobalite in humans, although this was not found in all industrial circumstances (presumably where silica exposure is encountered). He continues that the vote was very close and that few of the published studies included estimated of quantitative exposure-response trends and so an attempt was made to quantify existing exposure data from the cohorts used by IARC. Out of 10 silica-exposed cohorts in that analysis, follow-up was extended or exposure response added in 4 studies beyond the published data of the original study. The author then proceeded to review the evidence in great detail and finished by concluding that the weight of evidence was not sufficient to support silica being a cause of lung cancer.

The most recent IARC Monograph itself concluded that there was sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite in terms of lung cancer (IARC Working Group, 2012).

A review published in the same years as the IARC Monograph by (Fernández et al., 2012) highlighted the contrasting views on whether or not silica was a lung carcinogen. This review helpfully lists the work sectors in which silica is produced:

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[2] IIAC. Lung Cancer in Relation to Occupational Exposure to Silica. September 1992.

Table 2. Work Sectors in which Silica Dust is Produced

• Underground mining (coal, kaolin, fluorspar, iron)
• Surface mining (gold, coal, salt, copper)
• Exploitation of quarries (granite, slate)
• Excavations, tunnel digging
• Ornamental stone (sandstone, slate, granite)
• Construction, interior architecture (sand, gravel, travertine, quartz)
• Refractory product manufacturing
• Foundries (manufacturing and cleaning molds)
• Sand blasting
• Manufacture and use of abrasives (detergents, toothpaste)
• Use of ground silica (manufacture of plastics, wood, paint, flooring, artificial stone)
• Stone Mills
• Glass industry
• Pottery and porcelain industry (kaolin)

A German review from 2013 highlighted the importance of comparable exposure assessments to facilitate between study comparisons (Baur et al., 2013).

An updated meta-analysis (Poinen-Rughooputh et al., 2016) included 8 studies to 2016 and found an elevated risk of lung cancer in both silicotics and non-silicotics. The pooled SMRs were 2.32 (1.91 to 2.81) and 1.78 (1.07 to 2.96) respectively. Subgroup analyses showed that workers in the mining industry had the highest risk of lung cancer with a pooled SMR of 1.48 (1.18 to 1.86) and the weakest association was seen in potteries with a pooled SMR of 1.14 (1.05 to 1.23). A positive exposure-response was found for cumulative silica exposure and risk of lung cancer.

A more recent systematic review examined asbestos, crystalline silica and diesel exhaust emissions and lung cancer risk (El Zoghbi et al., 2017). Seven studies were included that examined the interaction between silica exposure and tobacco smoking, with the results suggesting an absence of a multiplicative interaction between silica exposure and tobacco smoking in relation to lung cancer.

The HSE WHEC concluded in 2017 that on the evidence currently available, silica is a cause of lung cancer and that silicosis is probably not a necessary precursor (HSE Workplace Health Expert Committee, 2017).

What is clear from the epidemiological literature is that there is now sufficient epidemiological evidence that occupational exposure to respirable crystalline silica increases the risk of lung cancer and there exists an exposure-response relationship for the association. This is regardless of whether those so exposed develop silicosis or not. The question now becomes: for which of the industries in which silica is at a sufficient level of exposure are there occupational circumstances in which the RR is doubled?

Each of the industries considered by IARC is separately evaluated.

For diatomaceous earth workers, there was some early evidence from the studies published in the last century that the RR was doubled. However more recent studies show a lack of evidence of a doubled RR. Further work could usefully be undertaken to consider the exposure levels to silica in this industry and how they compare to the levels in other industries in this report.

For metallic ore mining there is evidence of an association between silica and lung cancer, but insufficient evidence that the RR is doubled, especially in studies where there are good controls for smoking and occupational confounders such as asbestos, diesel engine exhaust and radon. As for the diatomaceous earth workers, it would be useful to consider silica exposure levels in this industry in the UK context.

For the single study of coal mining included in this review, there was no evidence of increased lung cancer. However, it would be worth looking at the analysis of the Lady Victoria mine (which had exposure to high levels of silica from cutting through a sandstone seam (Fairman et al., 1982) to see whether coal miners with high silica exposure should be considered for prescription.

There is some evidence that prolonged exposure to silica in the quarry industry may confer a doubled relative risk (e.g., (Koskela et al., 1994) discussed in the IARC review). This literature would benefit from a closer examination to determine if this degree of exposure could be identified and whether it could be converted to something that DWP decision makers could work with. The same is true for sand and gravel workers (e.g., (McDonald et al., 2005) discussed in the IARC review).

There is inconsistent evidence of a doubled RR of lung cancer in foundry workers. The literature as a whole would need further examination, both in terms of silica exposure, but also in terms of other co-exposures to lung carcinogens e.g. arsenic, chromium VI and nickel, as well as PAHs.
There is a lack of doubled RRs from the other industries and from the population-based studies.
It would also be worth IIAC examining relative silica exposures in any other industries in the table from the (Fernández et al., 2012) review and so see if those occupations with particularly high exposures to silica (e.g. stonemasons) have a doubled RR in epidemiological studies.

5 Conclusions

We have summarised the relevant epidemiological literature for occupational exposure to silica and lung cancer. Based on this review, we think several occupational circumstances are worthy of further examination for evidence of a doubled relative risk. These are coal miners (where there is evidence of silica exposure from sandstone), quarry workers, and sand and gravel workers. However, because our searches focussed on silica exposure, it's possible that some occupational groups such as stonemasons will not have been picked up. Thus we recommend that further literature searches for these specific industries are carried out before final conclusions are drawn.

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Appendix 1- Data Extraction Spreadsheet and List of All the References Considered

Data extraction silica + lung cancer final fo

Silica_and_Lung_Cancer_All_Papers.xlsx

Appendix 2- Tables for cohort, case-control and meta-analyses of silica and lung cancer

100C-08-Table2.1.pd
f

100C-08-Table2.2.pd
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100C-08-TableRefs.p
df

Appendix 3- Current prescription for Silica and Lung Cancer

D11	Primary carcinoma of the lung where there is accompanying silicosis.	Exposure to silica dust in the course of: (a) the manufacture of glass or pottery (b) tunnelling in, or quarrying sandstone or granite (c) mining metal ores (d) slate quarrying or the manufacturing of artefacts from slate. (e) mining clay (f) using siliceous materials as abrasives (g) cutting stone (h) stonemasonry (i) work in a foundry.

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