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THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 42

Occupational exposure to crystalline silica and its relation to connective tissue diseases

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Position Paper 42: Occupational exposure to crystalline silica and its relation to connective tissue diseases

Summary

This report updates an earlier review by the Council concerning occupational exposure crystalline silica and certain connective tissue diseases, namely systemic sclerosis/scleroderma, systemic lupus erythematosus and rheumatoid arthritis. A substantial amount of research is summarised, much of which has been published over the past decade. Collectively this provides reasonable evidence pointing to an occupational hazard, the evidence generally being deeper for systemic sclerosis/scleroderma than for the other two conditions. Prescription is hampered, however, by the difficulty of defining the qualifying levels of occupational exposure. The case for prescribing in workers with silicosis, who also have one of the connective tissue diseases, is considered as an alternative. However, unresolved methodological concerns about the few available reports of this kind have proved to be a stumbling block. For the reasons set out below, the Council has decided against recommending prescription, but it remains open to the possibility of reviewing its position as the research evidence base continues to grow.

Background

1. Silica,[1] otherwise known as silicon dioxide (SiO_2), is the basic constituent of sand, quartz and many types of rock. Exposure to silica has been linked with various diseases, including silicosis and lung cancer. Both silicosis (PD D1) and lung cancer, if accompanied by silicosis (PD D11), are prescribed diseases within the Industrial Injuries Disablement Scheme.

2. In 2005, in Position Paper 14 (IIAC, 2005), the Council reviewed the evidence linking exposures to respirable crystalline silica with renal disease and certain connective tissue diseases, including systemic lupus erythematosus, systemic sclerosis, scleroderma and rheumatoid arthritis. Some positive associations were found, but the evidence base was limited and a problem existed in defining the relevant qualifying exposures for purposes of prescription, which was not recommended. As part of a related inquiry, the Council has now taken the

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[1] Silicon (Si) is the chemical element which constitutes part of silica.

opportunity to update its review of the literature relating silica to systemic lupus erythematosus, systemic sclerosis, scleroderma and rheumatoid arthritis.

Connective tissue diseases

3. *Connective tissue* is body tissue that supports, binds, or separates other tissues or organs, typically having relatively few cells embedded in an amorphous matrix, often with collagen or other fibres, and including cartilaginous, fatty, and elastic tissues. Examples of connective tissue are fat, bone, and cartilage. The term *connective tissue disease* refers to a group of disorders, numbering more than 200, which affect the connective tissue. This report concerns three of these disorders.

4. *Systemic lupus erythematosus* (SLE or Lupus) is an autoimmune disease, which can affect almost all the body's organs. It has many manifestations, including fatigue, flu-like illness, skin rashes (notably a 'butterfly' rash on the cheeks and nose), hair loss, eye problems, mouth ulcers and internal organ involvement. Pleurisy, kidney disease, brain inflammation and a clotting tendency can sometimes arise. Over 30,000 people (90% of them women) have the disease in the UK. Aggressive drug treatment may be needed to control SLE.

5. *Scleroderma* is really a group of diseases that involve the abnormal growth of connective tissue. In some forms of (localised) scleroderma, hard, tight skin is the entire extent of the disease. But in other forms (*systemic sclerosis*) connective tissue is affected more widely, in blood vessels and internal organs such as the heart, lungs and kidneys. The muscles of the oesophagus may lose normal movement, affecting swallowing; and people with diffuse disease often suffer from fatigue, weight loss and swollen painful joints. Sometimes, severe kidney, lung, digestive, or heart problems occur. In scleroderma, the immune system is thought to stimulate certain cells (fibroblasts) to produce too much collagen, the build-up of which affects the skin and organs. Women of late childbearing years are at highest risk, suggesting that female hormones may play some part in the disease; exposure to viral infections in people who are genetically predisposed is thought to be another trigger, but the precise causes are not well understood.

6. *Rheumatoid arthritis* (RA) is an inflammatory disease caused by the body's own immune system attacking healthy tissue. Principal effects include pain, swelling,

tenderness and stiffness in the joints. The wrist and finger joints are most commonly involved, but many other sites can be affected, often in a symmetrical pattern. The disease may cause destructive changes in affected joints, with deformity and loss of function. It can also affect other bodily organs and cause general symptoms of fatigue, fever and malaise, anaemia, dry eyes and mouth, inflammation of the blood vessels, pleurisy and pericarditis (an inflammation of a sac that encloses the heart). The disease can be relapsing and remitting, with flare-ups and periods of improvement, or can be severe and relentless through a lifetime, with serious joint damage and disability. Modern specialist treatments have greatly improved the outlook. Again, genetic predisposition and hormonal factors may play a role in causation, and people who smoke are at an increased risk of developing RA.

Case studies and case reports

7. An association between connective tissue disease and work in certain occupations has been suspected for decades, much of the evidence on silica stemming from case reports and case series reports (e.g. Bramwell, 1914; Erasmus *et al*, 1957; Suratt *et al*, 1977). The association of silica exposure (with or without silicosis) with systemic sclerosis has come to be known as the "Erasmus Syndrome" and case reports continue to be published up to the present time. However, these have the limitation that, in the absence of comparative information, the described associations could have arisen by chance alone. Thus, for example, in a French study of the kind involving 87 patients with SLE (Koeger, 1995), 5% had a work history of $\geq$3 years of silica exposure but a lack of comparative information limited interpretation.

8. More persuasively, in a report by Sanchez-Roman *et al* (1993) the observed number of cases was compared with that expected, based on national statistics. Three cases of SLE and five of mixed SLE-scleroderma were found among 50 former workers (44 women) of a Spanish plant manufacturing scouring powder, and this was estimated to be more than 10 times the expected prevalence. Similarly, in a large cohort of uranium miners heavily exposed to quartz dust, the prevalence of SLE, based on diagnoses at a centre of occupational diseases in Niederdorf-Saxony, was estimated to be 90 per 100,000 men as compared with an expected prevalence of 10 per 100,000 in the male population (Conrad *et al*,

1996).

Epidemiological evidence

9. More formal epidemiological research has essentially followed two differing approaches, investigating 1) disease risk by level of exposure to silica, or 2) associations between silicosis and connective tissue disease.

10. Studies in the first category have usually been of the case-control design owing to the rarity of the diseases of interest, and seldom of the cohort design. In a case-control study subjects with the disease are identified, often through specialist hospital services, and compared with people who do not have the disease in terms of their previous exposures.

11. In the second category were a few studies that formally collected cases with silicosis and reported on whether they also had a diagnosis of connective tissue disease, usually comparing their risks with those of other people without silicosis.

Systemic sclerosis and scleroderma

Reports on scleroderma which have assessed disease risk by level of exposure to silica

12. A report by Englert *et al* (2000) identified 160 male cases of systemic sclerosis from death certificates and the records of hospitals and specialist clinics in Sydney and compared them with 83 living age-matched controls randomly chosen from local medical practices. Living cases and the controls were interviewed about their work history; the medical records of other subjects were checked for this information, and an occupational health officer, blinded to case-control status, classified subjects as definitely/probably exposed to silica or unlikely to be. (Blinding of the interviewers seems unlikely to have happened.) The report, although limited by a lack of reliable exposure information for some deceased and untraceable subjects, found the odds ratio (OR) for disease to be elevated 3.9-fold (p<0.05) where there was likely occupational exposure to silica.

13. A case-control study from Michigan compared 274 female cases of systemic sclerosis diagnosed between 1985 and 1991 with 1,184 female controls chosen by random digit dialling (Burns *et al*, 1996). Subjects were interviewed about silicone breast implants, but an occupational history was also taken and jobs or hobbies commonly resulting in silicone or silica exposure were identified by an

independent expert blinded to case-control status. These included abrasive grinding, sculpting or pottery making, work in a dental laboratory, and work with or around silica dust, sand, or other silica products. No cases were classed as exposed to abrasive grinding, all other ORs being 1.5 (p>0.05). In response to critical correspondence, the authors subsequently published a letter presenting analyses by self-reported rather than expert-assessed exposures (Lacey *et al*, 1997). For sculpting or pottery making, the OR became 2.13 (p<0.05) and for abrasive grinding, four exposed cases were now identified (OR 1.3); other risk estimates were lower than in the report by Burns *et al*.

14. A case-control study from Tours, France (Diot *et al*, 2002), compared 80 consecutive cases of systemic sclerosis (69 female), admitted to hospital during 1998-2000, with other hospital admissions over the period. All jobs held for 6 months or more were ascertained, and experts scored each according to the probability, intensity, frequency, and duration of exposure to silica, creating a score by multiplying the values and summing them across all employments. Subjects with a score >1 were counted as exposed. (These could have comprised, for example, a person with 10 years of certain exposure at low intensity and frequency; or 1 year of certain exposure at low intensity but all the time; or even someone with only a 30% probability of any exposure, but which, if incurred, was sufficiently large, frequent and prolonged.) It is not clear whether the experts were blinded to case-control status, which would be the ideal. The OR for exposure to crystalline silica was 5.57 (95% confidence interval (95%CI) 1.69-18.37). Raised risks were apparent in both women (6 cases; OR 13.04) and men (4 cases: OR 3.62) although findings were statistically significant only in the former analysis.

15. In Verona, another case-control study (Bovenzi *et al*, 2004) recruited and interviewed 55 cases (46 women) of systemic sclerosis from hospital services, comparing them with 171 patients admitted to hospital for other reasons. An expert JEM was applied but its content and the definition of occupational exposure to silica were not described. Three of the cases were exposed, as were three of the controls, the OR being 1.7; the finding was not statistically significant (p>0.05).

16. An earlier report from the same study group (Bovenzi *et al*, 1995), also a case-control study, reported an OR for scleroderma of 5.20 (95%CI 0.48-74.1, p>0.05)

among men, based upon 5 cases (3 exposed) diagnosed in hospitals in Trento, Italy, during 1976-1991 (apparently an independent sample to that mentioned in paragraph 15). Exposure assignments were made by occupational physicians blinded to case-control status, and required a minimum exposure duration of six months, but other details were not given. None of the 16 women in the study was exposed to silica.

17. In a small study of scleroderma in the UK, 55 cases were assembled from disease registers and compared with volunteers among their circle of friends as well as with matched patients from the same general practice (Silman *et al*, 1992). Only two cases with scleroderma were possibly or probably exposed to silica, the ORs in the two analyses being 1.4 (95%CI 0.12 to 16.1) and 1.0 (95%CI 0.13 to 7.2). It may be seen that the findings were essentially negative, although the study was too small to confidently exclude a doubling of disease risk.

18. Another small study, of men with systemic sclerosis diagnosed at a Danish medical department over 25 years, reported an OR for exposure to silica of 1.39 relative to control patients not suffering from connective tissue diseases (Zachariae *et al*, 1997).

19. In a French case-control study (Maitre *et al*, 2004), 93 cases of systemic sclerosis (83 female) diagnosed between 1995 and 1999 were compared with 206 matched controls chosen from telephone directories. Occupational histories were taken by an industrial expert and estimates made of the likely frequency, intensity and duration of exposure to silica, subsequently categorised into two broad levels of cumulative exposure. No strong association was found, however, with higher exposure (OR 1.2, 95%CI 0.1-1.2), although most cases were women and only four cases had exposure to any degree and only one at the highest level. However, 9.7% of cases worked in the construction industry, as compared with 5.3% of controls.

20. In a second French case-control study (Marie *et al*, 2014), 100 consecutive cases of systemic sclerosis (78 female) were identified through specialist services, together with 300 controls, recruited in part through local advertisements and in part from patients with other chronic diseases. Subjects were interviewed about their past exposure to silica, with subsequent semi-quantitative assessments by a blinded expert committee. As in the study described in paragraph 14, a

cumulative score >1 defined an individual as exposed. The overall OR was 5.32 (95%CI 2.25-13.05), based on 18 exposed cases; however, the risk was confined to men (15 exposed cases, OR 8.30).

21. In a study from Ontario, 67 patients with scleroderma (some 85% female) were identified from an outpatient database and compared with 87 controls from the same rheumatologist's practice (Thomson *et al*, 2002). A postal questionnaire asked for employment information and ever having certain exposures at the workplace or in the home. The RR for exposure to silica was 0.4 (95%CI 0.7 to 10.2), based on 3 cases with exposure, but the study lacked the power to rule out the possibility that risks could have been as much as doubled, allowing for statistical uncertainty in the data.

22. Walsh (1999) analysed death certificates from 25 US states during 1985-1992 and estimated the proportional mortality from systemic sclerosis in relation to silica exposure (defined as work in any of 36 non-mining occupations with "potential for substantial silica exposure" according to the National Institute for Occupational Safety and Health (NIOSH)). The proportional mortality ratio (PMR) was not elevated among men or women (1.0 and 0.8 respectively, p >0.05).

23. Calvert *et al* (2003), used data from the US National Occupational Mortality Surveillance system to perform a matched case-control analysis to examine occupational risks for various diseases in occupations defined as highly exposed to silica (e.g. earth drillers, mining machine operators, crushing and grinding machine operators, slicing and cutting machine operators). The diagnosis of systemic sclerosis appeared on death certificates roughly twice as often in this group as in subjects with no exposure or low exposure (OR 2.14), although this finding was not statistically significant; 66% of cases were among women.

24. Gold *et al* (2007) identified cases of connective tissue disease from US death certificates for 26 states between 1984 and 1998 and compared them with randomly selected and matched controls without autoimmune disease. In all, 5,578 cases of systemic sclerosis (about 75% female) were analysed together with 260,632 controls. Longest held occupations, as recorded on the death certificate, were coded, using an expert job-exposure-matrix (JEM) according to their probability of having any exposure to silica, the expected intensity of exposure and the expert's confidence in this assignment. However, analyses were presented only in terms of being exposed or not. The OR for systemic

sclerosis was very close to unity (OR 1.02, p<0.05), implying no association with the exposure. Separate analyses among men and women did not change this finding.

Reports on scleroderma which have assessed associations with silicosis

25. Rosenman *et al* (1999) examined the medical records of 463 individuals statutorily notified to a surveillance system for silicosis between 1987 and 1995. They found scleroderma was recorded more often than expected from the prevalence of that disease in the general population, but this involved only a single case of disease. The RR for systemic sclerosis was 15.65, but the 95%CI ranged from 0.21 to 87.03.

26. Brown *et al* (1997) studied a nationwide registry-based cohort of patients hospitalized for silicosis in Denmark and Sweden from 1965 to 1989 and assessed their subsequent mortality. An excess mortality from musculoskeletal disorders (standardised mortality ratio (SMR), 5.9) was due to six deaths from autoimmune diseases. Additional linkage to computerized hospital diagnoses in Sweden over the period identified 57 subjects with diagnostic codes both for silicosis and an auto-immune disorder, including five with scleroderma (RR 37.0, 95%CI 11.9-86.3).

27. The case-control study by Calvert *et al* (paragraph 23), as well as analysing risks by level of silica exposure, also considered the concurrence of different diagnoses on death certificates. Subjects with an entry for silicosis were twice as likely as others to also have an entry for systemic sclerosis (OR 2.00, 95%CI 0.39-10.31, p>0.05, based on 2 of 1,237 deaths from silicosis with systemic sclerosis).

28. Makol *et al* (2011) identified the general medical records reported to the Michigan Silicosis Surveillance System between 1985 and 2006, including 790 cases of silicosis. Two cases had scleroderma (RR 28.3, 95% CI 6.09-129.98). This study is likely to have overlapped with that by Rosenman et al (paragraph 25).

29. A case-control study of white South African gold miners (Sluis-Cremer *et al*, 1985) identified 79 cases of progressive systemic sclerosis during a benefits examination, together with control miners matched by year of birth. Two comparison groups were used, one based on benefits claimants, another from those undergoing a routine periodic examination. In both comparisons there was

an increased prevalence of silicosis (ORs of 1.29 and 2.50 respectively) although neither finding was statistically significant at the 5% level.

Meta-analyses relating to silica and scleroderma

30. The Council's search also identified two reports that presented meta-estimates of effect (i.e. pooled the results of other studies) for scleroderma. The later report by Rubio-Rivas *et al* (2017) incorporated all of the studies identified by the first analysis, by McCormic *et al* (2010). There was no apparent evidence of so-called 'publication bias' in the manuscripts that were examined.

31. Broadly, the papers included in these reviews were those described above, although a few reports not indexed by the US National Library of Medicine National Institutes of Health Pubmed database (Ziegler *et al*, 1997; Mehlhorn *et al*, 1999) and data from a Spanish PhD thesis were also incorporated. The number of reports that Rubio-Rivas *et al* combined is unclear (19 according to the text but 22 in the table and reference system); also, some reports appear to have been based on the same study populations, rather than independent samples (Burns *et al* and Lacey *et al*; possibly Ziegler *et al* and Mehlhorn *et al*). Notwithstanding these limitations, the risk estimates were noteworthy.

32. In the Rubio-Rivas report the meta-estimated OR across case-control studies was 2.8 (95%CI 1.7-4.2) and the meta-estimated RR across cohort studies was 17.5 (95%CI 5.6-51.4). (It should be noted that several of the studies said to be of cohort design were not truly so, hindering comparison.) These compared with estimates of 2.2 and 15.5 respectively in the review by McCormic *et al*.

33. No distinction was drawn in the two reviews between studies based upon occupational history and those based upon a concurrent diagnosis of silicosis. However, of the four studies which led Rubio-Rivas *et al* to calculate a high meta-RR for systemic sclerosis, three were certainly based on subjects with silicosis. It may be seen that RRs here ranged from 15.65 to 37.0, although reaching statistical significant in only one of the reports.

SLE

Reports on SLE which have assessed disease risk by level of exposure to silica

34. In a study by Parks *et al* (2002), work histories were assessed in 265 cases of SLE from Carolina, USA and compared with 355 controls identified through

driver's license records and matched to patients by age, sex, and state (the Carolina Lupus Study). A detailed occupational history was taken and all jobs held for $\geq$12 months were classed by three experts according to their likely exposure to silica. The OR for disease was elevated 1.7-fold in those with 'medium' exposure and 3.8-fold (p<0.05) in those with 'high' exposure relative to the least exposed group.

35. Using similar methods, a case-control study was mounted of women with SLE from Boston, identified through community screening and hospital databases (Finckh *et al*, 2006). Controls were volunteers from the community, screened to ensure the absence of connective tissue disease. In all, 95 patients and 191 controls were enrolled and a lifetime occupational history taken. The occupations classed as silica-exposed included those from the construction industry, ceramics and china manufacture. Using information on the length and extent of such work, experts classed subjects as "possibly" or "probably" exposed to silica. Probable exposure to silica for more than one year was associated with an OR of 4.3 (95%CI 1.7-11.2) vs. no or only brief exposures, the estimate for longer exposures being somewhat higher (OR for 1-5 years and >5 years respectively were 4.0 and 4.9).

36. In a case-control study from Canada, 258 cases of SLE (90% women) from 11 rheumatology centres were compared with 263 community controls randomly selected from phone number listings (Cooper *et al*, 2010). An OR of 1.6 (95%CI 0.90 to 2.7) was reported for working at least 8 hours/week in a job involving exposure to silica (plastering; drilling or cutting sheet rock or dry wall; loading, pouring or mixing concrete; drilling, cutting or chipping concrete or abrasive grinding of rocks or stone; grinding drilling, cutting or chipping concrete or abrasive grinding of rocks or stone; and sandblasting). However, pottery or ceramic work, undertaken as a hobby for 26 or more days in total, carried an OR of 2.2 (p<0.05). No sex-specific analyses were reported.

37. In the mortality analysis by Calvert *et al* (paragraph 23), the OR for SLE was 1.37 (p>0.05) among subjects (72% of cases female) classed as highly exposed to silica.

38. In the matched case-control mortality analysis by Gold *et al* (paragraph 24), 7,153 cases of SLE (about 80% female) were analysed. The OR among those with exposure to silica, as judged by an expert JEM was 1.02, p<0.05).

Reports on SLE which have assessed associations with silicosis

39. In the study of 463 patients with silicosis by Rosenman *et al* (paragraph 25), one case also had SLE. The RR was 11.37, but confidence intervals indicated a wide range of uncertainty in this estimate (95%CI 0.15–63.2), and it was not statistically significant.

40. In the study by Brown *et al* which linked hospitalization for silicosis with hospital care for other diseases in Sweden (paragraph 26), eight subjects had a diagnosis of SLE (RR 23.8, 95%CI 10.3 -47.0).

41. In the study by Makol *et al* (paragraph 28, overlapping that of Roseman *et al* in paragraph 25) of individuals reported to the Michigan Silicosis Surveillance system, one case of silicosis also had a recorded diagnosis of SLE (RR 2.53, 95% CI 0.30-21.64).

Combined analysis: systemic sclerosis and SLE

42. In a cohort study of over 240,900 Swedish male construction workers (Blanc *et al*, 2015), risks for scleroderma and SLE were presented in aggregate rather separately and combined with instances of another connective tissue disease, dermatomyositis. Hospital admissions were traced between 1997 and 2010 and a JEM used to classify exposure to various dusts including silica. Of 128 analysed cases, 63 had SLE, 39 had systemic sclerosis and 27 had dermatomyositis. The relative risk (RR) of incident disease when defined in this way was elevated 1.39-fold (p<0.05).

Rheumatoid arthritis

Reports on RA which have assessed disease risk by level of exposure to silica

43. The combination of RA and pneumoconiosis is well-recognised clinically, and called Caplan's syndrome. Sometimes, in a dust-exposed person, RA follows nodular changes on the chest X-ray, but sometimes it precedes it. Furthermore, the combination may be seen with coal-worker's pneumoconiosis and asbestosis, as well as with silicosis, and it has been suggested that the presence of RA alters a person's immune response to inhaled foreign materials. Moreover, RA is sometimes accompanied by a variety of 'interstitial' changes on chest X-ray.

44. The potential exists, therefore, for 'rheumatoid lung', Caplan's syndrome and

silicosis to be confused with one other clinically, potentially complicating interpretation of studies finding an association between RA and silicosis.

45. An initial study of Welsh coal miners (Miall, 1955) did not suggest that exposure to silica could increase the risk of RA, but other evidence has lent support to the idea.

46. In Finland, the number of disability pensions for RA among a cohort of granite workers was more than five times that expected (RR 5.08, 95%CI 3.31-7.79) and the number of patients granted free medication for RA was double the expectation (Klockers *et al*, 1987; Koskela *et al*, 1987). A potential concern, however, is that case ascertainment rested on award of a disability pension: conceivably, granite workers with RA could have been more disabled for work and more liable to be accepted as such than other workers from the general population.

47. This limitation is less likely to be shared by an analysis of death certificates (Steenland *et al*, 1992) in which arthritis was mentioned more often than expected on death certificates of granite workers from the United States. However, only a minority of certificates specified a diagnosis of RA.

48. A case-control study compared 58 cases self-reported RA (43 in men) with matched non-cases (Turner *et al*, 2000). Subjects were drawn from a cohort of pottery, sandstone, and refractory material workers undergoing statutory medical surveillance in Stoke-on-Trent. Exposures to silica were estimated from work histories. No significant difference was found between cases and controls in mean silica concentration. By contrast, men who had worked in the coal mining industry were at particular risk (OR 5.36, p<0.05).

49. In the mortality analysis by Gold *et al* (paragraph 24) 36,178 cases of RA (77% female) were analysed. Risks were not increased in mining machinists and the OR for RA was not elevated in relation to silica dust (OR 1.00, p<0.05), implying no association with the exposure.

50. In a study based on the Swedish Census to the Hospital Discharge Register, which linked first hospitalization for RA in Sweden with occupational title (>28,000 cases during 1964-2004) (Li *et al*, 2008), RRs for male miners and quarry workers were elevated 1.4 to 1.8-fold over different census periods. In comparison, the risk estimate for construction workers was 1.2 to 1.4.

51. The EIRA (Epidemiological Investigation of Rheumatoid Arthritis) study compared

276 male cases of RA, newly diagnosed by rheumatologists from a geographically defined area of Sweden, with controls from the same area, identified using a national population register (Stolt *et al*, 2005). Men with a self-reported history of work involving rock drilling, stone crushing, or exposure to stone dust were defined as silica-exposed. The OR for exposure overall was 2.2 (95%CI 1.2-3.9), rising to 3.0 (95%CI 1.2-7.6) in men whose jobs had involved rock drilling or stone crushing. Among this last group, risks were higher (OR 3.5) if the diagnosis was accompanied by a positive rheumatoid factor (an antibody directed against an individual's own proteins or 'auto-antibody', commonly found in RA). Risks from silica exposure overall appeared to be restricted to men who smoked, although the study was not sufficiently powered to exclude a doubling of risk in non-smokers.

52. A later publication from the EIRA study (Stolt *et al*, 2010) involved five more years of data collection and twice as many cases (577 incident cases of RA and 659 controls). This time risks were estimated separately for exposure to stone dust, rock drilling and stone crushing, as well as overall. Cases were also classified according to the presence or absence in their blood of antibodies to citrullinated peptides (ACPA), a group of auto-antibodies also commonly found in RA. Only for cases that were ACPA-positive were RRs as much as doubled and then only for rock drilling (OR 2.34, p<0.05, 18 exposed cases) and stone crushing (2.03, p>0.05, 11 exposed cases).

53. Smoking is a cause of elevated ACPA, as well as a recognised risk factor for RA. When the data were analysed by smoking history, elevated risks of RA were found in former and current smokers with no exposure to silica. In those with exposure to silica overall, risks were not increased in lifetime never-smokers although these remained few in number; but they were increased 1.7- to 3.6-fold in former and current smokers, and even more so in those who were ACPA-positive. The authors highlighted a potential interaction therefore between cigarette smoking and occupational exposure to silica.

54. A further analysis from the EIRA study, reported only in abstract form (Ilar *et al*, 2016), cited an OR for ACPA-positive RA of 2.6 (p<0.05) among male bricklayers and concrete workers, and of 2.8 (p<0.05) for male smelters and foundry workers, two occupational groups with potential exposure to crystalline silica.

55. The design of the EIRA study was replicated in Malaya (the MyEIRA study)

(Yahya *et al*, 2014), with similar findings to those described above. The OR for ACPA-positive RA was 2.4 in those exposed to silica, rising to 7.5 in those with silica exposure who smoked (p<0.05).

56. In the large cohort study of Swedish male construction workers by Blanc *et al*, (paragraph 42), 713 incident cases of hospital-treated RA were identified over follow-up. The RR in silica-exposed workers was 1.33 (95%CI 1.11-1.60), being somewhat higher when the rheumatoid factor was negative than when positive.

57. A meta-analysis of 10 studies from Europe, South Africa, and United States (242 cases) estimated an overall RR of 3.43 (95%CI 2.25-5.22) rising in men to 4.45 (95%CI 2.24-8.86) (Khuder *et al*, 2002). Most of the included studies are summarised above. In addition were three cohort studies by Steenland *et al* (1992, 1995, 2001) in which mortality from RA was considered in granite cutters, sand industry workers and gold miners. RRs were respectively elevated 3.36-fold (5 cases), 4.36-fold (23 cases), and 2.19-fold (17 cases), all findings being statistically significant (p<0.05).

58. A review by Murphy *et al* (2017), in focussing on most of the papers summarised above, postulated that male RA is an occupational disease.

Reports on RA which have assessed associations with silicosis

59. In the analysis by Calvert *et al* (paragraph 23), odds of RA were elevated 3.75-fold (95%CI 1.92-7.32, 15 cases) in men with silicosis relative to controls from the same national occupational mortality database without silicosis.

60. In the study of men with silicosis by Rosenman *et al* (paragraph 25), 24 cases had RA. The RR was 2.73 (95%CI 1.75-4.06), assuming an expected prevalence of 2% from population statistics.

61. In the overlapping report by Makol *et al* (paragraph 28), the RR was 2.26 (95%CI 1.57-3.25), based on 33 cases.

62. In the study by Brown *et al* which linked hospitalization for silicosis with hospital care for other diseases in Sweden (paragraph 26), 44 subjects in Sweden and 10 in Denmark had a diagnosis of RA with RRs of 9.1 (95%CI 5.9 -10.82) and 8.3 (95%CI 4.0-15.3) respectively

63. In a study from South Africa (Sluis-Cramer *et al*, 1986), workers with RA were identified from gold miners attending the Medical Bureau for Occupational Diseases for benefit examinations. These assessments were conducted to

assess eligibility for compensable disease, including silicosis. RA was diagnosed based on physicians' written reports. Some 157 miners with 'definite' or 'probable' RA were matched with control miners, those with any suggestion of RA being excluded. Chest radiographs were then compared blinded to case-control status. The odds of silicosis in those with RA were raised 2.84-fold (95%CI 1.36-4.32).

Other evidence

64. Several studies lend support to the plausibility of a causal relationship between exposure to silica and connective tissue disease. For example, in the studies by Sanchez-Roman *et al* and Conrad *et al* mentioned above, antinuclear antibodies, a feature of SLE, were found significantly more often in exposed workers, including those without SLE. Also, experimental exposures in mice have been linked with immunological responses relevant to disease pathogenesis (as reviewed by Parks *et al*, 2006). A high prevalence of antinuclear antibodies has been found in sandblasters with silicosis (Jones *et al*, 1976).

65. More generally, associations have been described between silica exposure and other systemic autoimmune and connective tissue diseases, such as certain forms of vasculitis.

66. Crystalline silica is very toxic to cells. Moreover, silica particles cannot easily be broken down by the body, and can act as foci of inflammation, immunological activity and fibrosis. Silica is known to have adjuvant properties – i.e. to non-specifically potentiate the body's immune response to antigens. Thus, there are *a priori* reasons to suspect that silica could promote autoimmune disease, although no pathogenic mechanism has been firmly established to date.

Discussion and recommendations

67. The evidence base on occupational exposure to silica and connective tissue disease is deeper than when this subject was last reviewed by the Council ten years ago. Collectively, it provides reasonable evidence of causal association.

68. Risks of scleroderma and systemic sclerosis have been more than doubled in several reports (e.g. Englert *et al*, Diot *et al*, Bonvezi *et al*, Marie *et al*, Roseman *et al*, Brown *et al*, Calvert *et al*, Makol *et al*); and, while risk estimates have fallen short of this threshold in other reports (e.g. Burns *et al*, Bovenzi *et al*, Gold *et al*, Silman *et al*, Zacharie *et al*, Thompson *et al*, Maitre *et al*), pooled risk estimates

have also been more than doubled in both men and women.

69. The evidence in relation to SLE and RA is smaller in volume than that for systemic sclerosis. A more than doubling of risk of SLE was reported in studies by Parks *et al*, Finckh *et al*, Rosenman *et al*, Brown *et al* and Makol *et al*, although not in studies by Cooper *et al*, Calvert *et al*, or Gold *et al*. A more than doubling of risk of RA was reported in studies by Klockers *et al*, Stolt *et al*, Yahya *et al*, Brown *et al*, Rosenman *et al*, Makol *et al* and Calvert *et al*, but not in studies by Turner *et al*, Gold *et al*, Li *et al*, or Blanc *et al*. Notwithstanding this variation, a substantial body of evidence points to an occupational hazard.

70. A major challenge to prescription lies in defining a suitable qualifying schedule of exposure. Much of the evidence stems from case-control studies whose definitions of exposure to silica (e.g. 'high', 'probable', 'potentially substantial', semi-quantitative cumulative score) have rested on expert judgements and are not amenable to replication within the IIDB Scheme.

71. Only occasionally have definitions been more explicit (e.g. plastering, pottery, quarrying, rock drilling, stone crushing). Here findings have been mixed and limited in replication – e.g. for RA, more than doubled risks for granite workers in two studies (Klockers *et al*, Steenland *et al* (1992)) and for workers engaged in rock drilling and stone crushing in a third (Stolt *et al*, 2010), but below this threshold for miners and quarry workers (Li *et al*), and mining machinists (Gold *et al*) in other studies; for systemic sclerosis, only the study by Diot *et al* offers a potential (fairly wide) range of job titles. The evidence base for any given occupation is therefore thin.

72. As an alternative to prescribing by job title the Council has considered the case for prescribing in the subpopulation of workers who have silicosis. The qualifying circumstance (that of having silicosis) would be more feasible to define and verify than for general definitions of substantial exposure to silica; it is certain to correspond to substantial exposure to silica; and estimates of risk, although based on only a few cases in each analysis (and sometimes only one), have, for systemic sclerosis and SLE, been among the highest reported (e.g. RR 11-37 in studies by Rosenman *et al*, Brown *et al* and Makol *et al*). For RA, RRs have been less elevated, but still more than doubled, generally consistent, and have been statistically significant at the 5% level, being based on larger numbers of cases (Rosenman *et al*, Calvert *et al*, Brown *et al*).

73. However, several methodological problems have been identified in the evidence base. A concern about studies that have explored the association between connective disease and silicosis is that such a link has long been suspected clinically. It is not easy, therefore, to rule out diagnostic bias. This could arise if a keener hunt for these diseases was performed in patients known to have silicosis, or if the chest radiographs of patients with known or suspected connective tissue disease were scrutinised more carefully for signs of fibrosis indicative of silicosis. Given the small number of cases and particularly the non-standardised ascertainment of disease outcomes, based on routine medical records (e.g. Rosenman *et al*, Makol *et al*, Brown *et al*), even a small degree of such bias (the finding of an additional case) could markedly influence findings for rare diseases like systemic sclerosis and SLE.

74. An example of this concern is provided by RA. This disease is known to be associated with Caplan's syndrome and other lung manifestations. Typically, it is also under-recorded by a wide margin on death certificates (the controls from the study by Calvert et al, for example, had a low prevalence relative to population norms): bias could arise if RA was documented more often on a death certificate when the principal cause of death was lung-related than when it was not.

75. A second possibility is that studies that select their subjects from hospital settings may recruit people who become hospitalised because they have several pathologies at the same time, and in this way associations between diseases may be observed even though they are in reality independent of one another. The study by Brown *et al* (paragraph 26), for example, being based on hospital admission data, could suffer the bias that patients may be more likely to be hospitalised for silicosis if they also have other serious medical conditions, in which case they would not be representative of all people with silicosis.

76. A further concern is that many connective tissues diseases, notably systemic sclerosis and RA, can directly affect the lung tissue and give rise to changes visible on chest radiology. Although these changes are considered by experts to be readily distinguishable from those of silicosis, there remains a possibility – again, perhaps, in a small but material proportion of cases – of diagnostic confusion.

77. Moreover, it seems possible that RA could predispose to silicosis. It is noteworthy that the study by Sluis-Cramer *et al* (1986) was framed around the hypothesis

that RA increases the risk of silicosis, rather than that silicosis (or heavy exposure to silica) increases the risk of RA. There has long been a clinical suspicion that RA can predispose to the development of silicosis – the mechanism has yet to be be established, but it seems possible that inhalation of fibrogenic particles in individuals with a predisposition to RA could enhance the fibrotic response. Since case-control studies are retrospective, this one for example involving subjects who had both conditions at the time of inquiry, the sequence of events in the causal chain cannot be distinguished. This uncertainty about the direction of causation undermines the case for compensating RA in claimants of IIDB with silicosis. Prospective studies would be needed to confirm that the reverse situation also happens sufficiently often to justify prescription.

78. A further limitation of the early literature in respect of RA lies in the potential for diagnostic error. In Sluis-Cramer *et al* (1986), for example, diagnosis of RA rested heavily on the presence of the blood marker called 'rheumatoid factor'; but with current knowledge this is considered too non-specific a marker to confirm the presence of RA – false positive results are reasonably common. Moreover, since mineral dust exposures can cause pro-inflammatory responses that induce these markers, associations between silica and the marker can be expected in circumstances that do not necessarily denote an elevated risk of RA.

79. The Council has drawn several conclusions.

(1) Taking this large body of evidence overall, there is clear evidence of a hazard: crystalline silica is likely to be a cause of connective tissue disease in some circumstances.

(2) It is not feasible to define a suitable exposure schedule based on actual exposures or on job title(s).

(3) Striking associations have been found between silicosis and connective tissue diseases, although the number of reports is small and unresolved methodological issues limit the scope for prescription in this subset of the silica-exposed workforce.

(4) The Council recognises the considerable challenge in acquiring sufficient evidence on doubling of risks for diseases that are rare, and in which excess risks may be manifest in small worker groups incurring exceptional exposures. Within the current framework for decision-making the Council balances this against a need to define the prescription schedule so that it is firmly grounded in

the evidence from research findings. At present, on this basis, the case for prescription is not made; but more and better studies on risks by job title and/or cohort studies of patients with silicosis may change the position in future. The Council remains open to this possibility.

Prevention

80. Silica-related diseases can be prevented by ensuring that workers who encounter silica-containing materials are not exposed to respirable dust released when working with such materials. The Control of Substances Hazardous to Health Regulations 2002 (COSHH) require employers to undertake a suitable and sufficient assessment of the risks created by such work and to identify and take measures to prevent exposure as far as is reasonably practicable.

81. Where it is not reasonably practicable to prevent exposure by substitution with a safer substance or total enclosure, exposure must be reduced by the use of appropriate work processes, systems and engineering controls and measures such as dust suppression and local exhaust ventilation that control exposure at source. Suitable respiratory protective equipment may be used in addition to further reduce exposure. Health surveillance of workers may be necessary and should be developed with the involvement of a suitable health practitioner.

82. Under COSHH, respirable crystalline silica is subject to a workplace exposure level (WEL) of $0.1 mg/m^3$ and there is a legal onus on employers to reduce exposure to the lowest reasonably practicable level below this value. With good practice exposure controls in place silica dust can usually be reduced to significantly below the WEL. Advice about good practice control measures for different work circumstances, including advice on air sampling and health surveillance, is freely available on the Health and Safety Executive's website.

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Glossary

Types of study

Cohort study: A study which follows up a population of individuals (usually defined by a workplace) over time and compared the **incidence** rate of disease or mortality among those within the cohort or with an external comparison population. The outcome is expressed as a Rate Ratio or **Relative Risk**, Standardised Incidence Ratio, Standardised Registration Ratio, or **Standardised Mortality Ratio**, depending on the type of analysis and the disease outcome being studied.

Case-control study: A study which compares people who have a given disease (cases) with people who do not (non-cases, also known as 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**. In a **nested-case control study**, cases and controls are sampled from the members in a **cohort study** – often, all the cases occurring in the cohort and a sample of non-cases.

Measures of association

Statistical significance and P values: Statistical significance refers to the probability that a result as large as that observed, or more extreme still, could have arisen simply by chance. The smaller the probability, the less likely it is that the findings arise by chance alone and the more likely they are to be 'true'. A 'statistically significant' result is one for which the chance alone probability is suitably small, as judged by reference to a pre-defined cut-point. (Conventionally, this is often less than 5% ($p<0.05$)).

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 indicates a positive association between exposure and disease. (This may be causal, or have other explanations, such as **bias**, chance or **confounding.**) RR is measured or approximated by other measures in this glossary, such as the **Odds Ratio**, **Standardised Incidence Ratio** and **Standardised**

Mortality Ratio.

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 of association between exposure and mortality; a form of **Relative Risk** 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, SMRs (and **proportional mortality ratios**, as described below) are usually multiplied by 100. Thus, an SMR (or PMR) of 200 corresponds to a RR of 2.0. For ease of understanding in this report, SMRs (or PMRs) 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**.)

Proportional Mortality Ratio (PMR): A PMR is the proportion of observed deaths from a given cause in a given population divided by the proportion of deaths from that cause expected (in a standard population).The value is often expressed on an age-specific basis or after age adjustment. It is a form of **Relative Risk**.

Other epidemiological terms

Job-exposure matrix (JEM): A tool used to assess exposure to potential health hazards in occupational epidemiological studies. A JEM comprises a list of levels of exposure to a variety of harmful (or potentially harmful) agents for selected occupational titles. In large population-based epidemiological studies, JEMs may be

used as a quick and systematic means of converting coded occupational data (job titles) into a matrix of possible exposures, obviating the need to assess each individual's exposure in detail.

Meta-analysis: A statistical procedure for combining data from multiple studies. When the treatment effect (or effect size) is consistent from one study to the next, meta-analysis can be used to identify this common effect. The effect may be summarised as a meta-estimate of relative risk.

Risk: The probability that an event will occur (e.g., that an individual will develop disease within a stated period of time or by a certain age).

Incidence rate or incidence: The rate of occurrence of a new event of interest (e.g. cancer) in a given population over a given time period. (The rate is often expressed in terms of cases per year of 'person-time', and so incorporates the numbers at risk of the event, the time for which they are at risk and the numbers that go on to develop that event.)

Confidence Interval (CI): The **Relative Risk** reported in a study is only an estimate of the true value of relative risk in the underlying population; a different sample 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.

Bias: A systematic tendency to over- or under-estimate the size of a measure of interest in a study.

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.

Blinding: The act of concealing (from the 'blinded' person) an aspect of a study, to reduce the potential for a biased response. For example, in a case-control study an interviewer may be blinded to (not know) whether the interviewee is a case or a control when asking about their past exposure; in a randomised controlled trial, a subject may blinded to (not know) which treatment they have received as may those assessing the outcome or analysing the data.

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