



IIAC

**THE INDUSTRIAL INJURIES ADVISORY
COUNCIL**

POSITION PAPER 46

**Occupational exposure to
silica or asbestos and anti-
neutrophil cytoplasmic
antibodies (ANCA)-
associated vasculitis**

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Position Paper 46: Occupational Exposure to Silica or Asbestos and ANCA-associated Vasculitis

Summary

The Council received an enquiry from an MP on behalf of a constituent concerning a possible relationship between exposure to silica and asbestos and development of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. Reviews of the available scientific literature for these issues are given in this report.

Earlier reports by the Council reviewed occupational exposure to crystalline silica and certain connective tissue diseases; ANCA-associated vasculitis was not included in the 2005 or the 2018 reviews. A substantial amount of research over the last 25 years is summarised which has indicated there is some evidence relating crystalline silica exposures to an increased risk of ANCA-associated vasculitis. However, the evidence is not consistent and is mostly derived from small studies which are potentially subject to selection and publication biases. The council found much less evidence relating asbestos exposure to ANCA-associated vasculitis. For the reasons set out below, the Council has decided against recommending prescription for both silica and asbestos exposure, but it remains open to the possibility of reviewing its position as the research evidence base continues to grow.

This report contains some technical terms, the meanings of which are explained in a concluding glossary.

Background

1. The Industrial Injuries Advisory Council (IIAC) reviewed the relationship between occupational exposure to crystalline silica and certain connective tissue diseases, namely systemic sclerosis/scleroderma, systemic lupus erythematosus and rheumatoid arthritis in 2005 (Position Paper 14; IIAC, 2005). Some positive associations were found, but the evidence base was limited and a problem existed in defining the relevant qualifying exposures for the purposes of prescription, and this was not recommended.
2. IIAC reviewed the matter in 2018 (Position Paper 42: Occupational exposure to crystalline silica and its relation to connective tissue diseases; IIAC 2018). A substantial amount of research was summarised, much of it published since the earlier review. Collectively it provided reasonable evidence pointing to an occupational hazard, the evidence generally being clearer for systemic sclerosis/scleroderma than for the other two conditions.
3. Prescription was hampered, however, by the difficulty of defining the qualifying levels of occupational exposure. The case for prescription in workers with silicosis, who also have one of the connective tissue diseases, was considered. However, there were unresolved methodological concerns about the few available relevant reports.
4. The Council decided against recommending prescription, but remained open to the possibility of reviewing its position as the research evidence base grew.
5. IIAC did not include anti-neutrophil cytoplasmic antibodies (ANCA) - associated vasculitis in the 2005 or the 2018 reviews. Following concerns raised by an individual about possible associations between ANCA-associated vasculitis and exposures to crystalline silica and asbestos, IIAC has now reviewed these topics.

Auto-immune disease and ANCA

6. There are many auto-immune diseases in which antibodies are produced to normal body structures, organs, or cells.
7. Anti-neutrophil cytoplasmic autoantibodies (ANCAs) have several targets within the cytoplasm of cells. The most important of these are the enzymes proteinase 3 (PR3) and myeloperoxidase (MPO). When ANCAs bind to these enzymes they activate the cells leading to the release of inflammatory mediators. ANCAs directed against PR3 and MPO are strongly associated with diseases of small blood vessels (vasculitis), specifically:
 - Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis),
 - microscopic polyangiitis
 - eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome).

8. These are rare diseases, with incidences in the region of 10 per million per year (Pagnoux 2016). Their rarity makes epidemiological studies of their causes difficult. There are likely to be genetic susceptibilities and some environmental associations are recognised or purported (Watts et al 2015). These include Staphylococcal infection, smoking, exposure to crystalline silica and medications such as propylthiouracil.
9. ANCA's can be identified by their pattern on immunofluorescent staining. Perinuclear staining (P-ANCA) is most closely associated with anti-MPO antibodies and cytoplasmic staining (C-ANCA) is mostly associated with anti-PR3 antibodies. There are atypical immunofluorescent staining patterns (known as atypical or A-ANCA's) that are associated with antibodies against other cellular components such as lactoferrin, lysozyme, azurocidin, elastase, cathepsin G, and bactericidal/permeability increasing enzyme (BPI).
10. These antibodies are not associated with inflammatory vasculitis, though associations have been reported with a variety of conditions including inflammatory bowel disease, rheumatoid arthritis, drug-induced vasculitis and infections (Bosch et al 2006).

Silica¹

11. Crystalline silica, otherwise known as silicon dioxide (SiO₂), is the basic constituent of sand, quartz and many types of rock. Exposure to silica has been linked with a number of 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.

Asbestos

12. Asbestos is a mineral fibre which was used extensively in the 20th century for insulation and other purposes. Asbestos exposures are associated with a number of diseases including pleural plaques, pleural effusions, pleural thickening, asbestosis, malignant mesothelioma and lung cancer. Asbestosis (PD D1), diffuse pleural thickening (PD D9), malignant mesothelioma (PD D3) and lung cancer (PD D10) are prescribed diseases within the Industrial Injuries Disablement Scheme. In the case of lung cancer, the prescription is limited to those with asbestosis and those who worked in a number of specified jobs.

Silica and ANCA-Associated Vasculitis

13. Papers examining the relationship between occupational exposures to silica-containing dusts and the presence of ANCA or ANCA-associated disease are outlined in tables 1 and 2.

¹ Silicon (Si) is the chemical element which constitutes part of silica (SiO₂)

Table 1 Silica exposures in subjects with ANCA-associated vasculitis and control subjects

Author	Disease/condition	Subjects; (n and % exposed to silica)	Controls; n (% and exposed to silica)	Odds Ratio (OR) (95% CI)	comments
Hogan 2001	ANCA-associated glomerulonephritis	30/65 (46%)	13/65 (20%)	4.4 (1.4:14.4)	
Stratta 2001	Vasculitis/ renal disease	14/31 (45%)	14/58 (24%)	2.4 (p=0.04)	Not clear if all subjects were ANCA +ve
Lane 2003	Primary systemic vasculitis	18/75 (24%)	42/220 (19%)	1.4 (ns)	7 subjects were ANCA -ve. Significant associations noted with exposure in the year of disease development OR 3.0 (1.0-8.2); >20 yr exposure OR 2.6 (1.0-6.7); agricultural silica exposures OR 4.4 (1.1:18.1).
Rihova 2005	Vasculitis with pulmonary and renal involvement	4/31 (13%)	0/30 (0%)		
Hogan 2007	ANCA-associated small vessel vasculitis	78/129 (60%)	49/109 (45%)	1.6 (0.9:2.0)	Exposure-response relationship shown with a significant association in those with longest exposure
Gregorini 1993	glomerulonephritis	7/16 (41%)	1/32 (3%)	14 (1.7:114)	
Nuyts 1995	Wegener's granulomatosis	5/16 (31%)	2/32 (6%)	5.0 (1.4-11.6)	
Beaudreuil 2005	ANCA +ve	13/60 (22%)	13/120 (11%)	3.4 (1.1-9.9)	20% of ANCAs were atypical
Flores- Suarez 2005	Primary systemic vasculitis	17/76 (23%)	13/189 (8.3%)	3.2 (1.1-9.2)	OR is for 'organic' silica
Stamp 2015	Granulomatosis with polyangiitis	16/49 (33%)	36/196 (18%)	3.1 (1.3-21.7)	

Table 2 Prevalence of ANCA in silica-exposed populations

Author	Disease/condition	Silica-exposed (n and % affected by condition)	Controls (n and % affected by condition)	OR (95% CI)**	Comments	
Stratta 2001	ANCA +ve	1/44 (2%)	0/65(0%)		33 subjects with silicosis; 11 silica-exposed	
Wichman 1996	ANCA +ve	14/52 (27%)	5/28 (18%)	1.4 (ns)	Exposures from a single factory; high prevalence of auto-immune disease in the control group	
Bartůnková 2006	ANCA +ve	15/86 (17%)	1/28 (3%)		ANCA +ve in >30% of those with silicosis; 7% in those with silica exposure without silicosis	
Knight 2010	Wegener's granulomatosis	Miner	10 (4.4)	Miner	64 (2.8)*	Swedish study linking inpatient care records with census information about work.
		Other mining	5 (2.2)*	Other mining	37 (1.7)*	
		Concrete/brick	8 (3.5)*	Concrete/brick	62 (2.7)*	
		Bricklayer	10 (4.4)*	Bricklayer	90 (3.9)*	
		Construction	33 (14.4)*	Construction	403 (17.6)*	
		Stonemason	1 (0.4)*	Stonemason	13 (0.5)*	
Gregorini 1993	glomerulonephritis	7/16 (41%)	1/32 (3%)	14 (1.7:114)		
Makol 2011	ANCA +ve vasculitis	6 (0.8%)		25.3 (6.3: 101.0)	RR with reference to general population	
Zaghi 2010	ANCA +ve	1/61 (2%)	0/62 (0%)			

** Relative risk in Makol study, odds ratios (OR) in all other studies.

* % x 10⁻³ Denominators = 2288 patients with Wegener's Granulomatosis and 22880 control subjects.

ns: non-significant

14. The association was reviewed in a 2012 US National Institute of Environmental Health Sciences (NIEHS) expert panel workshop (Miller et al 2012). Five case-control studies (Lane et al 2003, Rihova et al 2005, Hogan et al 2001, Hogan et al 2007, Stratta et al 2001) were noted to support an association with ANCA positivity, ANCA-positive small vessel vasculitis, or glomerulonephritis. The relative risk associated with silica exposure was said to be greater than 2.0 in almost all studies. The panel noted a large negative Swedish case-control study (Knight et al 2010) but concluded that they were confident of a positive association. The conclusion was reiterated in a subsequent publication from the same workshop (Parks et al 2014).
15. A later systematic review and meta-analysis (Gomez-Puerta and Gedmintas 2013) included 6 papers. Four were previously reviewed in the NIEHS workshop and there were 2 others (Gregorini et al 1993, Nuyts et al 1995). The summary odds ratio for silica exposure in those with ANCA-related disease was 2.57 (1.51-4.36) but the authors noted a moderate degree of heterogeneity amongst the studies and some evidence of publication bias. They excluded a further 8 studies: three which examined only the presence of ANCA antibodies (Wickman et al 1996, Bartůnková et al 2006, Beaudreuil et al 2005); one which was published in abstract form only (Flores-Suarez 2005); three which were considered to lack sufficient data (Duna et al 1998, Makol et al 2011, Rihova et al 2005) and the Swedish case-control study (Knight et al 2010) as exposure was based on job title only.
16. More recently the French Agency for Food, Environmental and Occupational Health & Safety reviewed a number of conditions potentially associated with silica exposures, including ANCA-associated vasculitis (ANSES 2019). The review commented on both the Miller and the Gomez-Puerta papers but noted that several factors limited the generalisability of their findings including disparate study inclusion criteria which were often defined by renal impairment associated with vasculitis and not by the diagnosis of ANCA-associated vasculitis *per se*. The report concluded that there was a possible, but not a certain, association between silica exposures and ANCA-associated vasculitis.
17. Tables 1 and 2 indicate a wide range of vasculitis-related diseases that have been reported to be associated with silica exposure, though ANCA positivity has not been demonstrated in all cases. There are 3 studies involving 313 subjects which demonstrated a more than doubled rate of silica exposure history in those with ANCA-associated disease compared with control subjects. A further 2 studies involving 204 subjects showed silica exposure rates which were less than doubled and were not significantly elevated. One study of 189 patients which primarily concerned agricultural work (Willeke et al 2015) did not identify any association with silica exposures. There are a number of additional single case reports of silica-exposure in patients with ANCA-related disease.
18. Of seven studies which investigated ANCA positivity or ANCA-related disease associated with silica exposure, two small studies showed more than doubled risks (table 2). The largest study of the Swedish population showed no

significant associations. The response rates were low in some studies (24% in Hogan et al 2001; 12% in Hogan et al 2007) leading to a potential for response biases.

19. Several papers reported very high prevalence of silica exposure in the control groups (up to 45%) suggesting the inclusion of workers with low level and / or infrequent exposure. It is estimated that approximately 1.5% of the UK workforce is exposed to silica (Cherrie et al 2011), much lower than the proportions reported in several of these studies.
20. Of the specific occupations included in the studies relatively few were in traditional high exposure groups such as mining, sandblasting, quarrying or foundry work. Hogan et al 2007 reported that only 19% of the silica exposures in their study occurred in those engaged in industrial trades. Other occupations considered to involve silica exposure included bakery work, shipyard work, coal delivery, and work as an electrician.
21. Many of the silica exposures were considered to occur in agricultural workers. Lane et al (2003) reported that 49% of their subjects had been exposed in this way. Hogan et al (2007) reported silica exposures through living or working on a farm in 49% of their subjects and through harvesting crops in 22%. Both these studies suggest that any risks of vasculitis might be confined to these exposures. It is recognised that sandy soils in some areas of the world pose a risk of substantial silica exposure, but agricultural work in the UK is not generally considered to pose a risk. There is some evidence that other agricultural exposures can be associated with ANCA-associated vasculitis leading to the potential for confounding with agricultural silica exposures.
22. Given the disparate nature of the evidence, and the unclear association with traditional high exposure work, IAC does not consider that ANCA-associated vasculitis in silica-exposed workers meets the criteria for prescription under the Industrial Injuries Scheme.

Asbestos and ANCA-associated vasculitis

23. There have been fewer studies of the association between asbestos exposure and ANCA-associated vasculitis.
24. Pfau et al (2005) reported in a review article that a study of asbestos-exposed workers in Montana did not detect any with ANCA antibodies. Philteos et al (2004) and Inoue et al (2004) each reported single cases of ANCA-associated vasculitis in individuals with asbestos exposure. In Philteos et al's case there was co-existing asbestosis. Rihova et al (2005) reported a history of asbestos exposure in 3 of 31 Czech patients with ANCA-associated vasculitis. There was no reference population and it was not clear that that prevalence was higher than expected.
25. Stratta et al (2001) reported asbestos exposure in fewer of their Italian patients with ANCA-associated renal problems compared with those with non-

vasculitic renal disease (16% vs 28%). Pelclova et al (2003) reported positive ANCA in 13 of 61 asbestos-exposed individuals and in 2 of 37 control subjects. The specificity of the antibodies was not determined in 7 subjects and none had detectable levels of the MPO or P3 antibodies that are associated with vasculitis. None of the asbestos-exposed or control subjects had clinical evidence of vasculitis.

26. There is no other substantial evidence relating asbestos exposures to ANCA-associated vasculitis. The evidence which does exist is insufficient to allow prescription under the Industrial Injuries Scheme.

Summary

27. There is some evidence relating crystalline silica exposures to an increased risk of ANCA-associated vasculitis. The evidence is not consistent and is mostly derived from small studies which are potentially subject to selection and publication biases. In several studies there appears to have been a liberal interpretation of silica exposure with over 20% of control subjects assessed as having been exposed. This figure is much higher than the proportion of the UK population considered to be exposed to silica. The single large study of the relationship based on the Swedish population did not show any significantly elevated risks.
28. Given the current evidence, IAC does not consider that ANCA-associated vasculitis associated with silica exposure meets the criteria for prescription under the Industrial Injuries Scheme.
29. There is much less evidence relating asbestos exposures to ANCA-associated vasculitis and that also is not sufficient to meet the criteria for prescription under the Industrial Injuries Scheme.

Prevention note

30. The risks of silica- and asbestos-related diseases should be mitigated by ensuring that workers are not exposed to respirable dust or fibres containing these materials. Where it is not possible to avoid exposure, the work must be carried out in such a way as to minimise the inhalation of harmful dust.
31. Work with silica-containing materials is regulated under the Control of Substances Hazardous to Health Regulations 2002 (COSHH). These regulations require employers to undertake a suitable and sufficient assessment of the risks created by any work involving substances hazardous to health and to identify and take measures to prevent exposure, as far as is reasonably practicable.
32. Where it is not reasonably practicable to prevent exposure by substitution of the crystalline silica with a less hazardous substance, exposure must be reduced by the use of appropriate work processes, systems and engineering controls, including 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. The risk assessment should show where there is a need to introduce health surveillance procedures. Where workers are regularly exposed to crystalline silica and there is a reasonable chance that silicosis may develop, health surveillance must be provided. HSE has provided specific guidance on health surveillance: <http://www.hse.gov.uk/pubns/priced/healthsurveillance.pdf>.

33. Under COSHH, respirable crystalline silica is a recognised carcinogen and subject to a workplace exposure limit (WEL) of $0.1\text{mg}/\text{m}^3$ which must not be exceeded. COSHH also requires duty holders to satisfy the principles of good practice for the control of exposure to substances hazardous to health which includes a legal duty on employers to reduce exposure to a level proportionate to the health risk. The importation, supply and use of asbestos in Britain has now been banned, but asbestos was extensively used as a building material up to the late 1970s. Those currently at risk from exposure to asbestos fibres include people who remove asbestos containing materials and building and maintenance workers who may unknowingly be exposed during the course of their work.
34. Work with asbestos is regulated under the Control of Asbestos Regulations 2012. These require an assessment of risk before any work with asbestos-containing materials, the use of appropriate control measures to reduce exposure and the provision of respiratory protective equipment. People who regularly work with asbestos may be required to have health examinations. It may be necessary to notify the Health and Safety Executive before starting some types of work with asbestos.
35. 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

Prevalence: is the proportion of a particular population found to be affected by a medical condition (typically a disease or a risk factor such as smoking). It is derived by comparing the number of people found to have the condition with the total number of people studied, and is usually expressed as a fraction, as a percentage, or as the number of cases per 10,000 or 100,000 people. It is the total number of cases of a disease in a given area during a given time period

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

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