Proceedings of Expert Workshop: Epidemiological Perspectives on Silica and health

New York 5-6 August 2004
Holiday Inn Wall Street District Hotel

EUROSIL

EUROSIL, the European Association of Industrial Silica Producers, is steadily looking at developing knowledge on the health effects of the naturally occurring materials produced by its Members. To this end, the Association regularly sponsors research and organizes expert meetings.

These proceedings are a collection of the various contributions to the “Expert Workshop on Epidemiological Perspectives on Silica and Health” held in New-York on 5-6 August, 2004.

Eurosil is a member of IMA-Europe aisbl, the European Industrial Minerals Association.

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Thursday 5 August, Morning Session

Introduction

Mrs. Wyart welcomed the thirty-six scientific individual experts and seventeen industry observers who had replied positively to the Workshop's invitation. The audience was very international with participants coming from Australia, China, Europe, Canada and the United States. Mrs. Wyart underlined that the first success of the Workshop was already to have gathered the main authors of the epidemiological studies on crystalline silica in the same room as well as a few toxicologists, and she was confident that the participants would seize this opportunity to share the results of their studies and their possible concerns with their colleagues. For EUROSIL[1], who was organising the Workshop, its main objective was to have experts discuss openly together on the bias of epidemiological studies and agree on what would be the optimal epidemiological study design for any future work. This would give guidance to industry for its future research funding decisions.

Update of current legislative position and future proposed legislation concerning crystalline silica in Europe and North America

In Europe, Michelle Wyart-Remy (*See PPT presentation in annex IV):*

After a brief introduction to Industrial Minerals Association (IMA)-Europe and EUROSIL, Mrs. Wyart presented the developments in Europe in the respirable crystalline silica issue.

In 1998, the EU Council requested the European Commission to establish an EU occupational exposure limit (OEL) for respirable crystalline silica. The SCOEL (Scientific Committee for the setting-up of Occupational Exposure Limits) was therefore put in charge of making a recommendation.

SCOEL's final recommendation was released in June 2003 and concludes that ***The main effect in humans of the inhalation of respirable silica dust is silicosis****. There is sufficient information to conclude that the* ***relative risk of lung cancer is increased in persons with silicosis*** *(and apparently, not in employees without silicosis exposed to silica dust in quarries and in the ceramic industry). (...) It arises that an OEL should lie below 0.05 mg/m3. (Quoted from SCOEL SUM Doc 94-final, June 2003).*

On 7 April 2004, the European Commission consulted the social partners on a possible enlargement of the scope of the Directive on Carcinogens at Work (90/394/EEC) and **crystalline silica** is listed among other substances like diesel exhaust, wood dust, solar radiation, tobacco smoke etc.

[1] The European Association of Industrial Silica Producers

Mrs. Wyart explained that the EU industry looks at reducing exposure at the workplace, at improving product safety and workers' health protection and at a better understanding of respirable crystalline silica toxicity. Industry undertook a series of initiatives towards these objectives such as gathering all concerned sectors into a Silica Task Force (more than 30 sectors), implementing a standard dust monitoring protocol, negotiating with the unions an agreement on exposure prevention, and finally, supporting research projects. Mrs. Wyart summarised the results of the two previous scoping meetings organised by EUROSIL. She explained that the objective of this workshop in New York was to gather the authors of the main existing epidemiology studies, identify the key health and exposure issues and identify gaps in knowledge. At the end of the workshop, the participants would hopefully agree on priorities for future work and the optimum methods for achieving this.

In North America, Robert E. Glenn *(See PPT presentation in annex IV):*

Mr. Glenn presented the history of regulation of crystalline silica in North America from 1971 to 2004. In 1974, NIOSH published a criteria document on occupational exposure to crystalline silica and OSHA announced a proposed rulemaking for crystalline silica.

In 1986, IARC evaluated silica as limited evidence for humans, sufficient evidence for animals. In 1987, IARC classified silica as Group 2A: probably carcinogenic to humans. In 1996, IARC revised its evaluation of Silica as Group 1: carcinogenic to humans.

The OSHA PEL (Permissible Exposure Level) for crystalline silica was set in 1971 by adopting the ACGIH formula: PEL (respirable dust) = 10 / (%quartz + 2). In 1997, OSHA announced rulemaking for crystalline silica in the regulatory agenda. Today in 2004, OSHA is working on a draft proposed crystalline silica standard to ensure that workers are protected from the hazards of crystalline silica.
Mr. Glenn pointed out some issues regarding this standard:

- Should the standard cover general industry, construction and maritime?
- What is the feasibility of reducing the current PEL?
- Can dust controls be specified for construction as an alternative to requiring exposure assessment & compliance with a PEL?
- How accurate are current sampling and analytical methods in detection of low concentrations of respirable quartz?

Mr. Glenn concluded his presentation by the list of questions which, according to him, remain unanswered in the crystalline silica scientific file:

- Does crystalline silica cause lung cancer?
- In what exposure situations?
- How do particle factors affect disease endpoints?
- What role does silicosis = fibrosis play?
- Does the lung cancer risk increase for radiographic severity of silicosis?
- Are there pathological differences between fibrosis from silica and asbestos that influence lung cancer?
- How does COPD in working populations affect lung cancer risks?
- At today's exposure level is silicosis a progressive disease?
- With the risk predictions for silicosis at the current PEL, where are the silicotics?

Overview of the key health and exposure issues *(See PPT presentation in annex IV):*

Dr. Rushton gave a brief overview of the epidemiological studies on silica to date. She highlighted six industry sectors where studies have been conducted: Mining, Diatomaceous earth, Pottery, Quarry operations, Refractory bricks, Industrial sand.

The health problems of concern are non-malignant respiratory disease, lung cancer (with/without silicosis), autoimmune disease, and non-malignant renal disease. Dr. Rushton showed the lung cancer relative risk of the different studies for silicotics and for non-silicotics, as well as the dose responses. Dr. Rushton then listed the many challenges faced by epidemiologists when doing a study, e.g. incomplete information on disease assessment, on exposure measurements and assessment, and a series of confounding variables like smoking information or information on other relevant exposures.

Finally, Dr. Rushton defined the goals of the workshops as being the following:

- To gain a clear understanding of the epidemiological studies
- To identify key health outcomes, exposures and confounders
- To compare and contrast the different methodologies
- To define the criteria for an "ideal" study
- To identify possible options for future work.

Summary of epidemiological research on silica to date:

The following summaries are only fragments of the powerpoint presentations shown by the studies' authors at the workshop and we refer the reader to the full presentations in annex IV of this report and to the scientific articles which were published on these studies.

UK Industrial Sand Workers *(Terry Brown)*

Literature:

- Mortality in the UK industrial silica sand industry: 1. Assessment of exposure to respirable crystalline silica. Brown TP & Rushton L, in press, Occup Environ Med.
- Mortality in the UK industrial silica sand industry: 2. A retrospective cohort mortality study. Brown TP & Rushton L, in press, Occup Environ Med.

Cohort: the original cohort, assembled by the UK Health & Safety Executive, contained details of 4749 (4185 men, 522 women, 42 sex unknown) employees and former employees of the company between 1950 and the end of 1986.

Results: the conclusion of the study is that it has not demonstrated any consistent relationship between respirable crystalline silica exposure, in the absence of other known carcinogens, and the development of lung cancer. Dr. Brown explained that it was planned to extend the cohort to include employees after 1985.

North American Industrial Sand Workers *(Janet Hughes)*

Literature:

- Cohort mortality study of North American industrial sand workers. I. Mortality from lung cancer, silicosis and other causes. McDonald AD *et al*., 2001. Ann Occup Hyg; 45: 193-199.
- Cohort mortality study of North American industrial sand workers. II. Case-referent analysis of lung cancer and silicosis deaths. Hughes JM et al., 2001; Ann Occup Hyg; 45: 201-207.
- Cohort mortality study of North American industrial sand workers. III. Estimation of past and present exposures to respirable crystalline silica. Rando RJ et al., 2001; Ann Occup Hyg; 45: 209-216.

Cohort: 2670 men employed before 1980 for 3 years or more in one of 9 North-American sand-producing plants. Of the cohort, 2644 (99%) were traced to 1994.

Results: the main analyses of deaths gave significantly elevated SMRs: tuberculosis 325, non-malignant respiratory disease 169, non-malignant renal disease 254, lung cancer 137; there were 30 deaths from silicosis (among the non-malignant respiratory disease deaths) and 7 deaths from silico-tuberculosis (among the tuberculosis deaths). Allowance was made for both smoking and asbestos exposure.

In her presentation, Dr. Hughes compared the North American sand cohorts of McDonald et al. with the one of Steenland et al. (Lung cancer among industrial sand workers exposed to crystalline silica. 2001; Amer J Epidem; 153: 695-703), showing the lung cancer odds ratios and the exposure estimates of both studies.

US Diatomaceous Earth Workers *(Graham Gibbs)*

Literature:

- Mortality among workers in the diatomaceous earth industry. Checkoway H et al., 1993; Brit J Ind Med; 50: 586-597.
- Reanalysis of mortality from lung cancer among diatomaceous earth industry workers, with consideration of potential confounding by asbestos exposure. Checkoway H et al., 1996; Occup Environ Med; 53: 646-647.
- Dose-response associations of silica with nonmalignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. Checkoway H et al., 1997. Amer J Epidem; 145: 680-688.
- Radiographic evidence of silicosis risk in the diatomaceous earth industry. Hughes JM et al., 1998; Amer J Respir Crit Care Med; 158: 807-814.
- Exposure to crystalline silica, silicosis, and lung disease other than cancer in diatomaceous earth industry workers: a quantitative risk assessment. Park R et al., 2002; Occup Environ Med; 59: 36-43.

+ unpublished reports by Gibbs & Christensen (1994), Hughes & Gibbs (2000)

Cohort: diatomaceous earth workers in Lompoc, California. The cohort is of 2570 white males, 37 black males, 242 white women, 8 black women. 104 white males were excluded because of asbestos exposure.

Results: the first study showed an overall excess lung cancer risk SMR of 1.43 (CI 1.09-1.84). An update to the first study taking into account asbestos exposures as developed by Gibbs and Christensen showed a lung cancer SMR of 1.41 (CI 1.05-1.85). The 1996 follow-up study which included an additional 7 years showed an SMR of 1.29 (CI, 1.01-1.61).

Dr. Gibbs pointed out some issues in the mortality and radiology assessments. In the update study which included pre-1930 exposed workers, asbestos exposure was not adequately taken into account.

British Coal Miners *(Brian Miller)*

Literature:

- The effects of exposure to diesel fumes, low-level radiation, and respirable dust and quartz on cancer mortality in coalminers. Miller B et al., 1997, Institute of Occupational Medicine, Edinburgh, IOM Report TM/97/04.
- Risks of silicosis in coalworkers exposed to unusual concentrations of respirable quartz. B.G. Miller et al., 1998, Occup. Env. Med., 55, 52-58.

Cohort: entire working population of 24 collieries representative of Great Britain's coal field. Data collection began in the 1950s and ran for 30 years.

Results: Dr. Miller highlighted the following mortality results:
- Increased risk with increased exposures
- Pneumoconiosis
- Chronic bronchitis & emphysema
- Stomach cancer
- No clear association with quartz content after dust.

There was an anomaly in the study: one Scottish colliery showed high exposures to quartz and unusual rapid radiological changes. This is due to the fact that the Scottish quartz was freshly fractured.

British Heavy Clay workers *(Brian Miller)*

Literature:
- Cross-sectional study of risks of respiratory disease in relation to exposures of airborne quartz in the heavy clay industry. Love RG et al., 1994, Institute of Occupational Medicine, Edinburgh, IOM Report TM/94/07.
- Risks of respiratory disease in the heavy clay industry. Love RG et al., 1999, Occup Environ Med, 56, 124-133.

Cohort: 18 heavy clay sites, health survey on 1934 workers

Results: very little abnormality was observed.
At the end of his presentation, Dr. Miller specified that both studies could be extended.

South African Gold Miners *(Eva Hnizdo)*

Literature:
- Study 1: Risk of silicosis in a cohort of white South African gold miners, E. Hnizdo & G.K. Sluis-Cremer, 1993, Am. J. Ind. Med., 24.
- Study 2: Silicosis prevalence and exposure response in South African goldminers, Churchyard G. et al., 2003, SIMRAC Report.

Cohort:
- Study 1: Cohort study - 2260 miners exposed 1940-1975
- Study 2: Cross-sectional study - 520 miners - 1978-2000.

Results:
- Study 1: The risk of silicosis increased exponentially with increasing cumulative dose of silica dust. However, the latency period was largely independent of the dose. Dr. Hnizdo showed that the cumulative risk of silicosis agreed with other studies.
- Study 2: The mean respirable quartz was ~ 0.05 mg/m³. The range was entirely below 0.1 mg/m³. The mean quartz fraction was 12 % to 16 %. The 30% quartz assumed by Hnizdo et al. was an overestimate.

Dr. Hnizdo concluded that new evidence from South African studies showed that an exposure limit of 0.1 mg/m³ for crystalline silica was not entirely protective for the prevention of silicosis and other diseases associated with silica dust.

Australian Gold Miners *(Nicholas De Klerk)*

Literature:
Silica, compensated silicosis, and lung cancer in Western Australian goldminers, N. de Klerk, B. Musk, 1998, Occup. Environ. Med. 55

Cohort: 2297 goldminers from Western Australia were examined in 1961, 1974, 1975 and followed up to the end of 1993.

Results: No reported silicosis in Western Australia (after previous standard). People with silicosis have raised rates of autoimmune disease mortality. People with silicosis have raised rates of lung cancer. Some evidence of a threshold for silicosis. The incidence of silicosis was clearly related to exposure to silica and the onset of silicosis conferred a significant increase in risk for subsequent lung cancer, but there was no evidence that exposure to silica caused lung cancer in the absence of silicosis.

Dr. De Klerk presented some further works related to this study such as matching x-rays with morbidity data up to 2002.

Chinese Tin Miners *(W. Chen, J. Bruch)*

Literature:
- Exposure to silica and silicosis among tin miners in China: exposure-response analyses and risk assessment, W. Chen et al., 2001, Occup. Env. Med., 58.
- Nested case-control study of lung cancer in four Chinese tin mines, W. Chen, J. Chen, 2002, Occup. Env. Med., 59.

Cohort: 4 Chinese tin mines. A cohort of 7837 tin miners was followed from 1972 to the end of 1994 and 1091 (14 %) of the miners had died.

Results: Cancer, cerebrovascular and cardiovascular diseases were the main diseases which threatened workers' health and accounted for 68.6 % of all deaths. Dust exposure caused elevated mortality in the four tin mines, especially high SMRs from cancers and pneumoconiosis were observed.
In order to answer the question "are some mixed dust particles more fibrogenic and carcinogenic than others", Dr. Bruch explained that he had studied the toxic and genotoxic effects of dust samples from the 4 tin mines through in vitro tests. The conclusion of the study was that the mineral dusts from the 4 Chinese tin mines cause lower cytotoxicity and cell damage, but induce AM (alveolar macrophage) to release elevated ROS (reactive oxygen species) and TNF-alpha (tumour necrosis factor - alpha).

US Granite Workers *(Michael Attfield)*

Literature:
Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers, M. D. Attfield, J. Costello, 2004, Am. J. Ind. Med., 45, 129-138.

Cohort: 5414 Vermont granite quarry workers employed in period 1950 to 1982. The mortality was followed until 1994.

Results: An exposure-response relationship was detected between cumulative exposure to respirable free silica and lung cancer (and tuberculosis, non-malignant respiratory disease and pneumoconiosis).
45 years of exposure to silica at 0.05 mg/m³ was associated with a lifetime excess risk of lung cancer for white males of 27 cases per 1000. At 0.1 mg/m³, 64 cases per 1000 were predicted.

The observation was made at the workshop that because of anomalies in the reported dose-response relationship, the lowest risk was seen in those with the highest exposure.

US Granite Workers *(William G. B. Graham)*

Literature:

- Vermont granite workers' mortality study, J. Costello, W.G.B. Graham, 1988, Am. J. Ind. Med., 13, 483-497.
- Vermont granite mortality study: an update with an emphasis on lung cancer, W.G.B. Graham, J. Costello, P.M. Vacek, 2004, JOEM, 46, n°5.

Cohort: 5414 workers in Vermont granite sheds and quarries employed between 1950 and 1982, followed up to end of 1996.

Results: the updated study recently performed by Dr. Graham examined the relationship between lung cancer and quartz exposure by comparing mortality in workers hired before and after 1940, when dust controls were introduced and exposures considerably reduced. There were no silicosis deaths in workers hired after 1940 who were exposed in the Vermont granite industry.

Dr. Graham concluded that control of quartz dust below the current OSHA PEL of 0.1 mg/m³ eliminated quartz related disease. Deaths from lung cancer appear not to be related to quartz levels. All cancer deaths occurred in smokers when smoking habits were known.

Finnish Granite Workers *(Riitta-Sisko Koskela)*

Literature:

- Cancer mortality of granite workers 1940-1985, Koskela RS et al., Simonato L & Saracci R (eds.), 'Occupational Exposure to Silica and Cancer Risk', 1990, IARC Scientific Publication No. 97: 43-54.
- Silica dust exposure and lung cancer, Koskela et al., 1994; Scand J Work Environ Health; 20: 407-416.
- Association of silica dust exposure with lung cancer and other diseases [dissertation]. Koskela R-S. 1995, University of Tampere, Acta Universitatis Tamperensis, ser A, vol. 460.
- Silica exposure and rheumatoid arthritis. Klockars M., Koskela R-S., Järvinen E., Kolari PJ, Rossi A. 1987, BMJ; 294: 997-1000.
- Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica exposed workers: an IARC multi-centric study. Steenland, K, Mannetje, A, Boffetta, P, Stayner, L, Attfield, M, Chen, J, Dosemeci, M, DeKlerk N, Hnizdo, E, Koskela, R, Checkoway, H. 2001; Cancer Causes Control, 12: 773-84.

Cohort: 1026 Finnish granite workers hired in 1940-1971. The cohort was followed up to 1993.

Results: Excess lung cancer mortality was found during several follow-up periods. Lung cancer risk increased with the length of exposure and latency. The cancer morbidity and mortality figures of the three different granite areas (black, grey, red), combined with the found differences in biological activity of granite dust and the hypothesis that there is a

cancer-inducing mechanism for ROS, point to a direct role of quartz in cancer induction. This was supported by the results on other malignant and non-malignant potentially silica-induced diseases.

German Stone Workers *(Kurt Ulm)*

Literature:
- Study 1: Silica dust and lung cancer in the German stone, quarrying, and ceramics industries: results of a case-control study, 1999, K. Ulm et al., Thorax, 54, 347-351.
- Study 2: Cohort study among silicotics, 2004, K. Ulm et al., Int. Arch. Occup. Environ; Health.

Cohort:
- Study 1: Non-silicotic subjects employed in the German stone, quarrying or ceramics industries and exposed to crystalline silica. 247 patients with lung cancer and 795 control subjects.
- Study 2: 440 patients with silicosis who were employed in the stone and quarry industry. Compensated for silicosis between 1988 and 2000.

Results of both studies:
- No or low lung cancer risk for non silicotics.
- Increased mortality rate for silicotics.
- Increased lung cancer risk for silicotics.

Dr. Ulm concluded that the prevention of silicosis was the priority by reducing exposures and preventing smoking.

UK Pottery Workers *(Nicola Cherry)*

- A mortality follow-up study of pottery workers: preliminary findings on lung cancer, Simonato L & Saracci R (eds.), 'Occupational Exposure to Silica and Cancer Risk'. Winter PD et al., 1990, IARC Scientific Publication No. 97: 83-94.
- Initial Findings from a cohort mortality study of British pottery workers. Cherry NM et al., 1995; Appl. Occup. Environ. Hyg.; 10: 1042-1048.
- Preliminary analysis of proportional mortality in a cohort of British pottery workers exposed to crystalline silica, McDonald JC et al., 1995; Scand J Work Environ Health;21: 63-65.
- A cohort mortality study of British pottery workers, Cherry NM et al., 1996; Appl. Occup. Environ. Hyg.; 10: 1042-1048.
- Crystalline silica and risk of lung cancer in the potteries, Cherry NM et al., 1998; Occup Environ Med; 55: 779-785

Cohort:
5115 men born 1916-1945 and employed in the pottery, refractory, and sandstone industries of Stoke-on-Trent.

Results: The findings from this cohort study show that men working in the pottery industry had more deaths than expected from lung cancer and non-malignant respiratory disease compared with the national population, or to a lesser extent, that of Stoke-on-Trent. Moreover, from the nested-case referent analysis, it seems that lung cancer was strongly related to the mean concentration of silica to which men had been exposed even after allowing fro smoking and duration of exposure. These findings indicate that exposure to crystalline silica, at least in this industry, carried an increased risk of lung cancer. Dr. Cherry concluded her presentation by listing the strengths and the weaknesses of this study. Allowance was made for both smoking and asbestos exposure.

Chinese Miners and Pottery Workers *(Weihong Chen-Frank Bochmann)*

Literature:
Mortality among dust-exposed Chinese mine and pottery workers, Chen W *et al*. 1992; J Occup Med; 34: 311-316.

Cohort: 74078 workers (51422 exposed workers). Employees worked for at least 1 year between 1960 and 1974 in the 29 Chinese mines/factories.

Results: Lung cancer risk showed limited/modest association with cumulative silica exposure. Other occupational hazards seem important in carcinogenesis of lung cancer. Risk of lung cancer increased among silicotic subjects in some mines, but not in others. Clear exposure-response relation was detected for silicosis and cumulative silica dust exposure. The characteristics of silica dust may affect the risk of silicosis.
Dr. Chen explained that it was planned to extend the follow up of this Chinese cohort to the end of 2003. She also presented the first results of a new nested case control study for lung cancer.

Italian Refractory Brick Workers *(Franco Merlo)*

Literature:
- A cohort study of workers employed in a refractory brick plant, Puntoni R *et al*. 1988; Tumori; 74: 27-33.
- Mortality among Italian refractory brick workers exposed to Si O_2, Merlo F *et* al. 2002; Medicina del Lavorro; 93: S31.

Cohort: 1050 Italian refractory brick workers from 1950 to 1987, and updated to 2000.

Results: Increased mortality from non-malignant respiratory diseases and a dose dependent relationship were observed only in workers hired $\leq$ 1957, suggesting that poor environmental conditions have entailed exposure to silica dust that were relevant to workers health. This may explain also the excess mortality from lung cancer that was observed again only among workers hired $\leq$ 1957. However, the increased mortality from mesothelioma casts some doubt on the possibility that silica exposure alone may

be responsible for the excess mortality from lung cancer observed among these workers.

Italian Graphite Rod Workers *(Franco Merlo)*

Literature:
A mortality cohort study among workers in a graphite electrode production plant in Italy, F. Merlo et al., 2004, Occup. Env. Med., 61.

Cohort: 1291 males employed between 1950 and 1989 in an Italian graphite electrode production plant.

Results: Results support the association between excess mortality from silicosis and occupational exposure to siliceous sands experienced during graphite electrode manufacturing. The observed excess from liver cancer may be due to exposures to phenolic and furfuryl resins treated products, although a role of lifestyle factors and viral infections cannot be excluded.

Thursday 5 August, Afternoon Session

Overview of design issues:

Exposure Assessment *(Dirk Dahmann)*

Dr. Dahmann identified the key aspects of Exposure Assessment which are of particular relevance to the design of silica studies as being occupational settings, sampling and analytical procedures, sampling strategy, and plausibility checks.

1. **Occupational settings key questions**

- Exactly what species of silica did the exposure consist of?
- What types of technical processes were used?
- How did these processes develop over time?
- What "relevant" species of co-exposures (workplace confounders) were present?
- How do the settings differ (homogeneity of the data)?

2. **Sampling and analytical procedures key questions:**

Sampling:

- Which type of sampler(s) were used (complete description of the technical equipment/processes)?
- How do these samplers comply with modern standards (respirable dust)?
- If they don't, can "conversion" be done (or do the actual samplers behave "erratically")?
- If conversion is possible, how was it done in the studies?

-

Analytical procedures:

- How has the content of crystalline silica been determined (especially the content in the respirable fraction)?
- How have the historical data been converted into modern (correct?) ones?

3. Sampling strategy key questions:

- Was a complete description of the actually applied sampling strategy given?
- How could that strategy be converted into eight hour shift data?
- How could these data be converted into lifetime exposure doses (number of shifts per year, actual shift lengths)?

4. Plausibility questions:

- Have efforts been made to check plausibility of the exposure assessment?
- How was the plausibility of the exposure levels checked during the process?
- How well are all the steps of exposure assessment documented?
- Would "an educated reader" be able to perform a plausibility check by using the published exposure data?
- Could the published data be used for a sensitivity analysis during the mathematical modeling (estimation of data uncertainty!)?

Physico-chemical features of the dust *(Bice Fubini)*

Overview of the basis of the "variability of crystalline silica hazard"

Dr. Fubini explained that since the IARC classification, new studies addressed the variability of the crystalline silica hazard and demonstrated the crucial role of the particle surface. According to Dr. Fubini, the inconsistence between the epidemiological studies might reflect differences in silica sources.
She insisted that only some silica particles, when inhaled, are pathogenic. She then summarized what we know in terms of adverse physicochemical features from experimental studies:

It is known that not all silica dusts are equal and the variability among surface modified samples may even exceed the variability among different polymorphs. Dr. Fubini presented the results of a European commercial quartz dusts experimental project (Bruch, Borm, Fubini labs) consisting of in vitro and in vivo tests on 16 samples from commercial quartz dusts of different origin. One of the conclusions of this study is that even if a complex interplay exists between cell responses and physico-chemical features, one single surface modification may inhibit several biochemical reactions generated by different surface sites.

Dr. Fubini summarized the physicochemical characteristics relevant to toxicity as being the following:

- Freshly fractured versus aged surfaces
- Particle generated free radicals
- Iron ions as contaminants
- Association with clay
- Pure silica surface vs aluminium covered
- Polymer coating e.g. PVNO
- Hydrophobic vs hydrophilic surfaces
- H-bonding to membranes

These relevant properties were mostly confirmed in vitro and in vivo.

Which physicochemical features should be considered, if possible, when examining exposures in epidemiological studies?

1. *For all kind of silica sources:*

   Collect information on crystallinity, respirable size, origin of comminution and procedure, extent of exposure to freshly fractured respirable particles, associated minerals and chemical compounds, average chemical composition of the dust up to 1%.

2. *For miners' studies (gold, tin, coal, Chinese mines and pottery):*

   Collect information on associated minerals, chemical composition, methods of extraction, exposure to freshly fractured fine dust.

3. *For granite and stone workers' studies*

   Collect information on kind of granite, define stones, assess associated minerals (clay, iron oxides, aluminium compounds), wet or dry grinding, freshly ground exposure, quarry workers vs shed workers.

4. *For industrial sand and diatomaceous earth workers' studies:*

   For sands, collect information on origin of sand, % crystalline silica, chemical composition, associated minerals, working procedures.

   For diatomaceous earth, collect information on chemical composition (residual impurities from original diatoms), % crystalline silica, processing procedures, stages in which exposure occurred.

5. For pottery and refractory workers' study:

   Collect information on kind of pottery, materials employed, development of crystallinity during processing, stage at which exposure occurred, re-grinding failed products customary.

Dr. Fubini concluded her presentation by stating that a multidisciplinary approach was required for silica studies.

Confounding Factors *(Patrick A. Hessel)*

Dr. Hessel explained that confounding factors are important because, in his opinion:

- Silica-cancer studies are inconsistent
- Silica-cancer exposure-response relationships have generally not been found
- Smoking is a strong risk factor for lung cancer
- Manual workers tend to smoke more and lifestyle may differ from the general population
- In silica-cancer studies, when risks are elevated, they are generally modestly elevated

Dr. Hessel gave the examples of four studies – Chan et al. (2000), Carta et al (2001), Kjaerheim et al (2002), Checkoway et al. (1997) – where the link between **smoking and lung cancer** was addressed. Regarding the link between **silicosis and smoking**, Dr. Hessel explained that out of 13 studies, 11 had shown a positive association, 1 no association, and 1 a negative association. So smoking is a clear confounding factor.

Another confounder are the **short-term workers**. Short-term workers are at increasing risk of having lung cancer. The **socio economic status**, i.e. the social class differences, is also a determinant factor. Dr. Hessel believes that **poor lung function** is also a risk for lung cancer even after controlling for smoking.

Dr. Hessel concluded that it was important to consider confounding factors in studies of occupational lung cancer. Recent studies of silica, silicosis, and lung cancer have been better at this. Research efforts should focus on the multiple factors that impact lung cancer risk in workers exposed to silica and other substances

Health Outcomes (*J. Corbett McDonald*)

Dr. McDonald identified the relevant health outcomes in epidemiological research and listed the sources of potential bias for each type of outcome in mortality studies, and in morbidity studies.

First outcome: **respiratory diseases**; e.g. pulmonary fibrosis, chronic obstructive pulmonary disease (COPD) and lung cancer.
Potential biases in mortality studies for respiratory diseases include registry data, coroners' reports, diagnoses by local physicians, existence of silicosis/NMRD, re-coded death certificates, autopsy findings and non-comparability of the referent base.
Sources of potential bias in morbidity studies include x-ray readings (are they blind, independent and with controls), function tests (are there controls), lack of information on smoking habits.

Second health outcome: **immunological diseases**: e.g. arthritis, renal disease, etc.

In mortality studies, it is difficult to determine whether immunological mechanisms were an underlying or an associated cause of the death; case-referent bias is also potentially important.
In morbidity studies, the cases of immunological diseases may be poorly identified, or case series unrepresentative.

Dr. McDonald mentioned other possible sources of bias such as lack of prior hypothesis, lack of information on exposure intensity, and insufficient allowance for socio-economic/health factors.

Statistical / Data Analysis Methodology (Janet Hughes)

According to Dr. Hughes, the main issues in statistical/data analysis are:
- Sufficient sample size and power
- In matched designs, retain matching in analyses
- Regarding SMR's, comparison population is important, as well as having regional (State, provincial?) rates
- Some adjustment for important covariates are important (smoking and lung cancer)

Dr. Hughes underlined that the health outcome can develop after the person ceases exposure.
So for Mortality, a sufficient follow-up should be ensured. For Morbidity (e.g. silicosis), studies of active workers may be inadequate.
When we want to include inactive workers (retirees/left), it is difficult to track and obtain participation, you may introduce possible bias and its is difficult to assess potential bias.

Another issue is that the risk in relation to cumulative exposure is not sufficiently informative for setting exposure standards.
Dr. Hughes asked the question: Is 40 years' exposure to 50 µg/m3 equivalent to 20 years at 100 µg/m³?

The effects of exposure duration and of exposure concentration (problems of sample size, follow-up time) should be separated.

Dr. Hughes insisted on the importance of validating exposure estimates but acknowledged that it was difficult. Relationship with known exposure-related outcome validates exposure estimates ordinally.

Dr. Hughes concluded her presentation with two unanswered key questions:

If crystalline silica is a human lung carcinogen:

- Are exposure levels that are sufficiently "safe" regarding development of silicosis also safe regarding lung cancer?
- Is exposure-induced lung cancer a consequence of lung fibrosis?

Separate Working Groups:

The participants divided into three separate groups to consider silica exposure experienced in:

- Diatomaceous earth (DE) and silica sand industries
- Stone, granite, quarrying, pottery, brick industries
- Mining

The groups were asked to discuss the following key questions where applicable and if time allowed:

1. What are the findings from the epidemiological studies and how do they vary?
2. How do the studies vary by:
   - Design
   - Health outcomes studied
   - Exposure data covered
   - Exposure assessment methodology
   - Confounding and other data collected
   - Statistical methodology
3. Do you agree with the interpretation of the findings?
4. Where are the knowledge gaps?
5. What are the key questions that need addressing?
6. How should the gaps be filled and the questions answered?
   - Review?
   - Pooled/meta analyses?
   - Expansion of current/on going studies? (Extension of cohorts, nested case-control etc)
   - New studies
   - Other?
7. What would be the optimal study design?
   - Design
   - Industry(ies)
   - Health outcome(s) data
   - Exposure measure(s)
   - Exposure assessment methods
   - Confounding/other data
   - Statistical methodology
8. What is achievable?

Friday 6 August, Morning Session

Reports from the Working Group

Diatomaceous earth and silica sand

Diatomaceous earth industry

The working group identified five main issues of concern with these studies:

- Exposure assessment
- Smoking
- Lagging of exposure
- Interpretation of chest radiography
- Morphology and distribution of cristobalite

They concluded that a key issue was the percentage of cristobalite present in the bulk product and were concerned about lack of knowledge about this and the reliability of measurements, particularly where the proportion of cristobalite was small. They identified three areas of uncertainty in the exposure assessment methodology used in these studies that might have lead to exposure misclassification. These were: the conversion factors used for converting total dust counts to respirable crystalline silica; the extrapolation methods used for exposures prior to 1950; and the lack of adjustment for calcining for exposures before 1930. They also drew attention to the potential effect of co-exposures to asbestos on the lung cancer risk estimates and the fact that this issue was not addressed in all studies. Exposure assessment errors would not effect the shape of the dose-response but could impact on its use for risk assessment, for example, for selection of a limit such as an occupational exposure limit.

The working group noted that smoking information was only available in the DE studies on 50% of the study populations. They were concerned that there might be an interaction between smoking and silica exposure, particularly at high levels of exposure.

Many of the studies report results from analyses in which the exposure is lagged by different periods, with 15 years being most often used. The working group agreed that lagging was acceptable based on biological plausibility. They suggested that it would be preferable to report analyses for several different lag periods.

The group also discussed an unpublished report by Gibbs and Hughes that suggested little to no excess risk in the workers hired after 1950. The numbers were small however leading to a lack of statistical significance. The group thought that this cohort was worthy of future study to increase the numbers; to see if the same trend held up; and to see if it could give some insight into the threshold level for silicosis and/or lung cancer.

With regard to the interpretation of chest radiography the group discussed the difficulty in separating small round opacities from small irregular opacities. No differentiation had

been made between these in the DE studies. It was suggested that this issue could be examined by comparing miners, in whom one might expect irregular opacities, and with DE workers, in whom one might expect rounded opacities. It was pointed out that it might be difficult to identify workers who only mined and had never worked with calcined DE.

The group concluded that it would be useful to know how cristobalite is distributed within particles of calcined DE and also how it is distributed in various size fractions of DE dust.

Silica sand

Exposure assessment and the origin and composition of the sand were identified as important issues in the studies of silica sand workers.

Different studies had used different conversion measures for conversion of particle counts to respirable crystalline silica gravimetric concentration. For example, Sanderson's study of industrial sand workers used 100μg/m^3 per mppcf and Rando's study used 276μg/m^3 per mppcf. This three-fold difference was paralleled in a three-fold difference in the dose-response results for lung cancer between the two studies.

There was a lack of exposure data in the studies prior to the 1970s and the working group drew attention to the potential uncertainties that might have occurred through the use of extrapolation methods to estimate past exposure.

The group stressed that the origin and composition of the sand might have affected the study results. In the North American studies some sands were almost pure quartz, others were dune sands or feldspar sands. There was a difference in the aluminium content between the UK and US sands. The group questioned whether these sands caused a different biological activity. Other participants also commented that dusts may differ in chemical composition, physical characteristics, cytotoxicity and clearance.

The DE and Silica sand working group made the following recommendations:

1. New focus on currently relevant exposure levels
2. Develop more robust count to gravimetric conversion factors base on side-by-side sampling in industrial sand industry
3. Examine dose-response in terms of threshold of effect and progression of disease after cessation of exposure
4. Enhance efforts to follow-up on retirees from industry
5. Gather existing and develop new information on use of respiratory protective equipment: frequency of use, workplace protection factors (important for future studies)
6. Encourage international standardisation of sampling and analytical methods
7. Identify new study populations that are large and have had long exposure (Europe, China?)

Mining

The working group discussed the question:

Can we use the results from studies of miners to set standards for (a) silicosis (b) lung cancer?

They considered that the advantages of the studies of miners were that they have

- Large cohorts with a stable workforce
- Comprehensive exposure data
- Special health programs and surveillance leading to good follow-up.

However the disadvantages were that they may have co-exposures, such as radon, asbestos and polycyclic aromatic hydrocarbons. The studies also report results from mining in different settings such as gold, coal, uranium.

They identified knowledge gaps in exposure data and health outcomes. With regard to the exposure the group agreed that there was a need for:

- A comprehensive description of the exposure data in the studies and an attempt to explain variation and differences
- Determination of the size and composition of the particles, including the quartz content and respirable fractions
- Development of a job exposure matrix and validation of this against measured values
- Collection of historical data

With regard to health outcomes the group agreed that there was a need to:

- Analyse the data for lung cancer by histological subtype
- Investigate the problem of missing cases of silicosis through misclassification or underreporting
- Explore the relationship between silicosis, lung cancer and other lung diseases such as chronic obstructive pulmonary disease (COPD).

The group suggested that the Chinese cohorts might offer an opportunity to study genetic differences in metabolism of xenobiotics and disease related pathways relevant for determining potential threshold levels. They drew attention to the need to ensure that cohort study populations are followed up outside the silica industry. The group suggested that pooling data from different studies might be hindered by heterogeneous exposure measurement methods. They supported the use of animal and in vitro studies to investigate the toxicological potency of different substances. They suggested that several of the cohorts of miners might be of potential use for future research. They stressed, however, that any study would need good exposure measurement data, the development of a JEM and reliable information on smoking and other confounders.

Workshop participants from other working groups also raised several point concerning the studies of miners. It was suggested that it would be useful to investigate intensity and peaks of exposure in addition to cumulative exposure. There was some discussion about whether there should be different limits for different industries, given that there appeared to be varying risks. Participants from industry and regulatory authorities outlined the difficulty in administering this and stated that pragmatic values applicable across all industries were preferable, although this has been done, for example, in the cotton and metal industries. It was stressed that, although much of the workshop discussion had focussed on issues related to exposure measurement and assessment, there also needs to be close attention paid to the collection of accurate data on confounders.

Stone, granite, quarrying, pottery and brick industries

With regard to studies of workers in the pottery, brick and carbon electrode industries the working group commented that the studies were mainly cohort studies and that the findings regarding silicosis and lung cancer varied. It was highlighted that there was a potential problem with co-exposures in these industries, in particular to heat sources, products that had undergone heat processes, metals and other chemicals and fumes such as polycyclic aromatic hydrocarbons.

The studies used different exposure sampling regimes, analytical methods and conversion factors and exposure measurements were made for different reasons. There had also been considerable changes over time in these industries. It was perhaps not surprising, therefore that the studies had reached different conclusions. The group emphasised that it was important to identify clearly potential sources of bias.

In future, the group recommended that more consideration should be given to identifying task specific intensity measurements and estimating the pharmacokinetic dose to tissues. It was suggested that it might be possible to collect more data to supplement and amend the exposure assessment for current cohorts. It was pointed out that, although there had been great improvements in exposure levels in the UK and US, exposures still remained high in developing countries.

With regard to the studies of stone, granite and quarry workers, again the working group drew attention to the variations between studies. For example, in the two studies of granite workers in Vermont, not only were there different results and conclusions but there were differences in timing of exposure, intensity and the relevant exposure metric used. The investigators of these two studies expressed an interest in collaborating to investigate and clarify the differences. The group discussed the issues of survivor populations and susceptibility. For example, in the Chinese studies there is a high incidence of non-malignant respiratory disease at an early age which has the impact that the lung cancer risk at older ages is found in a survivor population. The working group identified smoking as a major confounder but pointed out that, unlike the pottery and brick industries, there were few other co-exposures.

For all the industries considered, some participants felt that it was not necessary to review the literature again and were not in favour of a pooled analysis. However, it was

suggested that there could be opportunities to expand some of the ongoing studies. For the granite studies further analyses could be carried out, particularly considering other exposure metrics. A new case-control study based on the recent update of the UK pottery industry study and refining the exposure assessment could be considered. The Chinese pottery study could also be expanded to evaluate newly collected data.

It was suggested that new studies could be initiated including tunnel workers, construction industry workers (Dutch and Swedish cohorts were mentioned) and glass and ceramics workers (Germany). Studies of co-morbidity, i.e. occurrence of disease patterns in relation to the duration of follow-up, disease sequences, and disease combinations could be investigated. Also outcomes due to multiple exposure, for example exposure to silica and aluminium could be investigated. Genetic marker studies could also be considered.

Workshop participants from other working groups also commented on these studies. There was some dispute as to whether further refining of the exposure assessment would remove differences between studies. It was suggested that the quality and amount of exposure data should drive decisions regarding quantification of exposure assessment and the choice of exposure metric.

Friday 6 August, Afternoon Session

The main aim of this afternoon discussion was a free discussion by experts to give guidance to industry on future priorities.

At the beginning of the discussion, two priority areas that needed to be addressed were identified by most participants:

- "In what industrial settings, if any[2], does silica exposure at current compliance levels, essentially at established 'Western (US, EU)' limits, cause cancer?"

- What is the dose-response relationship between silica and silicosis/lung cancer?

The credibility of the meeting would be greatly enhanced by taking this approach, rather than addressing the simpler question "Does silica cause lung cancer?" An examination of these more detailed areas would enable the role of silicosis in the development of lung cancer to be identified, and the influence of co-exposures could also be investigated. In addition, it was mentioned that the progression of disease, especially silicosis, after cessation of exposure should be investigated more.

During their discussions the working groups had raised many issues and identified gaps in the current knowledge that needed to be addressed, and that it was anticipated would also be relevant to addressing the two priority areas above. These issues could be

[2] in review of the proceedings, participants and observers from NIOSH wished to note that inclusion of the words 'if any' in the summary statement is arguably at variance with the IARC statement on silica carcinogenicity and is inconsistent with the published NIOSH policy on silica and lung cancer.

grouped under the headings exposure assessment, health outcomes and surveillance, toxicology, and methodology. The main points from the afternoon's discussion have been collated under these headings.

Exposure Assessment

From the discussions of the three working groups, it appeared that exposure measurement and exposure assessment were main areas of uncertainty in studies to date. This included how samples were collected and analysed, and the metric used to express the exposure, particularly with regard to the factors used to convert dust counts to gravimetric values.

There did not appear to be coherence between the various studies on how dust samples were measured, i.e. the equipment used and whether any formal protocol had been developed for their collection. However, because studies retrospectively assessed exposure, they had little control on how historical dust measurements had been collected, whether they were dust counts or gravimetric samples, the analytical method used (e.g. infra-red spectrophotometry, X-ray diffraction, dust counts), and whether the quartz content was measured. Questions were raised about the correct factor to use to convert dust counts to gravimetric figures. For some cohorts within the same industry, the use of different conversion factors and different exposure metrics to assess exposure had contributed to the differing results. It was suggested that there was a need to determine why this occurs and that the research groups should work together to discuss their exposure assessment methods and how these vary, then come to an agreement on the optimum metric to use or develop a new standard one. Some participants suggested that more work was needed on side-by-side measurements of dust counts and gravimetric measurements to develop better more reliable conversion factors.

There was some discussion about how comparable the various studies are in other aspects of exposure assessment. Are there similarities within the industries studied or between each industry, e.g. work practices, job titles, construction of the job-exposure matrix, etc., that would allow comparisons to be made, and also allow the data to be pooled into one large database?

Alternatively, are there differences that would lead one to decide not to pool data, and could explain why different results are observed (mortality rate, dose-response relationships, etc.)? For example different estimates of risk were obtained in some of the sand studies, although job titles are broadly similar across the industry.

The identification of key areas that differ between studies, e.g. quarrying process, or methodological procedure, would be useful to provide an explanation of the different results. It was suggested that researchers could consider making their exposure databases available to other authors if requested.

Some participants were of the opinion that the main role of the collection of exposure measurements was not primarily for epidemiological research, but as part of health

surveillance. There is a need to carry out repeated personal sampling, which should be performed periodically on workers, for example, as carried out in China. Any anomalies (too high/too low) should be acted upon as soon as possible to prevent any adverse health consequences. Standard evaluation tools for monitoring data could be derived from the literature by undertaking a systematic review.

Specific protocols need to be developed and introduced, for example, similar to that developed by the Industrials Minerals Association (IMA) in Europe[3], which aims to develop a harmonised dust monitoring strategy for its members.

IARC[4] have stated that "crystalline silica inhaled in the form of quartz or cristobalite from occupation sources is carcinogenic to humans (Group 1)". Participants suggested that IARC were more concerned with hazard identification rather than the establishment of occupational exposure limits. However, what industry and regulators want is to see is a safe level of silica exposure which can protect against silicosis which would then probably protect against lung cancer. Unlike asbestos, circumstances of silica exposure vary across industry and this is not taken into account by regulators. Is it possible to set a level that would protect health and be technically achievable within industry? For example, in Germany the current limit is 0.15mg.m^{-3} as an 8-hour time-weighted average. It was mentioned that legislation to lower this limit would not be practical for industry, and would mean the closure of many companies. Some suggested, therefore, that there may be situations where the lowering of dust levels to a 'safe' level would be impossible to achieve, because the nature of the substances being mined/quarried. There was a discussion as to what to do in these situations. For example, should respiratory protective equipment be taken into account when establishing an occupational exposure limit?

Some participants agreed that methodology should be developed for taking account of the introduction of mechanical and engineering controls in any exposure assessment, whether for epidemiology, compliance or regulatory purposes. However, few studies take into account the use of respiratory protective equipment (RPE) in their assessment of exposure. This is important because RPE can drastically reduce the amount of respirable dust reaching the lungs.

All existing and future studies need to address this issue and gather any available information on the use of RPE, so that workplace protection factors can be calculated and incorporated into a job-exposure matrix.

[1.] Auburtin G, Meunier F, eds. IMA. *Industrial Minerals Association Hygiene Project: Standardised Dust Monitoring Protocol.* Brussels: Cnam-IHIE/Industrial Minerals Association (Europe), 2002.

[3] Auburtin G, Meunier F, eds. IMA. *Industrial Minerals Association Hygiene Project: Standardised Dust Monitoring Protocol.* Brussels: Cnam-IHIE/Industrial Minerals Association (Europe), 2002.

[2.] IARC. *Silica, Some Silicates, Coal Dust and para-Aramid Fibrils.* Lyon: International Agency for Research on Cancer, 1997.

[4] IARC. *Silica, Some Silicates, Coal Dust and para-Aramid Fibrils.* Lyon: International Agency for Research on Cancer, 1997.

In most studies there is a lack of detailed job description for each separate job for which exposure assessment is being carried out. IMA have developed descriptions for 11 practical job titles for the 8 associations (about 180 companies) they represent.

During the discussion a number of other issues were raised. Concerning the development of a harmonised dust monitoring scheme one key question is what is the target population? Should it be small-to-medium sized enterprises, where in most industries the highest exposures occur, or larger companies? Participants also agreed that we need to be aware of the testing and storage of samples, the archiving/retention of data, its accessibility and linkage with other information, for example on personal health outcomes.

Health Outcomes and Surveillance

There was debate as to whether efforts should be concentrated on finding whether there is a definite link between silica exposure and lung cancer, or on intervening to prevent other diseases like silicosis, non-malignant respiratory disease, autoimmune and renal diseases?

It was suggested that, in general, industry should develop better health surveillance systems for their employees, although individual companies would have to make their own decisions concerning this. The health surveillance should include lung function tests, x-rays, medical examinations, and the taking of smoking and occupational history. These could be costly but the frequency with which these examinations take place would depend on the age of the individual and when they entered the industry. The data from these would need to be integrated with other personnel, health and exposure data systems, and quality assurance checks carried out regularly. Discussions within companies would be needed to undertake this, and there must also be worker cooperation and acceptability. Health surveillance of current employees could be used to detect unexpected patterns of disease and sickness absence and inform the development of risk reduction strategies. However, problems arise in monitoring ill health after workers leave employment or retire, and most of the silica industry does not have a standardised method of monitoring the health of leavers, with the exception of death and cancer incidence for which many countries have national tracing systems that can be used.

A number of participants questioned whether there was a way of testing for people who were sensitive to dust, for example, looking for early indicators of lung damage or testing for a lung reaction before any changes occurred at the cellular level? One suggestion was that changes in the exhaled air could be monitored. Non-invasive biomarkers of exposure and/or outcome could also be developed for use, as could markers of inflammation.

Participants discussed the type of surveillance system that could potentially be used to look at silicosis. Registers do exist, but it was not known how good they are for identifying all cases. Silicosis is often not entered on death certificates as a contributory cause of death. Another problem with looking at silicotics is the misclassification of

diagnosis and the varying criteria used between countries. There is a need for improved radiological diagnosis of silicosis; a negative chest X-ray does not indicate the absence of pathologically demonstrable silicosis. Peter Morfeld's study of German coal miners will investigate the issue of the sensitivity and specificity of the diagnosis.

It was mentioned that there was a need to develop practical and effective methods to reduce and to prevent non-malignant respiratory disease (NMRD). NMRD, especially chronic obstructive pulmonary disease (COPD), needs to be studied over time with lung function tests. Death certificates cannot be relied upon to identify cases especially if an intervention is required. It was suggested that a morbidity index could be developed which identified early indicators of lung damage. Lung function tests were suggested as simple measurements but some participants questioned their practicality whereas others mentioned their use in many other industries/occupations. It is likely that most of the studies carried out on the effects of silica have, to some extent, historical records of lung function and also x-rays that could be examined in more detail. The availability of medical records could allow a more thorough examination of health issues in relation to silica exposure and hopefully examine the effects of smoking history on health outcomes.

The researchers present at the workshop suggested that this information is available for workers in diatomaceous earth, Vermont granite, Scottish coalmines, US industrial sand, Finnish granite, and Chinese mines.

Morbidity studies of renal effects of silica could also be undertaken by looking at clearance rates, but the substances to be used need clarification, and this cannot be done retrospectively. In Australia they are attempting to look at renal effects of silica exposure using hospital admission data.

It was suggested that it would be helpful to know the aetiology of lung cancer in the community, especially around the industry in question. Examination of birth cohorts could identify the groups at risk of lung cancer and other diseases. If the smoking habits of the community were also known this type of community study could be useful for investigating the relationship between smoking and the general lung cancer incidence. This could aid the interpretation of results from cohort studies where smoking data are not available.

Toxicology

A number of participants stressed the importance of characterising dust, because any dust <10µm in diameter will enter the lung and cause an inflammatory response. There was a discussion as to whether total dust or the silica component is important, as macrophages do not distinguish between the two. Good *in vitro* toxicological studies are needed that examine the effects of 'real' sands or 'real' life samples of crystalline silica on human cell cultures, as opposed to purer laboratory specific samples. Currently dusts like Min-U-Sil are used in tests but are not truly representative of the actual exposures experience by silica workers. *In vitro* studies avoid the difficulty of extrapolating results from rat studies to humans. Dusts from all current and future

cohorts should be characterised by their toxicological, morphological and chemical features. There is a need for simple, authentic and repetitive cellular tests to measure genotoxicity and inflammatory response, i.e. number of macrophages produced in response to silica exposure. The physicochemical and surface characteristics also need investigating, as does the potential to generate free radicals. There is a need to be able to investigate the biological plausibility of dust retention in the lungs. The results from these tests could then inform and help interpret the epidemiological results, for example, explaining why some studies give conflicting results, and assist in the design of exposure assessment methodology. It was highlighted that the potential effects of different types of silica can be detected in the sand studies, where deposits at different quarries varied and may be the reason that differing patterns of disease were found.

Studying different silica dust types could help to determine whether they lead to the development of different histological sub-types of lung cancer, and whether these sub-types have different latency periods. Genetic susceptibility to different dusts could also be investigated.

Methodology

There was a discussion about the appropriateness of the epidemiological methodology used to study the health consequences of exposure to silica. Nearly every study had been a historical cohort study, which can be very expensive to undertake and long term, and poor at detecting rare diseases. Some participants agreed that, for each study a protocol should have been developed and approved by a panel, data abstracted in a standard format, analysed and a report written. It was also suggested that it is best to consult with independent experts to provide advice during the study.

The construction of the various cohorts studied differed to some extent, and a few people especially questioned the application of a minimum employment period before entering the cohort, e.g. two sand studies used one-year whilst the other used six-months. It was stressed that standard cohort analysis usually applied a one-year absolute minimum.

Some participants suggested that high historical exposures may have had an undue influence on their results, partly because the measurement techniques in use at the time may have been less accurate than current methods. In some studies measurements were not available and had to be estimated, for example, by regression analysis. It was suggested that a re-analysis of the data from each cohort, excluding subjects starting work when exposure were “high”, e.g. 1920s/1930s, when exposure measurements are expected to be unreliable, might be a useful exercise. Alternatively, data could be analysed by year of hire for each study.

A number of people were uncomfortable with the use of the case-control approach as an alternative to a cohort study, but others were of the opinion that this was ideal for studying the rare diseases that have been linked with silica exposure. Nested case-control studies would enable detailed data on exposure, medical and job histories to be collected for a small number of individuals rather than the whole cohort, saving time and

money. In addition, occupations before joining and since leaving the industry could be investigated.

Some of the diseases of interest, e.g. silicosis, autoimmune disease, etc. are rarely coded on death certificates, so would not be detected in cohort studies and would therefore require the use of other sources of information such as registers of silicosis patients.

The issue of confounding was discussed, with smoking being particularly important in any study of lung disease. Co-exposures should also be considered, especially in mining industries.

There was a discussion about whether pooling data had any advantages and if it could answer any outstanding questions. It was suggested that the advantages of pooling data are that it increases the statistical power and that confounders can be treated in the same way, because the raw data is being used. The former also applies to meta-analytical approaches. Pooling enables the researcher to carry out a risk assessment and assess the exposure. It enables cases to be selected more specifically by defining the exact ICD code for the cause of death, or, if investigating silicosis, using specific ILO diagnostic criteria.

It also allows the incorporation of new exposure data and development of a larger JEM, although this can be problematical if exposure has been assessed differently by the studies being included in the analysis[5]. However, data pooling may entail a large amount of work, and simply combining together data from many studies without consideration of potential sources of heterogeneity could produce misleading and imprecise results.

A detailed protocol is thus required for pooling and each study must satisfy specified criteria for both diseases and exposures. Some studies were omitted from the IARC pooled analysis study for this reason[6]. Out of about 600 studies reviewed by IARC, only nine cohorts of workers in gold mining, stone, granite, diatomaceous earth, refractory brick, and pottery industries in the United States, several European countries, and China, and cohorts of registered silicotics from North Carolina, United States and Finland provided the least confounded examinations of an association between silica exposure and cancer risk *(see IARC Monograph Volume 68, page 207)*. The question was posed as to how many more studies could now be included in any new review, and was their inclusion likely to affect the previous conclusions.

[3.] Mannetje A, Steenland K, Checkoway H, *et al.* Development of quantitative exposure data for a pooled exposure-response analysis of 10 silica cohorts. *American Journal of Industrial Medicine* 2002;**42**:73–86.

[5] Mannetje A, Steenland K, Checkoway H, *et al.* Development of quantitative exposure data for a pooled exposure-response analysis of 10 silica cohorts. *American Journal of Industrial Medicine* 2002;**42**:73–86.

[4.] Steenland K, Mannetje A, Boffeta P, *et al.* Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes & Control* 2001;**12**:773–784.

[6] Steenland K, Mannetje A, Boffeta P, *et al.* Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes & Control* 2001;**12**:773–784.

Summary of Priorities for the Future

From the various presentations and discussions, EUROSIL (organisers of the workshop) identified eight priorities for the future:

- Effectively control workers' dust exposure and implement proper evaluation and prevention measures.
- Harmonise sampling and analytical methods for future collection of dust measurements and develop a standardised job/task industry wide Job Exposure Matrix.
- In parallel, collect information on the type and use of personal protective equipment and develop the methodology for incorporating this into the JEM and future exposure assessment.
- Investigate the toxicological potency of different types of silica.
- Focus on industries with similar exposures and review the differences that may have given rise to different estimates of risk.
- Consider whether pooling of the data might be useful and investigate what this might entail, e.g. development of a harmonised JEM and exposure assessment methodology, bearing in mind that indiscriminate pooling might give misleading and imprecise results.
- Consider whether current cohorts might be able to re-analyse their data to address the 2 priority areas of concern and/or whether they can collect supplementary data to assist with this.
- Alternatively carry out a new study(ies) but ensure that there is an agreed protocol and a design that ensures knowledge gaps will be filled. A steering group should be appointed to oversee the process.

Closing remarks

Mrs. Wyart thanked the participants for having accepted the invitation and travelled sometimes very long distances to attend a Workshop whose objectives were unclear for some at the beginning. She thanked all scientific experts for their active participation in the working session and in the Workshop's discussion, with a special gratitude for those who accepted to act as moderators, speakers and rapporteurs. Without the experts' contribution, the workshop would not have been what it was, i.e. efficient, open and conclusive. Mrs. Wyart underlined that this workshop would not have been possible without the support of industry, and especially EUROSIL Members. Finally, Mrs. Wyart warmly thanked Dr. Rushton and Dr. Brown for their assistance in the preparation of the programme and organisation of the Workshop.

Annex

Annex 1: Brief CVs of the Moderators and Speakers of the meeting

Update of current and future legislation concerning crystalline silica

Moderator: Dr. F. Merlo

Since 1986, **Dr. Merlo** is the Deputy Head of the Department of Environmental Epidemiology and Biostatistics, of the National Cancer Research Institute in Genova, Italy. He is responsible for the design, conduction and statistical analysis of epidemiological studies conducted amongst workers/populations exposed to suspected and potential carcinogens. These studies include subjects exposed to benzene, PAH and other airborne pollutants, extremely low frequency electromagnetic fields (ELMF), crystalline silica, pesticides, welding fumes and gases, asbestos.
These studies include cohort as well as biochemical and molecular epidemiological designs. The latter include the determination of biological markers of exposure, early biological effects, genetically based individual susceptibility (metabolic polymorphisms) used in the inferential process of evaluating cancer risk and its association with exposure to environmental agents.

Dr. M. Wyart-Remy is Doctor of Sciences (Organic Physical Chemistry) from the Free University of Brussels. She is the Secretary General of EUROTALC since 1979 (25 years). Since its creation in 1994, Dr. Wyart is Secretary General of IMA-Europe, the European Association representing the Bentonite, Borates, Calcium Carbonate, Diatomite, Feldspar, Kaolin, Clays, Silica and Talc producers. EUROSIL is the section representing the Industrial Silica Producers of which Dr. Wyart is also Secretary General.
Dr. Wyart is acting as IMA representative and expert in several committees like the EU Commission Raw Materials Supply Group, the UNICE Chemical Agents at Work working group. She has made numerous presentations at international conferences on the link between regulatory developments and scientific research related to crystalline silica, notably in ISSA conferences (International Social Security Association).

Mr. R. Glenn is a consulting scientist with the law firm of Crowell & Moring of Washington, DC. Previously, Bob was President and Chief Executive Officer of the Industrial Minerals Association - North America (IMA-NA), a trade association representing companies that mine and process ball clay, bentonite clay, borates, feldspar, industrial sand, mica, talc and soda ash. He was instrumental in the founding of the IMA-NA in 2002. In 1992 he was elected President of the National Industrial Sand Association and jointly served as president of both associations until his departure in 2004. His professional training is in the field of industrial hygiene, and he holds the degree of Master of Public Health from the University of Minnesota. He is certified in the comprehensive practice of industrial hygiene by the American Board of Industrial Hygiene. He is a past member of the Editorial Boards of the American Industrial Hygiene Association Journal and Applied Occupational and Environmental Health. Prior to his employment with the Industrial Minerals Association - North America, he was

Director of the Division of Respiratory Disease Studies of the National Institute for Occupational Safety and Health.

Overview of key health and exposure issues

Dr. L. Rushton is an epidemiologist and medical statistician carrying out research in both occupational and environmental health. She is currently Head of Epidemiology at the MRC Institute for Environment and Health, and together with Terry Brown has been carrying out the UK silica sand mortality and cancer incidence studies.

Summary of epidemiological research to date

Moderator: Dr. H. Weill

Dr. H. Weill received his B.A. and M.D. from Tulane University. Since 1962, Dr. Weill has been on the Tulane faculty. His most recent full-time position has been Professor of Medicine, Chief of the Section of Environmental Medicine, and the Schlieder Foundation Professor of Pulmonary Medicine at the Tulane University Medical Center in New Orleans. Until mid-1996, he directed an interdisciplinary research program in occupational lung diseases, and for over thirty years has been investigating the respiratory health effects of workplace exposure to such airborne inhalants as silica, asbestos, man-made mineral fibers, cotton, chlorine and isocyanates. Approximately 200 published papers appear in the scientific and medical literature as the result of this research. He retired from the active full-time faculty in June, 1997 and is now Professor Emeritus at Tulane.

Dr. T. Brown has an honours degree in Human Biology. For his PhD, he looked at the mortality and morbidity of biological research laboratory workers as part of an internationally coordinated study for the International Agency for Research. He joined the Medical Research Council's Institute for Environment and Health (Leicester, UK) in October 2000. Together with Lesley Rushton, he has been carrying out the UK silica sand mortality and cancer incidence studies.

Dr. J. Hughes is Professor of Biostatistics in the Tulane University School of Public Health and Tropical Medicine in New Orleans, LA, USA. She has been involved in many epidemiologic studies of occupational cohorts, including those exposed to asbestos, diatomaceous earth and silica. Dr. Hughes is co-author of the study of North American Industrial Sand Workers. An update to this study is in the final stages of completion.

Dr. G. Gibbs obtained his Doctorate in Epidemiology at McGill University in Montreal, Canada. He began his career working for the British Medical Research Council. He joined the Department of Epidemiology and Health at McGill University in 1966 and held various academic positions in that Department. In the 1980's he worked in the private sector as Director of Health and Safety Affairs for Celanese Canada. Dr Gibbs is now President of his own consulting company. He is also an adjunct Full Professor at the University of Alberta, Canada.

Dr. B. Miller is a Chartered Statistician and is Director of Research Operations at the IOM, Edinburgh, where he has worked since 1979. He worked extensively on the epidemiology of occupational lung diseases, and also has considerable experience in designing and analysing toxicological experiments.

Dr. E. Hnizdo is Senior Staff Fellow in the Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown since March 1999. In NIOSH She is doing research into work-related chronic obstructive pulmonary disease (COPD) and workplace screening for lung function impairment. She is also collaborating on NIOSH extramural studies into work-related COPD with University of California and Tulane, and with Kaiser Permanente Northwest in Oregon. From 1995 to 1999 She worked as Principal Scientist Specialist in the National Centre for Occupational Health, South Africa, conducting research into silica dust related lung diseases and developing a surveillance program for occupational respiratory diseases. From 1992 to 1994 she worked as Staff Fellow epidemiologist in the National Institute of Environmental Health Sciences (NIEHS), North Carolina. From 1982 to 1992 She worked as Senior Statistician/Epidemiologist in the Epidemiology Research Unit, Department of Health and Welfare, Johannesburg, South Africa, conducting research into lung diseases in South African gold miners.
She is an author of 55 publications in peer reviewed journals.

Professor N. de Klerk leads the Biostatistics and Genetic Epidemiology Division in the Telethon Institute for Child Health Research in Subiaco and the Centre for Child Health Research at the University of Western Australia. Before that, he coordinated the Occupational Respiratory Epidemiology Group in the Department of Public Health at the University of Western Australia and has over 25 years experience in biostatistics and epidemiology. He has published widely in the areas of occupational respiratory disease, cancer epidemiology, child health, and biostatistics.
He was co-author of the recent Australian exposure standard for crystalline silica. He has been a member of various state and national health advisory committees including the NH&MRC New Program Grants Committee and the Radiation Health and Safety Advisory Council, and he has recently joined the Australian Working Group developing Radiation Protection Standard for Exposure to ELF. He has also been an international advisor to the WHO on vaccine safety and the WTO on the risks of chrysotile asbestos.

Prof. Dr. med. J. Bruch works at the Institut für Hygiene und Arbeitsmedizin (IHA) of the Universitätsklinikum of Essen. He is also involved in the Institut für Biologische Emissionsbewertung GmbH, Essen.

Dr. M. Attfield graduated in statistics in 1968 and joined the new Institute of Occupational Medicine, Edinburgh as statistician. He worked there on epidemiologic morbidity studies of coal miners and other groups. He joined the National Institute for Occupational Safety and Health (NIOSH) at Morgantown, WV, in 1977 and undertook morbidity and mortality studies of coal miners and other occupational groups. Dr. Attfield attained PhD in industrial hygiene in 1985. He is currently Chief, Surveillance Branch, Division of Respiratory Disease Studies, NIOSH.

Dr. W. Graham is professor of medicine emeritus at the Unversity of Vermont School of Medicine and a Pulmonary physician at the Fletcher Allen Medical Center in Burlington Vermont. For 25 years, he ran the Tuberculosis program for the Vermont Health State Department, and was the treating physician at the Chest Clinic in Barre, Vermont. This clinic was responsible for health surveillance and treatment of granite stone shed and quarry workers.

Dr. R.-S. Koskela is PhD and Lic SocSc. She is a docent of epidemiology in the University of Tampere. She is working in the Finnish Institute of Occupational Health as a specialized research scientist. She has been working in the Institute for 34 years. Mainly she has studied morbidity and mortality of different occupational cohorts. Additionally, She is a person who coordinates and is responsible for personal register data and data protection questions in the Institute. She has also prepared national legislation and guidelines on registers and data protection with the ministries and other institutes.

Graduated from the Technical University of Munich, **Dr. K. Ulm** obtained a PhD from the University of Dortmund and started to work in occupational epidemiology during trainings at the University of Southampton and Washington. He is currently working at the Department of Medical Statistics and Epidemiology at the Technical University of Munich and is a member of the German MAK Commission with a special interest for dust and silica dust.

Dr. N. Cherry graduated in medicine and epidemiology at McGill but has worked in occupational epidemiology on both sides of the Atlantic, moving from the London School of Hygiene to McGill and from there back to the University of Manchester where she was Director of the Centre for Occupational and Environmental Health . She now chairs of the Department of Public Health Sciences at the University of Alberta and heads its occupational heath program.

Dr. W. Chen graduated in medicine in Tongji Medical University in China in 1990 and obtained her doctorate in Germany in the Institute of Hygiene and Occupational Medicine, at the University of Essen in 2001. She is now Professor in the Department of Occupational and Environmental Health, Tongji Medical College, Huazhong University of Science and Technology in China. She is the author of 13 scientific publications of epidemiological studies, mainly in Chinese tin miners and pottery workers cohorts.

After his involvement in the University of Bonn and Bremen, **Dr. F. Bochmann** joined the Institute for Occupational Safety (BIA) of the HVBG in 1994 where is at the Head of "Applied Epidemiology". He is member of CEN TC 137 WG 1 "Influence of the Reference Period on the Presentation of Exposure Data". He was the project manager of several international BIA-Symposiums. He is Member of the GMDS (German Society of Medical Information Science, Biometry and Epidemiology) and of the IEA (International Epidemiological Association), and one ISSA – Research Section working group. He is the Project manager of the project "Injuries in the glass- and ceramic industry", co-operation of the BIA, BGAG, IBS and the Berufsgenossenschaft for Glass- and Ceramic Industry. Finally he is Consultant and Reviewer for "CIDR NEWS", CIDR (Consortium for Injury and Disability Research, USA, union of governmental institutions

(NIOSH), NSC and private research institutes). He is the author of more than 30 publications related to Epidemiology.

Overview of Design Issues

Moderator: Dr. K. A. Mundt

Dr. K. A. Mundt is a Principal of ENVIRON International Corporation and also serves as Director of Epidemiology for the ENVIRON Health Sciences Institute. Prior to joining ENVIRON, Dr. Mundt served as President and Founder of Applied Epidemiology, Inc. from 1991-2003. He has over 20 years of experience in the application of epidemiological concepts and methods; occupational and environmental exposure to chemicals; cancer, reproductive, cardiovascular, musculoskeletal injury and other health outcomes; quality-based critical reviews (QBCR) of epidemiological literature; expert testimony; epidemiological instruction and training. Dr. Mundt has applied epidemiological concepts and methods to diverse occupational and environmental health challenges on behalf of corporations, government agencies, international organizations, and law firms.

Dr. D. Dahmann studied chemistry at the Ruhr-Universität Bochum starting in 1970. Degree of Dipl.-Chem. in 1975 and PhD (silicon-phosphorous-chemistry) in 1978 in Bochum as well. 1978 to 1982 research as a post-doc at the Ruhr Universität. Starting 1982 work in the VDI commission „Reinhaltung der Luft“ (emphasis: „measurement methods for air polutants“. Starting 1988 work in the Silicosis Research Institute („Silikose-Forschungsinstitut“, SFI), now Institute for the Research on Hazardous Substances (“Institut für Gefahrstoff-Forschung, IGF), at the Ruhr Universität Bochum. From June 1994 head of the institute as technical director. Intense activity in national and international standardisation organisations: For example convenor of the working group „Lung hazards from exposure in workplace-air“ in the Committee Industrial Medicine of the German Hauptverband der gewerblichen Berufsgenossenschaften and convenor of the DIN Working group „Dust“ as well as speaker of the German group in the corresponding CEN working group. Several publications in the field of dust sampling and prevention in workplace air. In the summer of 2003, stay in the People’s Republik of China as a WHO-expert in the field of dust measurement in workplace air.

Dr B. Fubini was educated at the University of Torino (Italy) where she is now full Professor of Chemistry in the Faculty of Pharmacy. She has developed studies on the chemical basis of the toxicity of solid materials, mainly inhaled particles, and is currently the Head of the Interdipartimental Center “G.Scansetti” for Studies on Asbestos and other Toxic Particulates, which coordinates research & formation activities carried out in a large spectrum of departments, form earth sciences to occupational medecine and epidemiology. She authored more than 150 original scientific papers, and 20 review articles and book chapters, mostly devoted to the relationship between physico-chemical properties and toxicity of particles and fibres. Six reviews and more than 50 original articles mostly concern crystalline silicas. Since 1988 she has been in the scientific committees and/or delivered lectures at various international meetings on particle toxicology, mainly

crystalline silica and mineral fibers. She took part in various consensus workshops and served in IARC (*International Agency for Research on Cancer 1996-2002, Scientific Publication 140, Monographs on the Evaluation of Carcinogenic Risks to Humans n 68, 81, 86*); JRC-ECVAM *(Joint Research Center-European Centre for the Validation of Alternative Methods ATLA 24 (1996) and 26 (1998, chaired)* and ILSI (*International Sciences Institute, US, 2003*) working groups for the assessment of fiber and particle toxicity. She has been selected as expert by EPA (Environmental Protection Agency) to give plenary lectures in two workshops on asbestos (Oakland, CA, 2001 and Chicago IL, 2003).

Dr. P. A. Hessel is a Senior Managing Scientist in Exponent's Health/Epidemiology practice and is the Director of their Chicago office. Dr. Hessel is an epidemiologist with a focus on occupational and environmental lung diseases. He has conducted research on the pneumoconiosis, asthma and respiratory diseases. He has been heavily involved in the ongoing debate regarding the carcinogenicity of silica. Dr. Hessel holds a masters degree in Environmental Health from the University of Minnesota and a doctorate in Epidemiology from the University of Pennsylvania.

Dr. J. C. McDonald: Emeritus professor of McGill University in Epidemiology, and Emeritus professor of London University in Occupational Medicine, currently working in the Department of Occupational and Environmental Medicine, National Heart & Lung Institute, Imperial College London. Dr. Mc Donald is author of many papers on the epidemiology of work-related respiratory disease."

Rapporteur Reports from Individual Working Groups
Expert Summaries of Design Issues Across all Working Groups

Moderator: Mr. F. Hearl

Mr. F. Hearl earned his Bachelors Degree in Chemical Engineering from Purdue University in 1974; and a Masters in Chemical Engineering from MIT in 1980. He is a registered Professional Engineer in West Virginia and Maryland. Frank retired after 30 years of service in the U.S. Public Health Service where he worked predominantly in Morgantown, West Virginia at the National Institute for Occupational Safety and Health (NIOSH) Laboratory, studying lung disease among miners and millers. Frank worked as an industrial hygienist on the joint NIOSH-NCI-Tongji Medical College studies of Chinese workers exposed to Silica. He is author of over 30 technical papers and book chapters, etc. and many oral presentations. His present position is as NIOSH's Deputy Chief of Staff, with the NIOSH Office of the Director in Washington, DC.

Priorities for Future Epidemiological Research on Crystalline Silica and Optimum Methods for Achieving It. Conclusion of Workshop and Future Steps

Moderator: Dr. L. Levy

Dr L. Levy gained his doctorate in experimental pathology at the Institute of Cancer Research, London. He has held academic positions at the University of Aston. He has had a long involvement as an independent member on the Health and Safety Commission's Working Group on the Assessment of Toxic Chemicals (WATCH) and the Advisory Committee on Toxic Substances (ACTS). He is also the UK nominee on the EC Scientific Committee on Occupational Exposure Limits (SCOEL) for DG Social Affairs. He has published more than 200 papers on occupational carcinogenesis, occupational toxicology, and regulatory aspects of both environmental and occupational air standards. Until he the Institute for Environment and Health (IEH) in 1996, Len Levy was a Reader in Occupational Health at the University of Birmingham. Dr. Levy has spent a good part of his research and regulatory time looking at the toxicity of a wide range of occupational and environmental substances.

Annex 2: Participants List

Scientific Experts:

Dr. M. Attfield, NIOSH, United States

Dr. H. E. Ayer, Research Industrial Hygienist, Cincinnati, Ohio, USA

Dr. F. Bochmann, Berufsgenossenschaftliches Institut Arbeitssicherheit, BIA, Sankt Augustin, Germany

Dr. R. C. Brown, Toxicology Services, Oakham, UK

Dr. T. Brown, Medical Research Council's Institute for Environment and Health, University of Leicester, UK

Prof. Dr. J. Bruch, Institut für Biologische Emissionsbewertung GmbH, Essen, Germany

Dr. T. Bruening, BGFA, Bochum, Germany

Dr. W. Chen, Department of Labor Health and Occupational Diseases, Tongji Medical College, Wuhan, Hubei, People's Republic of China

Dr. N. Cherry, Occupational Health Program, University of Alberta, Canada

Dr. D. Dahmann, Institut für Gefahrstoff-Forschung (IGF), der Bergbau-Berufsgenossenschaft, an der Ruhr-Universität Bochum, Germany

Dr. N. De Klerk, Department of Public Health, University of Western Australia, Western Australia

Dr. P. Dumortier, CUB Erasme Hospital, Chest Department – Laboratory of Mineralogy, Brussels, Belgium

Dr. M. Fidalgo, Instituto Nacional de Silicosis, Oviedo, Spain

Dr. B. Fubini, Università degli Studi di Torino, Italy

Dr. John F. Gamble, Epidemiology Section Exxon Biomedical Sciences, Annandale, USA

Dr. G.W. Gibbs, Safety Health Environment International Consultants, Alberta, Canada

Dr. W. G. B. Graham, University of Vermont, USA

Mr. F. Hearl, National Institute for Occupational Safety and Health (NIOSH), Washington DC

Dr. P. A. Hessel, Exponent, USA

Dr. E. Hnizdo, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health (NIOSH), Morgantown, USA

Dr. J. Hughes, Department of Biostatistics, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana, USA

Dr. R-S Koskela, Finnish Institute of Occupational Health, Department of Epidemiology and Biostatistics, Helsinki, Finland

Dr. L. Levy, Medical Research Council's Institute for Environment and Health, University of Leicester, UK

Dr. K. Linch, National Institute for Occupational Safety and Health, NIOSH, Morgantown, USA

Prof. Dr. JC McDonald, Dept of Occupational & Environmental Medicine, University of London Imperial College, School of Medicine, National Heart & Lung Institute, London

Dr. D. F. Merlo, Environ. Epidemiology/Biostatistics, National Cancer Institute, Genova, Italy.

Dr. B. Miller, Institute of Occupational Medicine, IOM, Edinburgh, United Kingdom

Dr. K.A. Mundt, ENVIRON Health Sciences Institute, United States

Dr. B. Pesch, BGFA, Ruhr-University Bochum, Germany

Dr. R. J. Rando, Tulane University, New Orleans, Louisiana, USA

Dr. L. Rushton, Medical Research Council's Institute for Environment and Health, University of Leicester, UK

Dr. K. Ulm, Institut für Medizinische Statistik und Epidemiologie (IMSE), Technische Universität München, Germany

Dr. P. Vacek, University of Vermont, USA

Dr. B. Voss, BGFA, Ruhr-University Bochum, Germany

Dr. H. Weill, Tulane University, New Orleans, Louisiana, USA

Government Observer

Mrs. F. L. Rice, NIOSH, United States

Industry Observers:

Dr. E. G. Astrup, EUROSIL* (ELKEM ASA, Norway)

Mr. J. Austin, US Crystalline Silica Panel

Mr. K. Bailey, US Crystalline Silica Panel

Mrs. L. Boens, EUROSIL (SCR Sibelco, Belgium)

Mr. R. Chan, US Crystalline Silica Panel

Dr. G. Duval-Arnould, Saint-Gobain, France

Mr. M. Ellis, US Crystalline Silica Panel, IMA-North America President

Mr. R. Glenn, US Crystalline Silica Panel

Dr. A. Lombard, IDPA** (CECA S.A., Paris, France)

Mrs. F. Lumen, EUROSIL / IMA-Europe***, Belgium

Mr. F. Meunier, EUROSIL, Occupational Hygienist Observer, Angers, France

Mr. M. Mirliss, IDPA Director, USA

Dr. T. Pütter, EUROSIL (Quarzwerke, Frechen, Germany)

Dr. M. Réfrégier, IMA-Europe (Talc de Luzenac, Toulouse, France)

Dr. P. Sébastien, Saint Gobain CREE, Cavaillon, France

Mr. J. A. Ulizio, US Crystalline Silica Panel

Dr. M. Wyart-Remy, EUROSIL / IMA-Europe Secretary General, Belgium

* *European Association of Industrial Silica Producers*
** *International Diatomite Producers Association*
*** *Industrial Minerals Association - Europe*

The following persons were also invited but prevented from attending: Mr. J. Biosca (European Commission, Luxembourg), Dr. T. Birk (ENVIRON Health Sciences Institute, Germany), Dr. P. Borm (Centre of Expertise in Life Sciences – CEL, Netherlands), Dr. P. Brochard (CHU Aquitaine, France), Dr. G. L. Burgess (Centre for Occupational and Environmental Health, University of Manchester, UK), Dr. P. L. Carta (Università degli Studi di Cagliari, Italy), Dr. H. Checkoway (University of Washington, Department of Environmental Health, USA), Dr. P. Cocco (Università degli Studi di Cagliari, Italy), Dr. M. Coggiola (Università degli Studi di Torino, Italy), Dr. J. Costello (NIOSH, USA), Dr. H. Cowie (IOM, Edinburgh), Dr. J. Deddens (University of Cincinnati, USA), Dr. P. De Vuyst (CUB Erasme Hospital, Belgium), Dr. K. Donaldson (Edinburgh University, UK), Prof. V. Foa (Università degli Studi di Milano, Italy), Dr. P. Guenel (Institut National de la Santé et de la Recherche Médicale – INSERM, France), Dr. A. Huici-Montagud (Centro Nacional de Condiciones de Trabajo, Spain), Dr. J. K. McLaughlin (International Epidemiology Institute, USA), Dr. W. H. Mehnert (Department of Epidemiology and Reportable Diseases, Germany), Mrs. M. Meldrum (Health & Safety Executive, UK), Dr. P. Morfeld (RAG, Germany), Dr. H. Muhle (Fraunhofer Institute, Germany), Dr. R. Park (National Institute of Environmental Health Sciences, USA), Prof. G. Piolatto (Università degli Studi di Torino, Italy), Prof. E. Pira (Università degli Studi di Torino, Italy), Dr. V. Rafnsson (Administration of Occupational Safety and Health, Iceland), Dr. W. Sanderson (Department of Occupational and Environmental Health University of Iowa College of Public Health, USA), Dr. R. Schins (University of Düsseldorf, Germany), Dr. K. Steenland (NIOSH, USA), Dr. V. Stone (Napier University, UK), Dr. E. Tjoe Nij (Institute for Risk Assessment Sciences, Netherlands), Dr. L. Tran (IOM, UK), Dr. K. Ziegler (European Commission, Luxembourg).

Annex 3: Programme

Wednesday 4 August

16:30	**Organisation meeting for speakers and moderators**
18:30	Cocktail Party, Holiday Inn San Marino's restaurant

Thursday 5 August, Morning Session

07:30	BREAKFAST, Holiday Inn San Marino's restaurant	Moderator
08:00	**Welcome Address** - *Michelle Wyart-Remy*	**Franco Merlo**
08:15	**Update of current legislative position and future proposed legislation concerning crystalline silica** *Michelle Wyart-Remy, Robert Glenn*	
09:00	**Overview of the key health and exposure issues** - Lesley Rushton	
09:45	**Summary of epidemiological research to date** UK Industrial Sand Workers *(Terry Brown)* US Industrial Sand Workers *(Janet Hughes)* US Diatomaceous Earth Workers *(Graham Gibbs)* Scottish Coal Miners *(Brian Miller)* Scottish Heavy Clay workers *(Brian Miller)* South African Gold Miners *(Eva Hnizdo)* Australian Gold Miners *(Nicholas De Klerk)* Chinese Tin Miners *(Weihong Chen - Joachim Bruch)*	**Hans Weill**
11:15	TEA/COFFEE	
11:30	**Summary of epidemiological research to date** US Granite Workers *(Michael Attfield – William G. B. Graham)* Finnish Granite Workers *(Riitta-Sisko Koskela)* German Stone Workers *(Kurt Ulm)* UK Pottery Workers *(Nicola Cherry)* Chinese Cohort *(Weihong Chen –Frank Bochmann)* Italian Refractory Brick Workers *(Franco Merlo)* Italian Graphite Rod Workers *(Franco Merlo)*	
12:30	LUNCH, Holiday Inn San Marino's restaurant	

Thursday 5 August, Afternoon Session

		Moderator
13:30	**Overview of Design Issues** Exposure Assessment *(Dirk Dahmann)* Physico chemical features of the dust *(Bice Fubini)* Confounding Factors *(Patrick A. Hessel)* Health Outcomes *(J. Corbett McDonald)* Statistical Methodology *(Janet Hughes)*	**Kenneth A. Mundt**
14:30	BREAK	
15:00	**Separate Working Groups** Silica Sand & Diatomaceous Earth Mining Stone/Granite/Quarrying Pottery/Brick	
16:00	TEA/COFFEE	
16:15	**Separate Working Groups**	
17:30	FINISH	
19:00	DINNER, Holiday Inn San Marino's restaurant	

Friday 6 August

08:00	BREAKFAST, Holiday Inn San Marino's restaurant	Moderator
08:30	**Rapporteur Reports from Individual Working Groups**	**Frank Hearl**
09:30	**Expert Summaries of Design Issues Across all Working Groups**	
10:30	TEA/COFFEE	
11:00	**Definition of Ideal Protocol and Identification of Cohorts with Strongest Potential for Future Studies** (Facilitators: Lesley Rushton / Terry Brown)	
12:30	LUNCH, Holiday Inn San Marino's restaurant	
13:30	**Decision on priorities for Future Epidemiological Research on Crystalline Silica and Optimum Methods for Achieving It** (Facilitators: Len Levy / Lesley Rushton / Terry Brown)	**Len Levy**
15:30	TEA/COFFEE	
16:00	**Conclusion of Workshop and Future Steps** (Len Levy / Michelle Wyart-Remy)	
16:30	End of Workshop	

New York Epidemiology Workshop

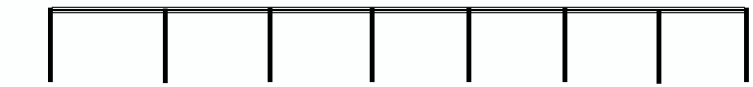
Regulatory Developments in the EU

M. Wyart-Remy
Aug 5-6, 2004

IMA Europe

IMA - Europe — The context

the EU representation of Industrial Minerals



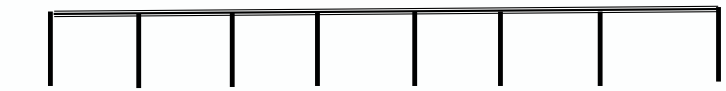
EUROTALC	KPC	EUROFEL	EUBA	IDPA	EUROSIL	CCA	EBA
Talc	Kaolin Plastic Clays	Feldspar	Bentonite	Diatomite	Silica	GCC/PCC Dolomite	Borates

14 EU (15) Member States (MS)
+ 3 new MS (Czech Rep., Cyprus, Poland)
+ Norway, Switzerland, Turkey, Ukraine

IMA Europe

EUROSIL — The context

the EU representation of Industrial Silica Producers



Belgium	France	Germany	Italy	Netherlands	UK	Scandinavia	Spain Portugal
SCR Sibelco	APPMI	Arbeitskreis Quarz	Prosil	Lieben Sigrano Sibelco NL	SAMSA	Askania Baskarpsand Brogardsand Elkem Radasand	Sibelco Minerales Caobar Mario Pilato Blat Sibelco Esp. Sibelco Port. Silices Gilarranz Molturciones Castellol

9 EU Member States (MS)
and Norway

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Possible EU Regulatory Scenarios

IARC
+ Scientific Evidence
national experts evaluation

EU
DG Environment-JRC-ECB
CMR Working Group

Classification & Labelling

Dangerous Substances Directive
67/548/EEC - 92/32/EEC

EU
DG Employment & Social Affairs
or Member States

Workers Protection
OELs

BLV in Annex III
Carcinogens Directive
90/394/EEC

ILV OR BLV in
Chemical Agents Directive
98/24/EC

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Classification consequences

Dangerous Substances Directive 67/548/EEC - 92/32/EEC
EU DG Environment - European Chemical Bureau

- carcinogen **category 1 or 2** + preparations containing **> 0.1%** of it
- **labelling** R49 may cause cancer by inhalation +
- marketing & use restriction → **ban from public products**
  → **professional use only**
- **dangerous transport** regulations
- **dangerous waste** regulations
- **emissions**, **permits**

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Carcinogens Directive Scenario

Protection of workers from risks related to exposure to carcinogens at work
90/394/EEC - 97/42/EC - 99/38/EC

Only BLV – EP/Council co-decision

Risk assessment

⇩

Agents

- substance
- preparation
- process

Obligations

- replacement
- exposure reduction
- information of Authority
- workers information & training
- hygiene & health surveillance
- medical record-keeping (40 years)

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Possible EU Regulatory Scenarios

IARC
+ Scientific Evidence
national experts evaluation

Risks of obligations as if classified carcinogen:

voluntary labelling recommendation

emissions limits

EU
DG Employment & Social Affairs
or Member States

Workers Protection
OELs

BLV in Annex III Carcinogens Directive 90/394/EEC

ILV OR BLV in Chemical Agents Directive 98/24/EC

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Chemical Agents Directive scenario

98/24/EC Article 5.4

When risk assessment shows

because of quantities → slight risk

\+ preventive measures taken reduce this risk

specific protection measures **shall not apply** **including substitution**

ILV: very low value, adopted by some MS without socio-economic arguments (e.g. NO)

BLV: would be favoured

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Possible EU Regulatory Scenarios

IARC
+ Scientific Evidence

national experts evaluation

CS is ubiquitous
IARC limited its hazard to workplace

CS is not a priority for classification

DG ENV-JRC-ECB
Ispra Oct. '98 & Sept '02

EU
DG Employment & Social Affairs
or Member States

Workers Protection
OELs

BLV in Annex III
Carcinogens Directive
90/394/EEC

ILV OR BLV in
Chemical Agents Directive
98/24/EC

SCOEL SUM Doc

IMA Europe

Silicosis control prevents cancer

SCOEL SUM Doc 94-final, June 2002

The main effect in human of the inhalation of respirable silica dust is silicosis*. There is sufficient information to conclude that the* ***relative risk of lung cancer is increased in persons with silicosis*** *(and*
? *apparently, not in employees without silicosis exposed to silica dust in quarries and in the ceramic industry). Therefore preventing the onset of silicosis will also reduce the cancer risk. Since a clear threshold for*
? *silicosis development cannot be identified, any reduction of exposure will reduce the risk of silicosis. (...) It arises that an OEL should lie below 0.05 mg/m³*

SCOEL's chairman informal recommendation:
BLV in Carcinogens Directive

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National Expert Committees' opinion

- **NL: DECOS** (1998)
  Inhaled quartz is carcinogenic to man and mediates its carcinogenicity by a non-stochastic genotoxic mode of action, which implicates the existence of a quartz exposure level below which cancer risk can be considered nil
- **D: MAK Committee** (1999)
  Respirable crystalline silica is a human carcinogen (category A1)
  Rem**:** preventing silicosis will reduce cancer risk
- **UK: WATCH Committee** (2001-2002)
  Variability of RCS fibrosis capability (Potency Matrix)
  Variability in RCS carcinogenic potency less clear than fibrosis variability
  Suggested relationship between silicosis & lung cancer

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Member States (MS) Positions

EU

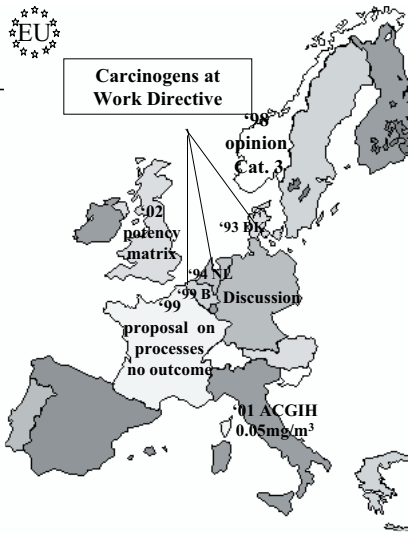
The Netherlands and Denmark: RCS in Carcinogens Directive 90/394

Belgium: all IARC cat 1 & 2, including CS, in 90/394 (but RA may exempt)

France: unachieved discussion on carcinogenic processes in 90/394

Germany: from classification to workers protection (pending)

The UK: Good Practice Guide: *Silica Essentials*



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Next EU regulatory process

- EC may decide not to decide, provided no request to do so
- EC may set up a limit on the basis of SCOEL recommendation

  after consultation of the Advisory Committee for Safety & Health at Work (ACSHW, tripartite)
- EC decided to revise Carcinogens Directive

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EC Consults Social Partners on Carcinogens Directive Revision

EC Questions

- Extending 90/394 to substances toxic to the reproduction?
- Revising OELVs for Carcinogens listed in 90/394?
- Simplifying procedures by introducing IOELVs?
- Establishing OELVs for carcinogens not yet listed in 90/394 i.e. “occupational carcinogens”, such as **crystalline silica**, diesel exhaust, wood dust, radon decay products, solar radiation, passive smoking?

Opposed by UNICE, CEFIC, etc., the Employers of the Social Dialogue Committee Mines

IMA Europe

What the IM industry wants

To continue producing, processing and using products that are safe for the workers, the environment and the users

- Reducing exposure at the workplace, by monitoring dust exposure and implementing good practices in the silica and end-users industries, to continuously improve working practices
- Aiming at improving product safety ('passivation') and workers' health protection (biomarkers)
- Better understanding respirable crystalline silica toxicity

IMA Europe

EU Industry Response

- **Gathering the concerned sectors**

  EU Silica Task Force: > 30 EU trade association

- **EUROSIL voluntary labelling of silica flours**

  Xn harmful: R 48/20 *"May cause irreversible effects by inhalation"*, S 22, S 38

- **EUROSIL Socio-Economic Survey**

  To document consultation process in case a Binding Limit be proposed

  Assessing impact of 3 OEL proposals

IMA Europe

EU Industry Response (cont'd)

- **IMA-Europe Standard Dust Monitoring Protocol**

  To collect reliable & comparable exposure data in the IM industry
  To build up Job Exposure Matrix allowing epi-study at low doses

- **Prevention Plan for Exposure Control**

  EUROSIL is working on a detailed prevention plan taking into account various existing Member States documents & initiatives possibly negotiated in a Social Dialogue Agreement Employees/ Employers

- **Supporting Research Projects**

  e.g. Mortality Survey of UK Silica Sand Workers (I EH, Leicester)
  In vitro - in vivo genotoxicity study (Uni-Essen, Uni-Düsseldorf, Torino University)
  Expert Scoping Meeting: Santa Margherita de Ligure Oct '02 - Florence Sept '03
  New York Aug 2004

Results of the 1st Scoping Meeting

Determining a threshold for silicosis is essential
Only human epidemiology could provide risk quantification

Gaps in risk quantification and the existence of a silicosis threshold are past exposures poor assessment, and no doses-responses at low doses

Studies investigating **hazard variability** may provide:

+ Tool to rank materials by potential hazard (risk prevention), but cytotoxicity ranking does not necessarily reflect carcinogenicity
+ Biomarkers allowing practical medical follow-up of workers
+ Mechanisms prevailing in cancer occurrence, incl. clearance

Santa Margherita de Ligure, 23 October 2002

Results of the 2d Scoping Meeting

Interdisciplinary approach would be a must

Epidemiology session

Consolidation of knowledge on existing cohorts favoured

Need for better exposure characterisation

Toxicology session

Toxicology can provide information on the nature of exposure
and identify the factors affecting crystalline silica toxicity
(protective factors/substances, identification of biomarkers, etc.)

Florence, 28 September 2003

Objectives of the NY Workshop

Gathering the Authors of existing key epi-studies

- Provide an update on current & future regulatory developments
- Identify key health & exposure issues
- Summarise epidemiological research to date & identify knowledge gaps
- Reach decision on priorities for future work & optimum methods for achieving this

Philosophy of the NY Workshop

"It is surely for regulators and employers to work at the most cost-effective strategies for risk prevention, not for scientific agencies to fiddle with the evidence to make it more easy for them"

C. McDonald & N. Cherry
Crystalline silica and lung cancer: the problem of conflicting evidence
Indoor Built Environment ***8*** *121-6 (1999)*

Thank you for your attention

I wish you a fruitful Workshop

crowell moring

History of Regulation of Crystalline Silica in the US

EUROSIL Expert Workshop:
Epidemiological Perspectives on Silica and Health
August 5-6, 2004
New York City
Robert E. Glenn, CIH

crowell moring

Early Years (1971-1982)

- **1971 –** OSHA adopts National Consensus and Established Federal Standards
- **1972 –** OSHA publishes Crystalline Silica Compliance Directive (CPL 2-2.7)
- **1974 –**NIOSH Publishes Criteria Document: Occupational Exposure to Crystalline Silica (HEW Publication No. (NIOSH) 75-120)
- **1974** – OSHA announces an Advance Notice of Proposed Rulemaking for Crystalline Silica
- **1976** – OSHA announces an Advance Notice of Proposed Rulemaking for Amorphous Silica

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1971 - OSHA adopts National Consensus and Established Federal Standards

TABLE Z-3 Mineral Dusts		
Substance	mppcf(a)	mg/m(3)
SILICA:		
CRYSTALLINE		
QUARTZ (RESPIRABLE)	250(b)	10mg/m(3) (e)
	%SiO(2)+5	%SiO(2) + 2
QUARTZ (TOTAL DUST)	-	30 mg/m(3)
		%SiO(2)+2
CRISTOBALITE: Use < the value calculated	-	-
from the count or mass formulae for quartz		
TRIDYMITE: Use < the value calculated from	-	-
the formulae for quartz		

crowell moring

1972 - OSHA Crystalline Silica Compliance Directive

Directives
CPL 02-02-007 - CPL 2-2.7 - Crystalline Silica

- Record Type: Instruction
- Directive Number: CPL 02-02-007
- Old Directive Number: CPL 2-2.7
- Title: Crystalline Silica
- Information Date: 10/30/1978

OSHA Instruction CPL 2-2.7 October 30, 1972

OSHA PROGRAM DIRECTIVE #300-3

TO: Field and National Offices/OSH

SUBJECT: Crystalline Silica

1. PURPOSE

This directive provides guidelines to be followed in inspections, and where necessary, the issuance of citations, regarding exposure to silica in the workplace.

2. DOCUMENTATION AFFECTED

This directive cancels the Silica Sampling Data Sheet of January 3, 1972.

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1974 - NIOSH Criteria Document: Occupational Exposure to Crystalline Silica

Section 1 – Environmental (Workplace Air)

Concentration

Occupational exposure shall be controlled so that no worker is exposed to a time-weighted average (TWA) concentration of free silica greater than 50 micrograms per cubic meter of air as determined by a full-shift sample for up to a 10-hour workday, 40-hour workweek.

crowell moring

1974 – OSHA Announces Proposed Rulemaking for Crystalline Silica

Signed at Washington, D.C., this 23rd day of December 1974.

JOHN STENDER.
Assistant Secretary of Labor.
[FR Doc.74-30223 Filed 12-26-74; 8:45 am]

[29 CFR Part 1910]
STANDARD FOR OCCUPATIONAL EXPOSURE TO CRYSTALLINE SILICA

Advance Notice of Proposed Rulemaking

FEDERAL REGISTER, VOL 39, NO. 250 – FRIDAY, DECEMBER 27, 1974

crowell moring

1976 – OSHA Announces Proposed Rulemaking for Amorphous Silica

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

[29 CFR Part 1910]
[Docket No. H-104]

AMORPHOUS SILICA
Advance Notice of Proposed Rulemaking

The Occupational Safety and Health Administration, U.S. Department of Labor is studying the general health implications, safe exposure levels, and methods of sampling and measurement for amorphous silica.

FEDERAL REGISTER, VOL. 41, NO. 250 – TUESDAY, DECEMBER 28, 1976

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Middle Years (1983-1992)

- **1982** – Goldsmith Paper Proposes Three Hypothesis for a Silica-Cancer Relationship (AJIM 3:423-440-1982)
- **1984** – Goldsmith Symposium - "Silica, Silicosis and Cancer", Chapel Hill, North Carolina, April 3-5, 1984
- **1986** – IARC Working Group Evaluate Silica as – *Limited Evidence for Humans; Sufficient Evidence for Animals*
- **1987** – IARC Working Group Classifies Silica as *Group 2A - Probably Carcinogenic to Humans*
- **1989** – OSHA PEL Update Establishes a 0.1 mg/m^3 Crystalline Silica Limit
- **1991** – NTP Lists Silica as *Reasonably Anticipated to be a Carcinogen* in the 6th Annual Report on Carcinogens
- **1992** – OSHA PEL Update Overturned by *11th Circuit Court of Appeals*

crowell moring

1982 – Goldsmith Proposes Three Hypothesis for a Silica-Cancer Relationship

Does Occupational Exposure to Silica Cause Lung Cancer?

David F. Goldsmith, MSPH, Tee L. Guidoti, MD, MPH, and Donald Johnston, MSPH

Silica is not generally considered to be a carcinogen, however, …. respiratory cancer excesses have been reported from ….the following dusty trades in which exposure to silica is a common factor; iron and steel foundry workers, steel casting workers, sand blasters, metal molders, non-uranium miners, and ceramic workers. Animal studies suggest that silica can be an initiating carcinogen or can act as a cocarcinogen or promoter when combined with benzo(a)pyrene. We propose three candidate hypotheses and two pathways for silica carcinogenesis.

(1) Silica directly induces lung cancer.

(2) Silica causes silicosis, an intermediate pathologic state leading to lung cancer

(3) Silica linked with PAH impairs clearance and increases retention.

American Journal of Industrial Medicine 3:423-440 (1982)

crowell moring

1984 – Goldsmith Symposium - Chapel Hill, North Carolina, April 3-5, 1984

SILICA, SILICOSIS, AND CANCER

Controversy in Occupational Medicine

Edited by

David F. Goldsmith, Ph.D.

Deborah M. Winn, Ph.D.

Carl M. Shy, M.D., Dr.P.H.

Chapter 49 – Is Silica the Next Asbestos? A Study in Contrasts

B. Mandula and D.L. Davis

crowell moring

1986 – IARC Working Group Evaluate Silica

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Silica and Some Silicates

Volume 42 – 1987

4.4 Evaluation

- **There is sufficient evidence for the carcinogenicity of crystalline silica to experimental animals.**
- **There is limited evidence for the carcinogenicity of crystalline silica to humans.**

crowell moring

1989 – OSHA PEL Update

OSHA Permissible Exposure Limit Update

Federal Registers
Air Contaminants - 54:2332-2983

- Publication Date: 01/19/1989
- Publication Type: Final Rules
- Fed Register #: 54:2332-2983
- Standard Number: 1910.1000
- Title: Air Contaminants

SILICA, CRYSTALLINE - QUARTZ CAS: 14808-60-7;
Chemical Formula: None H.S. No. 1355

The former OSHA limit for silica-containing dusts is a respirable dust limit expressed as the following formula: (10 mg/m(3))/(% respirable quartz + 2).

At one time, the ACGIH also expressed its silica limit in terms of this formula. However, the current ACGIH TLV is 0.1 mg/m(3), measured as respirable quartz dust. OSHA proposed, and the final rule establishes, a permissible exposure limit of 0.1 mg/m(3) TWA, as respirable quartz. Quartz is a colorless, odorless, noncombustible solid.

crowell moring

1989 – OSHA PEL Update

OSHA Permissible Exposure Limit Update

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1991 – NTP Lists Silica as *Reasonably Anticipated to be a Carcinogen*

Sixth Annual Report on Carcinogens Summary 1991

U.S. Department of Health and Human Services
Public Health Service

Substances or groups of substances, and medical treatments which may reasonably be anticipated to be carcinogens.

- **Silica, Crystalline (Respirable)**
  - Quartz
  - Cristobalite
  - Tridymite

crowell moring

1992 – OSHA PEL Update Overturned by *11th Circuit Court of Appeals*

OSHA Permissible Exposure Limit Update Overturned

Federal Registers

Air Contaminants - 58:35338-35351

- **Publication Date:** 06/30/1993
- **Publication Type:** Final Rules
- **Fed Register #:** 58:35338-35351
- **Standard Number:** 1910.1000
- **Title:** Air Contaminants

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Part 1910

RIN 1218-AB26

Air Contaminants

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Final rule.

SUMMARY: This document announces the revocation of the exposure limits specified in the "Final rule limits" columns of Table Z-1-A of 29 CFR 1910.1000. This implements the Court of Appeals decision in **AFL-CIO** v. **OSHA**, 965 F.2d 962 (11th Cir., 1992), vacating those limits. Enforcement of those limits was suspended starting March 23, 1993.

crowell moring

Later Years (1993-2004)

- **1996** – OSHA Launches Silica Special Emphasis Program
- **1996** – IARC Working Group Classifies Silica as *Group 1 – Carcinogenic to Humans*
- **1997** – OSHA Announces Rulemaking for Crystalline Silica in the Regulatory Agenda
- **2000** - NTP Lists Silica as a *Known Human Carcinogen* in the 9th Report on Carcinogens
- **2003** – Small Business Panel Convened to Review Draft Silica Standard
- **2004** – OSHA Regulatory Agenda
  - Completed Small Business Panel Report (12/19/04)
  - Complete Peer Review of Risk Assessment (02/00/05)

crowell moring

1996 – OSHA Launches Silica Special Emphasis Program

Special Emphasis Program (SEP) for SILICOSIS

May 2, 1996

MEMORANDUM FOR: REGIONAL ADMINISTRATORS

FROM: JOSEPH A. DEAR

SUBJECT: Special Emphasis Program (SEP) for SILICOSIS

This memorandum provides inspection targeting guidance for implementing an OSHA-wide Special Emphasis Program (SEP) to reduce and eliminate the workplace incidence of silicosis from exposure to crystalline silica. The policy set forth in this memorandum is effective immediately. This SEP covers most SIC codes where an exposure to crystalline silica may exist.

crowell moring

1996 – IARC Classifies Silica as *Group 1 – Carcinogenic to Humans*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 68, Silica, Some Silicates, Coal Dust and *Para*-Aramid Fibrils

SILICA

Crystalline silica - inhaled in the form of quartz or cristobalite from occupational sources (Group 1)

5.5 Evaluation

- There is ***sufficient evidence*** in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources
- There is ***sufficient evidence*** in experimental animals for the carcinogenicity of quartz and cristobalite.

Continued…..

crowell moring

1996 – IARC Classifies Silica as *Group 1 – Carcinogenic to Humans*

Overall evaluation

- In making the overall evaluation, the Working Group noted that ***carcinogenicity in humans was not detected in all industrial circumstances*** studied. Carcinogenicity may be dependent on ***inherent characteristics of the crystalline silica*** or on external factors affecting its biological activity or distribution of its polymorphs.
- Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources *is carcinogenic to humans (Group 1)*.

crowell moring

1997 – OSHA Announces Rulemaking for Crystalline Silica

OSHA Semiannual Agenda of Regulations – 62:57714-57779

Federal Register

2133 Occupational Exposure to Crystalline Silica

- Publication Date: 10/29/1977
- Publication Type: Unified Agenda
- Title: Semiannual Agenda of Regulations

- **In 1996 IARC classified silica as "carcinogenic to humans".**
- **Over 30% of silica samples from 1982 -1991 exceeded the OSHA PEL.**
- **A recent study concluded that a 45-year exposure at the current OSHA PEL would lead to a lifetime risk of silicosis of 35-47%.**
- **OSHA concluded that there will be no significant progress in the prevention of silica-related diseases without the adoption of a full comprehensive silica standard.**

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2000 - NTP Lists Silica as a *Known Human Carcinogen*

9th NTP Report on Carcinogens

Silica, Crystalline (Respirable Size)

- **Respirable crystalline silica dust occurring in industrial and occupational settings is *known to be a human carcinogen.***
- **Based on sufficient evidence of carcinogenicity from studies in humans**
- **Including a causal relationship between exposure and lung cancer rates in workers exposed to silica**

(IARC 1997, Brown et al. 1997, Hnizdo et. al. 1997)

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2003-OSHA Small Business Panel

Small Business Advocacy Review Panel

OSHA Draft Proposed Crystalline Silica Standard

08/21/03 **Docket H006A**

4-2. Occupational Exposure to Crystalline Silica in General Industry and Maritime

(a) Scope and Application: This section applies to occupational exposures to respirable crystalline silica except construction activities.

(b) Permissible Exposure Limit (PEL): The employer shall ensure that no employee is exposed to an airborne concentration of respirable crystalline silica greater than [50/75/100] µg/m^3, calculated as an eight (8) hour TWA.

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2004-OSHA Regulatory Agenda

Federal Registers

Semiannual Regulatory Agenda. - 69:37785-38319

- **Publication Date:** 06/28/2004
- **Publication Type:** Unified Agenda
- **Fed Register #:** 69:37785-38319
- **Title:** Semiannual Regulatory Agenda.

1972. OCCUPATIONAL EXPOSURE TO CRYSTALLINE SILICA

The American Society for Testing and Materials (ASTM) has published a recommended standard for addressing the hazards of crystalline silica. The Building Construction Trades Department of the AFL-CIO has also developed a recommended comprehensive program standard.

OSHA has determined that rulemaking is a necessary step to ensure that workers are protected from the hazards of crystalline silica.

Completed SBREFA Report	12/19/03
Complete Peer Review of Risk Assessment	02/00/05

crowell moring

Crystalline Silica

- **SBREFA process**
  - Initiated-June 2003
  - draft standard reviewed by small business representatives as part of process
  - report completed-Dec. 19, 2003
- **Current status**
  - SBREFA panel recommendations under evaluation
  - options being developed to proceed with a proposal

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Crystalline Silica: Issues

- Should the standard cover general industry, construction and maritime?
- What is the feasibility of reducing the current PEL for general industry/maritime & for construction?
- Can dust controls be specified for construction as an alternative to requiring exposure assessment & compliance with a PEL (a type of control-banding approach)?

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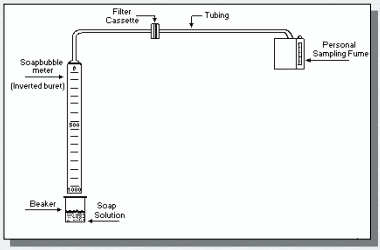
Crystalline Silica: Issues

- How accurate are current sampling & analytical methods in detection of low concentrations of respirable quartz?
- Whether & how to implement ancillary requirements (regulated areas, exposure assessment, hygiene facilities), particularly for construction?



crowell moring

??????????

- Does crystalline silica cause lung cancer?
  - In what exposure situations?
  - How do particle factors affect disease endpoints?
- What role does silicosis = fibrosis play (IPF)?
- Does the LC risk increase for radiographic severity of silicosis?
- Are there pathological differences between fibrosis from silica and asbestos that influence lung cancer?
- How does COPD in working populations affect lung cancer risks?
- At today's exposure level is silicosis a progressive disease?
  - Absent continued exposure?
  - After leaving work?
- With the risk predictions for silicosis at the current PEL – where are the silicotics?

Overview of the key health and exposure issues

Dr. Rushton

- Brief overview of studies to date
- Challenges
- Goals of the workshop

Many studies in different industries including

- Mining
  - gold
  - tin
  - tungsten
- Diatomaceous earth plants
- Pottery industry
- Quarry operations
  - granite etc
  - slate
- Refractory Brick works
- Industrial Sand Works

Health Problems of Concern

- Non-malignant respiratory disease
  - Silicosis
  - TB
  - Chronic bronchitis
  - Chronic obstructive pulmonary disease
- Lung cancer (with/without silicosis)
- Autoimmune disease
- Non-malignant renal disease

Lung cancer relative risk

Industry	Country	Silicotics	Non-silicotics
Pottery	Italy	3.9	1.4
Mines, quarries	Italy	1.9	0.9
Refractory brick	Italy	1.7	2.1
Gold mine	South Africa	0.6	1.0
Slate quarry	Germany	1.8	0.9
Non-uranium metal mines	USA	1.7	1.2
Refractory brick	China	2.1	1.1
Mines	Canada	2.5	0.9
Ceramics	Netherlands	2.2	0.7
Diatomaceous earth	USA	1.6	1.2

Dose-response

- Is there a dose-response relationship with cumulative quantitative exposure to silica?
- For Silicosis – good evidence from many industries
- For Lung cancer where silicosis status is unknown
  - Yes (SA goldminers, China tin miners, USA DE, UK pottery, Dutch pottery, US sand)
  - No (USA goldminers, China pottery, Chinese tungsten miners)
- For Lung cancer
  - Silicosis present
    - Yes (USA DE, Chinese brick, Germany slate quarry)
    - No
  - Silicosis absent
    - Yes (USA DE)
    - No (China brick, Germany slate quarry)

Challenges: disease assessment

- Diagnosis of silicosis
  - method (radiograph, HRCT, tissue sample)
  - interaction with cigarette smoke
  - timing of surveillance (particularly post-exposure)
  - ascertainment of onset
- Incomplete/inaccurate death certification
  - underlying versus contributory cause

Challenges: exposure measurements

- Mineralogical composition
  - polymorphic type of crystalline
  - other minerals eg aluminium
- Particle concentration measurement
  - number
  - size
  - surface area
- Freshly cut or aged surfaces
- Changes in measurement methods and units over time

Challenges: exposure assessment

Varies between studies

- ever/never exposed
- qualitative index (high, medium, low)
- length of service
- occupational category
- quantitative
  - Measurements +/- modelling
  - JEM

Exposure metric

- mean $\Rightarrow$ cumulative
- little information on maximum levels and variation over time

Challenges: Other study design considerations

- Lack of data and/or adjustment for important confounding variables or effect modifiers
  - Smoking
  - Other relevant exposures e.g. asbestos, radon
  - Socio-economic variables
- Use of national rather then local comparison rates
- Difficulty in assessment of separate roles of silica exposure and silicosis in developing lung cancer
- Misclassification of exposure
- Non detection of cases after employment termination (e.g. silicosis)

Goals of the workshop

- To gain a clear understanding of the epidemiological studies including their
  - Health outcomes
  - Exposure data and assessment
  - Confounding data
  - Statistical methodology
  - Interpretation
- To identify key health outcomes, exposures and confounders
- To compare and contrast the different methodologies
- To define the criteria for an ‘ideal’ study
- To identify possible options for future work

T. Brown
UK Industrial Sand Workers:

- Exposure assessment:
  - Personal (2429) & static (583) RCS samples 1978-2001 (900 Cristobalite from one quarry)
  - Collected by cyclone sampler
  - Analysed gravimetrically and IRS/XRD
  - Samples available by date/job/quarry
  - JEM developed
  - Regression models fitted to group similar quarries and time periods
  - No data available prior 1978
  - Back-extrapolation of regression line (based on existing data) back to 1950 used to assess exposure

UK Industrial Sand Workers:

- Health and Confounding Data:
  - Data Collected:
    - Death certificates, 1950-
    - Cancer registrations, 1974-
  - Data Not Collected:
    - Morbidity data
    - Silicosis status
    - Presence of other respiratory disease
    - Smoking history
    - Other exposures

UK Industrial Sand Workers:

- Statistical methodology & overall results:
  - External analysis (compared with national data)
    - SMR
    - SIR
    - Sensitivity analysis of exposure assessment
  - Internal analysis
    - Poisson regression
  - Overall results
    - ↓ Overall mortality (Resp ↓; Circ ↓; 2x Pneumoconiosis)
    - Lung cancer mortality ↓ M, ↑ F
    - Lung cancer not related to job or quarry with high RCS/Cris.
    - Lung cancer decreased with cum. RCS exp.
    - Cancer incd ↓; Lung cancer showed no pattern

UK Industrial Sand Workers:

- Current study status & future plans:
  - Study members continually followed-up (mortality/cancer registration)
  - Future plans:
    - Extend cohort to include employees after 1985
    - Gain access to medical records (silicosis, smoking, etc.)
    - Nested case-control study
    - Detailed investigation of cancer clusters

North American Industrial Sand Workers

McDonald, McDonald, Rando, Weill, Hughes

9 plants

n = 2670 employed ≥ 3 years (some time in 1940+)

Little confounding exposures

Follow-up: through 1994

Significantly elevated SMRs*:

TB	325	(17/5.2)
NM Resp Disease	169	(113/67)
NM Renal Disease	254	(16/6.3)
Lung Cancer	137	(96/70.3)

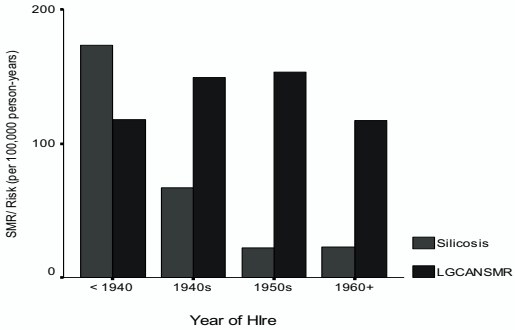
30 silicosis, 7 silico-TB

* U.S. male rates, all follow-up periods

Silicosis risk and Lung Cancer SMR

Duration employed: no relationship for either outcome

Decade of hire:



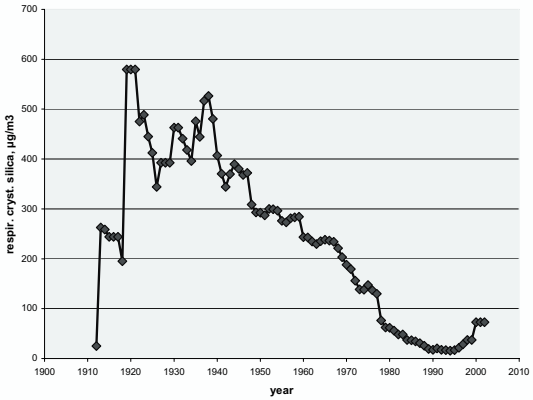
Case-control study of lung cancer and silicosis cases

2 controls/case sought

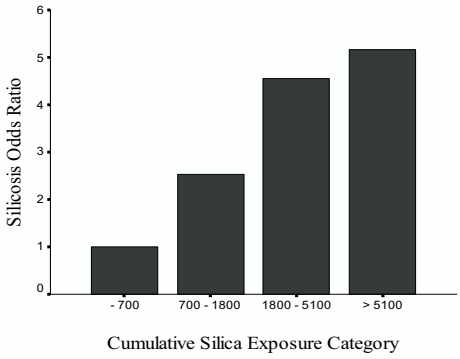
Job and smoking histories sought.
(smoking hx for 79% of lung ca c+c)

Estimates of respirable crystalline silica exposure levels by job/year

Estimated average silica concentration levels
(jobs in case-control study)



Silicosis Odds Ratios by Cumulative Silica exposure lagged 15 years (µg/m^3-years)



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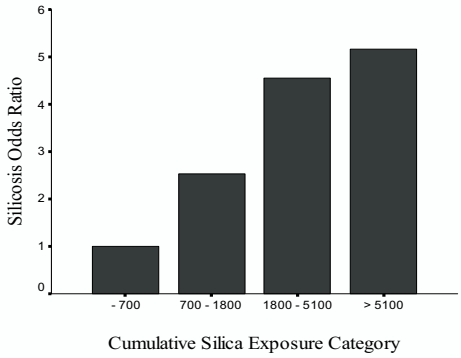
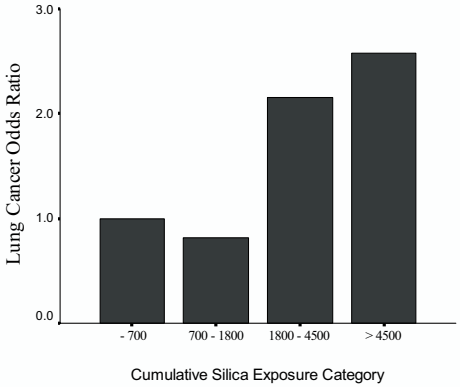
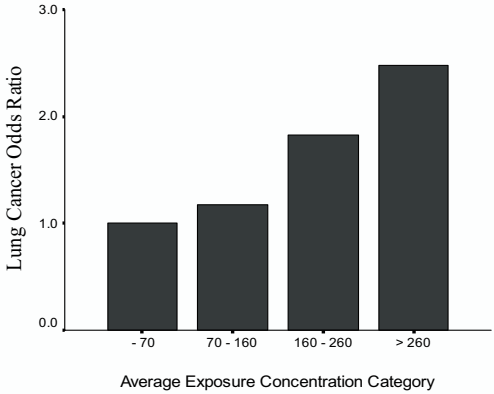


Adjusted Lung Cancer Odds Ratios by Cumulative Silica Exposure (μg/m^3-years)



Adjusted lung Cancer Odds Ratios by Average Silica Exposure Concentration (μg/m^3)

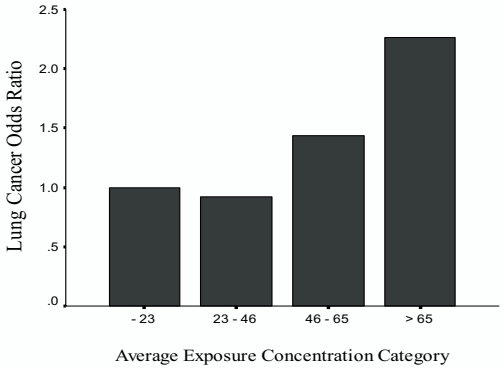


Comparison of N.A. sand cohorts

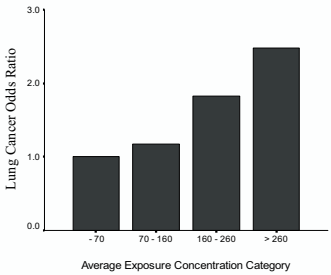
	Steenland et al	**McDonald et al**
Plants	18	9
N	4027	2670
Min. employment	1 week	3 years
Mean Year of Hire	1967	1957
Follow-up	1960 – 1996	1940 - 1994
% Deceased	24%	39%
TB cases	5	17 (7)
Silicosis/pneumoconiosis	17	30
Lung Cancer SMR	160 (n = 109)	137 (n = 96)

Lung Cancer Odds Ratios by Average Silica Exposure Concentration ($\mu g/m^3$) – Steenland et al

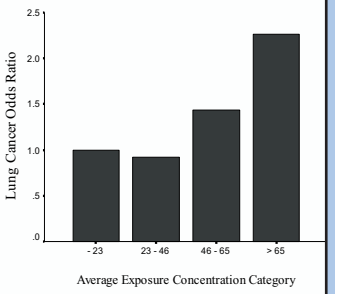
(case-control study, employed 6+ months)



McDonald et al



Steenland et al



Lung Cancer Odds Ratios

McDonald et al			Steenland et al		
Concen. ($\mu g/m^3$)	N cases	OR	Concen. ($\mu g/m^3$)	N cases	OR
≤ 70	23	1.00	≤ 23	15	1.00
> 70, ≤ 160	24	1.17	> 23, ≤ 46	12	0.92
> 160, ≤ 260	23	1.83	> 46, ≤ 65	20	1.44
> 260	20	2.48	> 65	28	2.26
Total:	90		Total:	75	

Estimating exposures in 2 studies

Factor	Rando	Sanderson
Plants	9	18
Time frame	1912 – 1994	1930s – 1996
Exposure data < 1974	7 Hatch reports 1947 – 1955	Hatch 1947 report
Exposure data ≥ 1974	14,249 measurements in company databases	4,269 measurements in databases of MSHA, 7 plants
Conversion factor	276 $\mu g/m^3$ per mppcf – measurements in sand plants	100 $\mu g/m^3$ per mppcf – studies in Vermont granite sheds
Personal respiratory protective equipment	Frequency of use with WPF = 5 factored in after ~ 1974	Not addressed
History of determinants of dust exposure	Specific histories of major plant/process changes, controls	None obtained. Inferences from stat. analyses
Validation	Positive correlation of silicosis mortality and exposure	Positive correlation of silicosis mortality and exposure

DIATOMACEOUS EARTH STUDIES

MORTALITY
RADIOLOGICAL CHANGE

G. GIBBS

DIATOMACOUS EARTH LOMPOC CALIFORNIA

- Checkoway et al 1992, 1993, 1996, 1997
- Hughes et al 1998
- Seixas et al 1997
- [Unpublished reports Gibbs & Christensen 1994. Hughes & Gibbs 2000].
- Mining and calcining.
- Amorphous/ Quartz / Cristobalite.

COHORTS

- Two plants
- 2570 white males. 37 black males, 242 white women, 8 black women.
- 104 white males excluded because of asbestos exposure.

FIRST STUDY

- 628 deaths
- SMR NMRD=2.59 [56]
- SMR LUNG CANCER = 1.59

RR trends

- NMRD 1.0, 1.19,1.37, 2.74
- Lung Cancer 1.00, 1.13, 1.58, 2.71
- (15 year lag chosen).
- Authors: “unlikely that smoking responsible”.

RE-ANALYSIS ASBESTOS.

- SMR Lung cancer = 1.41
- Rate ratios “after adjusting for asbestos” 1.0, 1.37, 1.80, 1.79.
- SMR = 8.31 (O=3) for highest cumulative exposure to both dusts.
- Pre-1930 workers excluded from the analysis.

SECOND FOLLOW-UP

- Quantitative dose-response.
- 749 deaths
- NMRD SMR = 2.01 [67]
- RR rose to 5.35
- Lung Cancer = 1.29
- RR for lung cancer rose to 2.15

Table 1
Lung cancer SMRs[a] by period of hire and termination of follow-up

Follow-up period	Year of hire < 1930 (n = 66)	1930 – 1949 (n = 903)	≥ 1950 (n = 1373)	Total (n = 2342)
1942 - 1987	8/3.2 252 109 - 497	36/26.0 139 97 - 192	16/11.9 135 77 - 219	60/41.1 146 112 - 188
1988 – 1994	0/0.2 -	9/9.2 98 45 - 185	8/9.4 85 37 - 168	17/18.9 90 52 - 144
1942 - 1994	8/3.4 234 101 – 462	45/35.2 128 93 - 171	24/21.3 113 72 – 168	77/59.9 129 101 – 161

a. Each cell contains observed/expected, SMR and 95% confidence interval for the SMR

Crystalline silica exposure (mg/m^3-yrs)	Hired 1930 – 1949 (n = 903)	Hired ≥ 1950 (n = 1373)	Total Hired ≥ 1930 (n = 2276)
< 0.5	12/8.7 138 71 – 240	10/9.3 108 52 – 197	22/18.0 122 77 – 185
0.5, < 1.1	4/6.1 66 18 - 170	8/5.6 142 62 – 282	12/11.7 103 53 – 179
1.1, < 2.1	6/7.3 82 30 – 179	3/3.8 78 11 - 229	9/11.1 81 37 – 153
2.1, < 5.0	11/7.7 143 72 - 257	3/2.2 137 28 - 400	14/9.9 142 78 – 238
≥ 5.0	12/5.5 219 113 – 383	0/0.4 -	12/5.8 206 106 – 360
Total	45/35.2 128 93 - 171	24/21.3 113 72 – 168	69/56.5 122 95 – 155
p-value for trend with exposure[b]	.032	NS	.041

1373 white males hired ≥ 1950

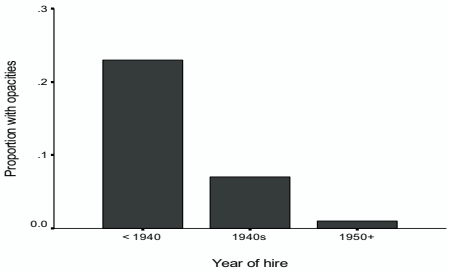
Crystalline silica exposure (mg/m^3-yrs)	O/E SMR	95% C.I.[a]
< 0.1	6/5.3 114	42 – 248
0.1, < 0.7	7/6.3 111	45 – 229
0.7, < 1.0	5/2.8 181	59 – 423
≥ 1.0	6/7.0 86	32 – 187
Total	24/21.3 113	72 - 168
p-value[b] for trend with exposure	NS	

'onfidence interval
ne-tailed test

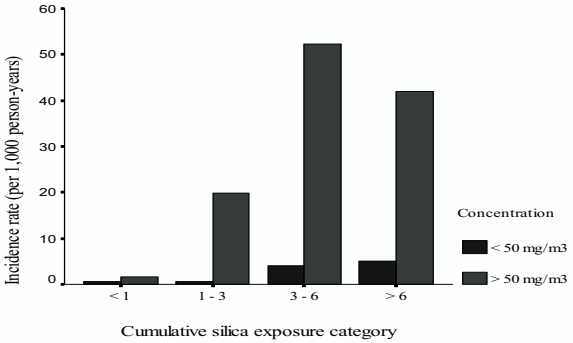
N = 1809 with post-hire chest x-ray

81 (4.5%) with opacities (small, ≥ 1/0, or large)

Prevalence related to year of hire:



Incidence of opacities by cumulative silica exposure category (mg/m^3-years), by concentration level



Estimated cumulative risk (%) of opacities

Cumulative Exposure (mg/m^3-years)	Average concentration (mg/m^3) ≤ .50	> .50
2.0	1.1	3.7
4.0	3.3	12.4

ISSUES-MORTALITY

- Pre-1930 workers
- Smoking data
- Lag period
- Asbestos exposure and adjustments
- Patterns in follow-up periods not consistent
- ? Synergy with asbestos?
- Exposure. Dust Conversions. Cristobalite - % in products.

ISSUES-RADIOLOGY

- No systematic follow-up after employment ceased.
- 82 retirees continued in surveillance program
- Participation not mandatory (77% pre-1940 – 91% post 1960).
- 2342 workers films for 1978 – 1 film only for 169.
- On average latest film 11 years after hire (22% more than 20 years after hire).
- “irregular opacities”? Out of 51 with 1/1, 14 were irregular opacities (predominant or exclusive)
- Not silicosis – DE pneumoconiosis.

ISSUES - RADIOLOGY

- Separate miners and millers
- While denominator substantial, the dose-response curve for the less than 0.5mg/m3 workers was only 23 with opacities.
- Post 1950 worker analysis would have been cleaner.

Two silica-exposed cohorts

Brian G Miller

INSTITUTE OF OCCUPATIONAL MEDICINE EDINBURGH, EH14 4AP, UK

Pneumoconiosis Field Research (PFR) Study

Entire working populations of 24 (later 10) collieries representative of GB coal fields

Regular (~5-year) x-rays, respiratory symptoms and smoking questionnaire, lung function

Very detailed work histories linked to regular job-specific sampling for respirable dust and silica

High differentation in individual exposure estimates

Radiological results used to set 1970s dust limits in UK, US

Mortality follow-up (to 1990) on all coal workers studied (>50,000)

Buchanan *et al* reported on >18,000 in Phase II, with best estimates of exposure

Principal PFR results

Clear, broadly consistent relationships for radiology

- Radiology related to individual dust exposures
- Cumulative exposure a reasonable metric
- No clear association with quartz content after dust

Mortality results:

- Increased risk with increased exposures
- Pneumoconiosis
- Chronic bronchitis & emphysema
- Stomach cancer
- No clear association with quartz content after dust

The Scottish anomaly

One colliery in Scotland

- Only Scottish colliery of 10 in Phase II of PFR
- Sandstone roof and floor
- High exposures to quartz in early 1970s
- Associated with one of three seams
- Unusually rapid radiological changes noticed

Scottish quartz freshly fractured, not ‘dirt band

Maximise information from ‘natural experiment’

- Follow-up in 1990 showed extensive changes
- Changes since exposure ceased
- Appearances described as typical of silica exposures
- E-R relationships - higher risks from higher concentrations

Study of GB heavy clay workers

Studied at 18 heavy clay sites

Health survey on 1934 workers

- Chest radiograph
- Respiratory, smoking and work history questionnaires

Personal sampling for respirable dust and quartz

Exposure concentrations by job, kiln type applied retrospectively

- Individual exposure estimates

Observed very little abnormality

Comparisons of risks

PFR data reanalysed in detail for HSE (Buchanan *et al* 2004)

Gave logistic regression equation for predicting risks of radiological abnormalities (2/1+, 1/0+)

Apply PFR risk prediction equation to observed exposures in heavy clay workers

Compare totality of predicted risks with observed risks

Predicted risks

Profusion Category	Quartz exposure assumption	Total Risk (No of cases)	
		Predicted	Actual
Cat 1/0 +	No Latency	**468**	**26**
	15 Years Latency	**331**	
Cat 2/1 +	No Latency	**86**	**8**
	15 Years Latency	**31**	

Table 6
Predicted risks and observed frequencies of radiographic abnormalities

Possible extensions

PFR coal workers

- Already 'flagged' for mortality by ONS
- Time-varying exposures
- We could analyse with additional 10 years' follow-up
- Including >1400 at Scottish colliery, low and high quartz

Heavy clay workers

- Could follow-up for longitudinal analysis of silicosis
- Could follow-up and trace for mortality study

Exposure-response for silicosis in South African (SA) gold miners E. Hnizdo

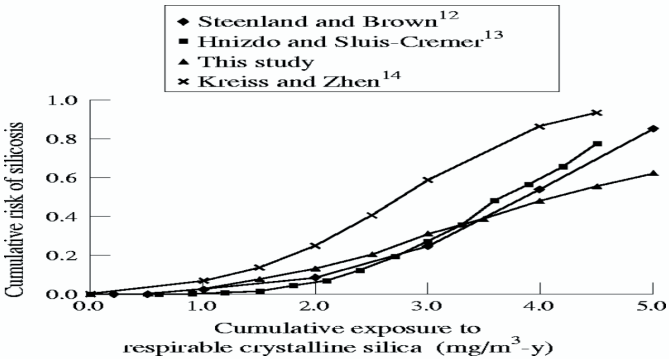
- Two studies used gravimetric measurements:
- Study 1: Cohort - 2260 miners exposed 1940-1975 (Hnizdo & Sluis-Cremer, Am J Ind Med, 1993)
- Study 2: Cross-sectional study-520 miners 1978-2000 (Churchyard, *et al*. SIMRAC Report, 2003)
- Dust exposure surveys 1930-2003 in gold mines

Study 1: Incidence of silicosis

- Onset of silicosis x-ray ILO category ≥1/1, 1940-death
- CDE=∑no. of shifts · the mean respirable dust concentration · the average number of hours spent underground /(270 ·8)
- Mean respirable dust concentrations derived from Respirable Surface Area and respirable particle counts after heat and hydrochloric acid treatment

Du Toit RSJ, NCOH Report, 1991

Cumulative risk of silicosis agrees with other studies



Chen JQ, *et al.* Occup Environ Med 2001;58:31-37.

Study1: Estimation of quartz exposure

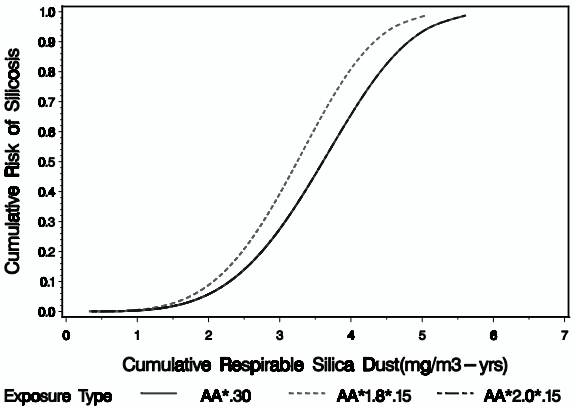
- Suggested:
- Respirable Surface Area before acid treatment should have been used → × 1.8

- 1. Resp. silica dust = resp. dust AA×1.8×0.30
- 2. Resp. silica dust = resp. dust AA×1.8×0.15
  = resp. dust AA× 0.27

Gibbs GW and DuToit RSJ. Quartz exposure in SA gold mines. Ann Occup Hyg 2002; 46:597-607.

Kielblock AJ, et al. Health risk in SA mines. SIMRAC 1997.

Cumulative risk of silicosis



Study 2: Year 2000

- Cross-sectional study of 520 miners ≥38 yrs old
- 23% - ILO profusion ≥1/1
- Dust exposure:
  - Personal sampling on 112 workers, 506 samples
  - Routine surveillance measurements, 715 samples
  - Quartz: x-ray diffraction (NIOSH method)
  - JEM: 23 occupational categories

Churchyard G, et al. Silicosis prevalence and exposure response in SA goldminers. SIMRAC Report, 2003.

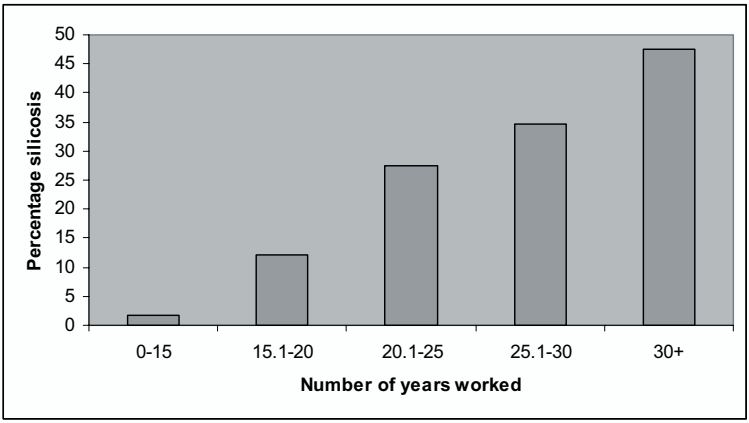
Respirable dust and α-quartz concentrations and percentage in 506 and 715 samples

Research measurements	**Mean**	**SD**
TWA resp. dust (mg/m^3)	0.35	0.46
Alpha quartz fraction (%)	12.0	5.6
TWA resp. quartz (mg/m^3)	0.048	0.072
Routine measurements		
TWA resp. dust (mg/m^3)	0.36	0.44
Alpha quartz fraction (%)	16.0	5.8
TWA resp. quartz (mg/m^3)	0.051	0.072

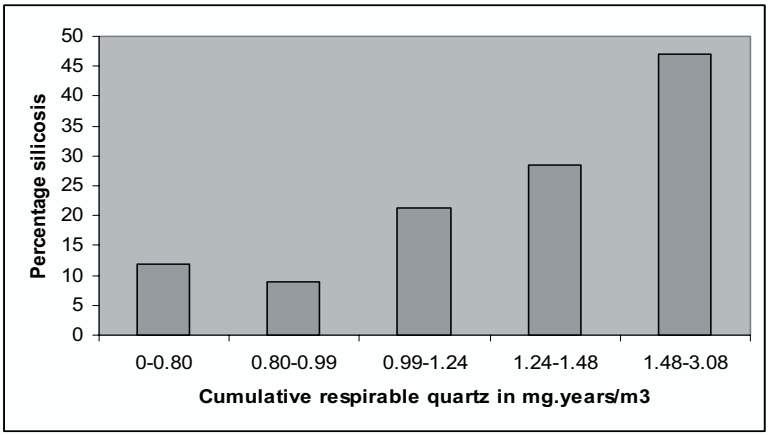
Study 2: Results

- Mean duration of service - 22 yrs (6-35)
- Mean respirable dust - 0.37 mg/m^3 (0-3.7)
- Mean quartz - 0.053 mg/m^3 (0-0.095)
- Cumulative resp. dust exp. - 8.2 (0-22.7) mg/m^3-yr
- Cumulative resp. quartz exp. - 1.2 (0-3.1) mg/m^3-yr

Study 2: Prevalence of silicosis by length of service



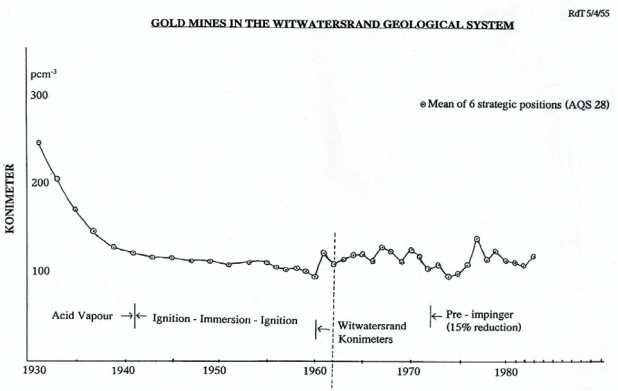
Study 2: Prevalence of silicosis by quintile of cumulative quartz exposure



Study 2: Conclusions

- The mean respirable quartz was ≈ 0.05 mg/m^3
- The range was entirely below 0.1 mg/m^3
- The mean quartz fraction was 12% to 16%
- The 30% quartz assumed by Hnizdo *et al*. was an overestimate
- The limit of 0.1 mg/m^3 is not adequately protective for silicosis

Dust levels in SA gold mines



DuToit RSJ, Ph.D. Thesis 1980s

Respirable dust in South African surveys (Rendall REG, 1999)

Table 4.8 Mean Respirable Dust and Quartz Concentrations Encountered in Mines and Foundries

SURVEY DATE	MEAN DUST (mg/m^3)	MEAN QTZ (mg/m^3)	AGENCY	REMARKS
Gold Mines				
1987-88	0,39	0,06	COM	Table 4.1
1977	0,40	0,08	COM	para 4.2.1.2
1977	0,46	0,08	CHL	Table 4.2
1964	0,40	0,09	CHL	Table 4.3
1956	0,35*	-	CHL	Table 4.4
Foundries				
1986	2,41	0,27	Rendall	Table 4.7
1984	1,82	0,17	Rendall	Table 4.5
1983	1,90	0,12	Rendall	Table 4.6

*Estimated from TP particle count.

Conclusion— silicosis prevention in South African goldmines

- The new evidence from SA studies shows that exposure limit of 0.1 mg/m^3 for crystalline silica is not entirely protective for the prevention of silicosis and other diseases associated with silica dust.

Respirable dust and quartz concentrations (mg/m^3): mine survey 1987-1988

	Developer		Stoping							Haulage		Supervisor	
JOB	1	2	1	2	3	4	5	6	7	1	2	1	2
RD	.48	.30	.38	.51	.41	.35	.37	.42	.36	.41	.40	.28	.42
RQ	.06	.03	.06	.11	.07	.07	.14	.07	.06	.05	.04	.04	.06
RQ %	13	10	16	22	17	20	38	17	17	12	10	14	15
n	35	19	59	55	51	54	29	125	81	22	20	13	25

6-mine survey of SA gold mines-1977

Statistic	Drilling	Lashing	Team Lead	Winch Driver	Trammer	Loco Driver	Mean
Resp dust	0.68	0.52	0.52	0.49	0.43	0.29	0.46
Quartz mg/m3	0.13	0.11	0.02	0.08	0.05	0.02	0.08
Quartz %	19	21	4	16	12	7	17

Respirable dust and quartz concentrations (mg/m^3) by job categories (Rendall)

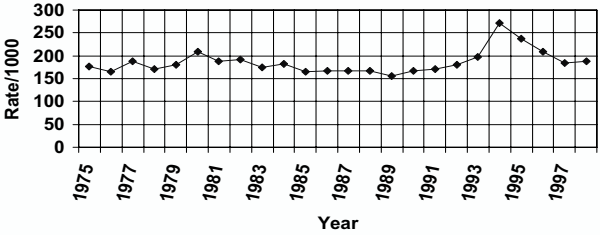
Job category	Respirable dust	Quartz
1. Shaft sinkers	0.52	0.12
2. Developers	0.43	0.12
3. Stopers	0.40	0.09
4. Work in haulage	0.36	0.06
5. Shift bosses	0.28	0.05
6. Senior officials	0.12	0.04
7. Banksmen	0.30	0.04
8. Workers near shaft	0.15	0.04
9. Other artisans	0.15	0.04

Respirable dust and quartz concentrations (mg/m^3) assigned to job categories

Job category	Respirable dust	Quartz 30%	Quartz 54%
1. Shaft sinkers/developers	0.48	0.14	0,26
2. Stopers	0.37	0.11	0.20
3. Assist. Miners/trammers	0.27	0.08	0.15
4. Shift bosses	0.30	0.09	0.16
5. Other Officials	0.30	0.09	0.16
6. Banks/skips	0.13	0.04	0.07
7. Workers near shaft	0.10	0.03	0.05
8. Boilermakers	0.19	0.06	0.10
9. Other artisans	0.19	0.06	0.10

Prevalence of silicosis at autopsy in gold miners

FIG 4-2 PREVALENCE RATES OF SILICOSIS FROM 1975-1998 in SA GOLD MINES



Western Australian Gold Miner Studies
N. De Klerk

- Nick de Klerk[1,2]
- Gina Ambrosini[1]
- Bill Musk[1,3]
  - [1]School of Population Health, University of Western Australia.
  - [2]Centre for Child Health Research, UWA & Telethon Institute for Child Health Research, Perth.
  - [3]Dept of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth.

Previously:

Silicosis:

Log months underground	1.96 (1.65-2.34)
Rank intensity of exposure	1.24 (1.18-1.30)
Log months surface	1.58 (1.31-1.91)

Lung cancer:

log(exposure-score year)	1.31 (1.01-1.70)
After adjustment for silicosis	
log(exposure-score year)	1.20 (0.92-1.56)

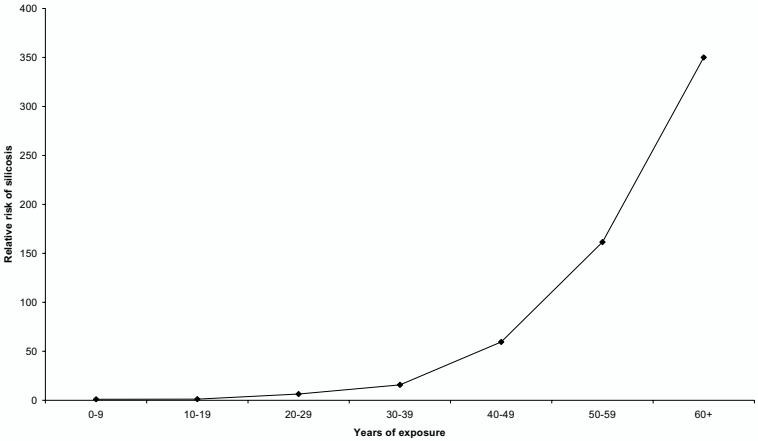
Methods

- Cohort assembled from x-sectional surveys in 1961, 1974, 1975
- Job histories obtained from Perth Chest Clinic
- All jobs (~400) ranked for dust exposure by expert team
- Jobs related to detailed dust counts and annual averages using regression smoothing

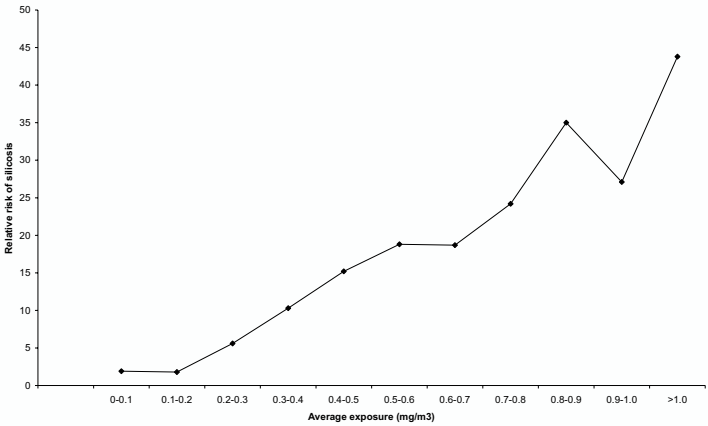
Methods

- Follow-up after work through electoral roll, death registers, telephone books
- Onset of silicosis – first award by Medical Board
- Lung cancer and other mortality from death certificates
- Data analysis using Cox regression and propensity score matching

Silicosis and duration of silica exposure



Silicosis and average silica exposure



Mortality and silica exposure

Outcome	N cases	Adjusted	RR Log (mg/m^3-yr)	Silicosis
Lung cancer	136	Smoking	1.2 (0.9,1.6)	1.6 (1.1,2.2)
AID	12	-	1.3 (0.5,3.6)	7.3 (1.9,29)
ESRD	13	-	1.2 (0.4-3.1)	1.4 (0.4,4.8)

Silica, silicosis and lung cancer

	RR-log (mg/m^3-yr)	RR-silicosis
After silicosis adjustment	1.0 (0.7,1.4)	--
After propensity score matching – each alone	1.2 (0.7,2.2)	1.6 (1.1,2.5)
After propensity score matching - together	1.0 (0.6,1.9)	1.6 (1.1,2.5)

Table 2. Estimated person-years at risk of silicosis for goldminers in Western Australia, 1979-1998*

Years of exposure	Person-years
1-9	54,917
10-19	6,818
20-29	175
30+	0
TOTAL	61,910

*Subjects with more than 5 years since first exposure, first exposed after 1974.

Upper confidence limit for zero observed cases

Based on the observation of zero cases and the estimate of 61,910 person-years at risk, an upper 95% confidence limit for the rate of compensated silicosis in Western Australian gold miners under current workplace practices is estimated at 4.8 cases per 100,000 person-years (3 divided by 61 910).

Conclusions

- No reported silicosis in Western Australia (after previous standard)
- People with silicosis have raised rates of autoimmune disease mortality
- People with silicosis have raised rates of lung cancer
- Some evidence of a threshold for silicosis

Further work

- ILO classification for x-rays
  1400 completed
- Matched to National Death Index, National Cancer Clearing House, Linked Hospital Morbidity Data up to 2002

Epidemiological research of Chinese miners and pottery workers

- Depart. Of Occup. & Environ. Health,Tongji Medical College, China (W Chen, J Chen, Z Wu, R Chen)
- Division of Respiratory Disease Studies and Health Effects Laboratory Division, NIOSH, CDC, U.S.A (FJ Hearl, W Wallace, MD Attfield, H Eva)
- Occupational Epidemiology branch, National Cancer Institute,U.S.A (JK Mclaughlin, M Dosemeci, W Blot)
- BG-Institute for Occupational Safety and Health (of HVBG), Germany (F Bochmann, Y Sun)

Design of research

Objectives

To assess whether silica or silicosis induce lung cancer.

The exposure-response relationship between exposure to crystalline silica and risk of silicosis.

To evaluate mortality from respiratory diseases,cancer and other causes among silica dust-exposed workers.

The cohort

Total subjects: 74033 workers (51422 exposed workers)

The selected criteria: employees worked for at least 1 year between 1960 to 1974 in 29 Chinese mines/factories.

- **Workers or miners with dust exposure are stable, the most of them work in the same mine/factory more than 20 years.**

Statistical methodology

Retrospective cohort study and nested case-control study

Exposure assessment methodology

Environmental dust monitor was started from 1950, 22890 historical estimates were developed for 21 calendar-year periods, using 2.3 million monitoring data points.

American measurements (NIOSH) did side by side dust samples with Chinese dust samples in 1988-89. Total dust, percent free silica and respirable dust, and potential confounding were measured.

A facility, job title, calendar year exposure matrix was created base on above information.

Health outcome

Diagnoses of Silicosis: based on Chinese pneumoconiosis roentgen diagnostic criteria and comparison with ILO criteria.

Mortality ascertainment **(Cause-of-death)**

Level 1: Medical record in hospital — 57%
Level 2: Personal doctor — 40%
Level 3: Oral sources — 3%

The results

Cohort data in the end of 1994

	Tungsten	Iron/copper	Tin	Pottery	Total
Mine/factory (n)	10	6	4	9	29
Subjects (n)	32912	18581	8243	14297	74033
Dust-exposed workers (n)	26143	11336	4913	9350	51422
Silicosis (n)	7788	689	1085	1218	10780
Lung cancer (m+f)	183	77	147	132	539
Lc+silicosis	43	8	63	22	128
Decased (n)	7870	1262	1391	2733	13434

Results and conclusion

Lung cancer risk showed limited/modest association with cumulative silica exposure. Other occupational hazards seem important in carcinogenesis of lung cancer.

Risk of lung cancer increased among silicotic subjects in some mines, but not in others.

Clear exposure-response relation was detected for silicosis and cumulative silica dust exposure. The characteristics of silica dust may affect the risk of silicosis.

Current status and future plans

Extend follow up to the end of 2003. To obtain complete health outcome for workers with 40-year occupational exposure to crystalline silica. Less expensive

Exposure-response analyses for exposure to crystalline silica dust and silicosis and lung cancer. Adjust or eliminate the interference from other confounders such as smoking, PAH, arsenic.

Re-evaluate environmental confounders and conversion factors for silica exposure.

Thank you

The Evaluation of Hazard of Mixed Dust Particles in Four Chinese Tin Mines

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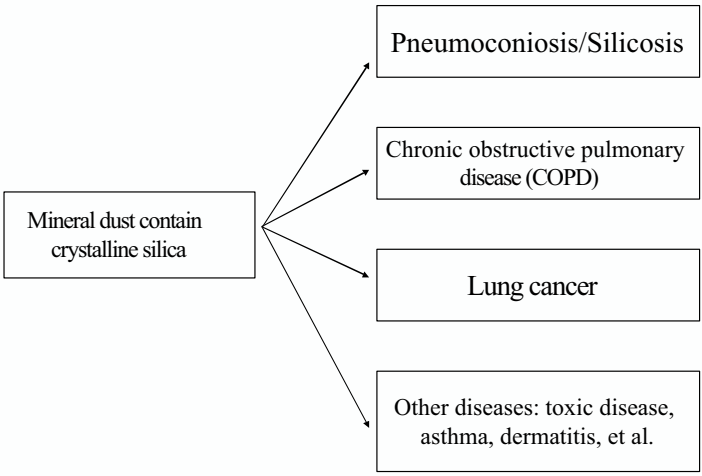


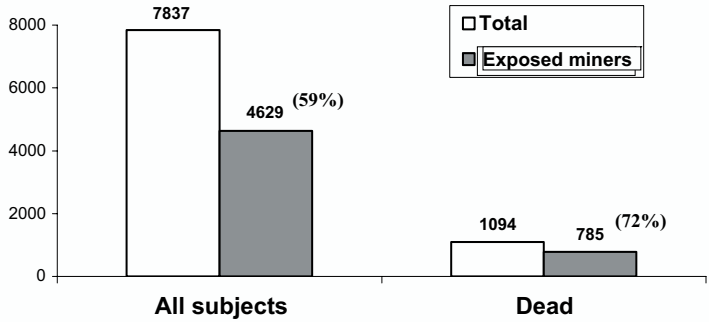
Introduction: four Chinese tin mines

• Elemental composition of dust particles from tin mines

Elements	Changpo (%)	Bali (%)	Tongken (%)	Limu (%)
Cryst. silica	**43.60**	**10.40**	**15.10**	**12.00**
Aluminum	2.80	0.51	0.58	2.24
Iron	2.02	3.16	6.72	3.73
Arsenic	**0.40**	**0.26**	**0.72**	**0.05**
Calcium	9.62	38.87	19.22	17.83
Zinc	0.33	1.55	2.39	0.12
Tin	0.04	0.02	0.06	0.06

Dust concentration > 25mg/m³ before 1957, dramatically decreased to 1-4 mg/m³ after the 1980s.

• A cohort of 7837 tin miners was followed to the end of 1994 and 1094 (14%) miners had died.



Cause-of-death determination

Level 1: Medical record in hospital — 57%

Level 2: Personal doctor — 40%

Level 3: Oral sources — 3%

Standardized mortality ratios (SMR) among dust exposed miners by cause of death in four tin mines

Cause of death	Changpo	Bali	Tongken	Limu
All causes	1.07	1.17	1.52*	0.95
Cancer	1.77*	2.35*	2.52*	1.15
Liver	2.32*	3.69*	5.03*	1.36
Lung	4.13*	4.83*	5.94*	1.69*
Respiratory disease	0.63*	0.87	0.00	1.73*
Pneumoconiosis	27.78*	21.43*	0.00	87.88*

* 95% confidence interval of SMR excludes 1.00.

Results in epidemiological study

1. Cancer, cerebrovascular diseases, and cardiovascular diseases were main diseases threaten workers' health and accounted for 68.6% of all deaths

2. Dust exposure caused elevated mortality in four tin mines. Especially, high SMRs from cancers and pneumoconiosis were observed.

Question

Are some mixed dust particles more fibrogenic and carcinogenic than others?

How to evaluate the harm of mixed mineral dust exposure early?

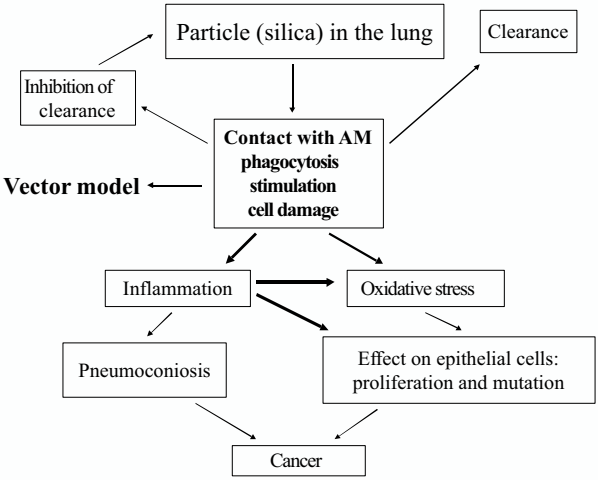
Biological tests

In vivo test — cost too much money and time

In vitro test

- Classic test — quantity of one effect; mostly toxicity
- Vector model — comprehensive qualitative and quantitative analysis of various stimulatory and toxic effects of particles in a multi dose array

Key Role of Alveolar Macrophages in the Inition of Dust Related Lung Diseases



The objects of this research

I. Determine toxic and inflammogenic effects of dust samples from four tin mines by *in vitro* tests.

II. Evaluate the relationship between *in vitro* tests on particles and epidemiological studies among miners.

Materials and methods

Study subjects
Dust samples
Methods — vector model
Cytoxicity determination: glucuronidase
Cell damage determination (release of H_2O_2)
Reactive oxygen species (ROS) assay (H_2O_2 methods)
TNF-alpha assay — cell lytic assay

The results of *in vitro* tests

Summary

1. The release of glucuronidase (cytotoxicity)

DQ12 > 4 tin mines ~ corundum

2. Cell damage percentage

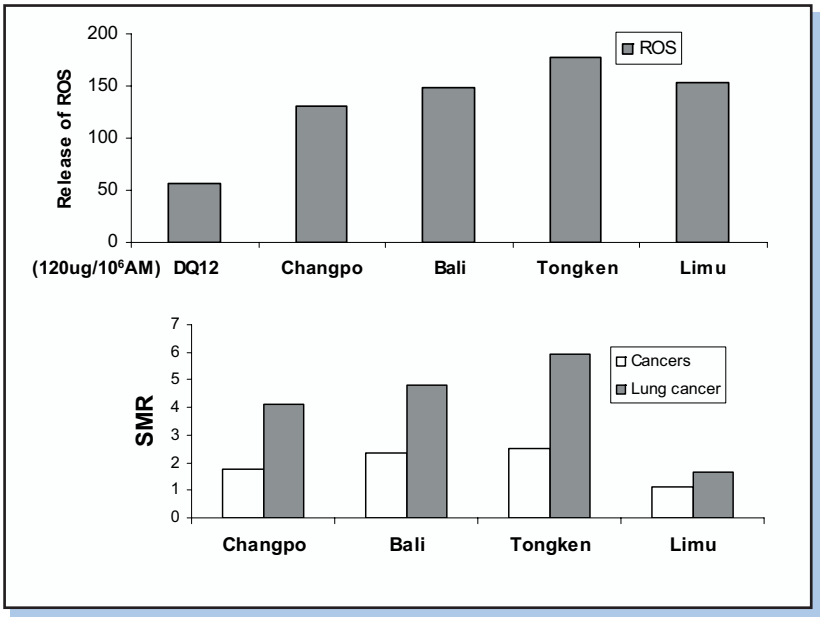
DQ12 > Tongken > Changpo, Bali, Limu ~ corundum

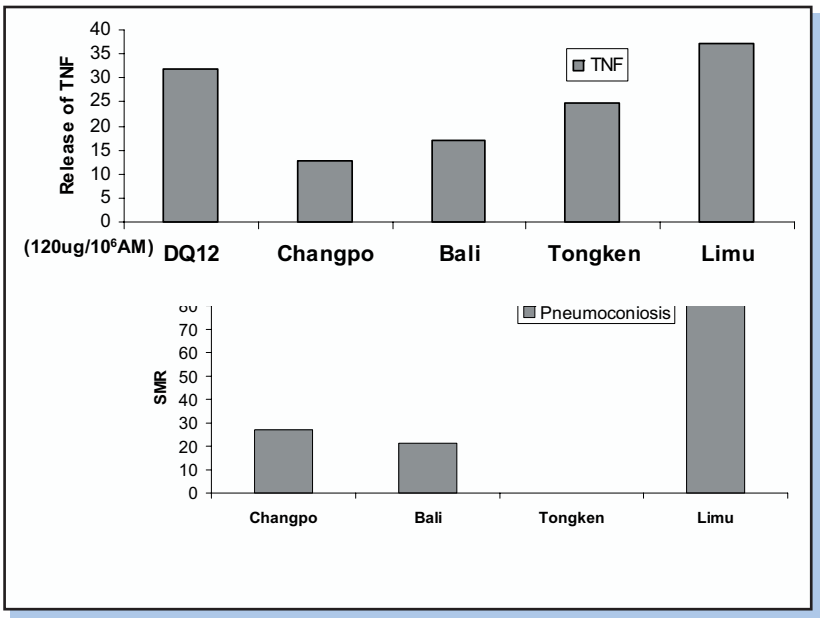
3. The release of ROS

4 tin mines > corundum ~ DQ12

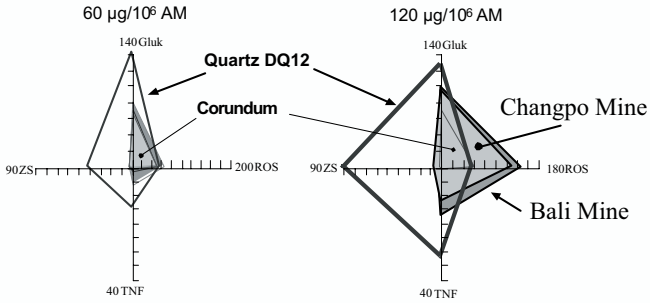
4.The releases of TNF-alpha

Limu >> DQ12 > Chanpo, Bali, Tongken > corundum


Release of ROS
200
150
100
50
0
ROS
(120ug/10⁶AM)
DQ12
Changpo
Bali
Tongken
Limu
SMR
7
6
5
4
3
2
1
0
Cancers
Lung cancer
Changpo
Bali
Tongken
Limu

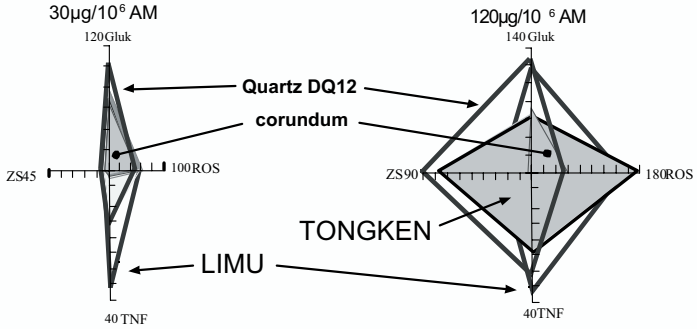

Release of TNF
40
35
30
25
20
15
10
5
0
TNF
(120ug/10⁶AM)
DQ12
Changpo
Bali
Tongken
Limu
SMR
70
60
50
40
30
20
10
0
Pneumoconiosis
Changpo
Bali
Tongken
Limu

Vectorgrams of respirable dusts from the mines CHANGPO (43% silica) and BALI (10 % silica); samples tested in dose doubling steps, two doses are shown



Key results: the tin mine dusts stimulate the ROS secretion by AM; quartz does not (in a dose range up to 160 µg/ 10^6 AM, where other critical substances (TNF alpha) are secreted).

Vectorgrams of respirable dusts from the mines TONGKEN (15% silica) and LIMU (12% silica); dust samples were tested in dose doubling steps (2 doses are shown)



Key result: the respirable dust from Limu mine exerts a very high potential to elaborate TNF alpha, even at the lowest dose of 30 µg/10⁶ AM

Conclusion

I. Mineral dusts from four Chinese tin mines cause lower cytoxicity and cell damage, but induce AM to release elevated ROS and TNF-alpha

II. The high potential to stimulate TNF secretion (Limu Mine) exceeds that of the standard toxic reference quartz DQ12; the ROS secretion cannot attributed to the silica content alone. The tin mine dusts represent a very particular entity of toxic mixed dusts as compared to other silica species from various European deposits. These silica powders represent a large variety of the extension of toxicity, some of them come close to low toxic reference dust.

III. *In vitro* tests (vector model) can be used as a powerful tool to screen and monitor hazards such as tumour and pneumoconiosis caused by mixed mineral dust exposure.

Perspectives (1)

I. Recent studies[1] on respirable silica flours (99% CS) show variation in intrinsic toxicity by about 3 to 4 dose doubling (factor >10 X)

II. The intrinsic pathogenic potency of the dust at the worksites strongly influence the epidemiological results

III. An upcoming paper[2] substantiate the relevance of dust related variety of toxic potency. Chinese tin and tungsten mine cohorts are linked to much higher risk figures based on silica exposure than pottery cohorts

1 Bruch, J., Rehn, S., Rehn, B., Borm, P. J. A. and Fubini, B., Int J Hyg Environ Health, 207, 203-210 (2004). Seiler, F., Rehn, B., Rehn, S. and Bruch, J., Int J Hyg Environ Health, 207, 115-24 (2004).

2 Harrison, J., Chen, J.-Q., Miller, W., Chen, W., Hnizdo, E., Lu, J., Chisholm, W., Keane, M., Gao, P. and Wallace, W., (2004). Chen, W., Hnizdo, E., Chen, J.-Q., Attfield, M. D., Gao, P., Hearl, F., Lu, J. and Wallace, W., (2004).

Perspectives (2)

IV. The toxicological research is able to identify particular risks in various exposure settings
V. The existing high level of differences in risk figures at different epidemiological studies necessitate the clarification of the exposure related variables

Acknowledgment

Prof. Dr. med. J. Bruch

Prof. W. Dr. med. Chen and her colleagues in China

Ms. K. Stempelmann, Ms. S. Rehn, Mr. H. Diederichs,

and Dr. rer. nat. B. Rehn

Lung cancer risk and silica: First results of a new nested case control study

W. Chen[1], F. Bochmann[2]

[1]Tongji Medical College, Department of Occupational and Environmental Health, Wuhan, China

[2]BG-Institute for Occupational Safety and Health (of HVBG), Sankt Augustin, Germany

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Legislation, Questions

- Is silica a carcinogen ?
- TLV for silica ?

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Translation into Epidemiology

- Causality (Silica, Lung Cancer)
- Dose-Response Relationship

Strength of the Chinese silica study

- Largest epidemiological silica study world-wide
- Detailed monitoring data of dust exposure since early 1950s (more than 10,000 Measurements)
- Complete information on vital status (95%), cause of death (98%) and incidence of silicosis
- Only cohort that assessed relevant occupational confounders (radon, PAH, arsenic) quantitatively

Nested case control study for lung cancer

Why a “nested case control study” ?

Confounders (occupational and non-occupational) have rarely been considered in the evaluation of lung cancer risk among silica exposed workers.

Sampling strategy: “density sampling” (1:4)

Matching criteria: decade of birth
mines or factories

Statistical analysis: conditional logistic regression

511 cases and 1879 controls (among men)

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Effects (OR) without consideration of occupational confounders

Respirable silica (mg/m^3-year)	Tungsten (OR*, 95%CI)	Potteries (OR*, 95%CI)	Tin (OR*, 95%CI)	Iron/copper (OR*, 95%CI)
Non-exposed	Reference	Reference	Reference	Reference
1. quintile (0.1–1.1)	2.0 (0.97 – 4.19)	0.8 (0.29 – 2.19)	1.6 (0.75 – 3.52)	1.0 (0.51 – 1.77)
2. quintile (1.1– 2.6)	1.4 (0.64 – 2.81)	1.3 (0.63 – 2.64)	1.9 (0.96 – 3.78)	1.3 (0.56 – 3.07)
3. quintile (2.6 – 5.4)	0.6 (0.32 – 1.30)	1.7 (0.82 – 3.58)	1.8 (0.94 – 3.29)	1.8 (0.57 – 5.48)
4. quintile (5.4–10.1)	0.8 (0.42 – 1.51)	1.5 (0.71 – 3.21)	2.1 (1.14 – 3.80)	– –
5. quintile (10.1–72.4)	1.0 (0.55 – 1.66)	3.5 (1.45 – 8.66)	3.3 (1.66 – 6.61)	– –
But typical confounder	no	PAH	Arsenic	PAH, Radon

*adjusted for smoking

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Lung cancer risk among silica exposed workers in China

Effects (OR) with consideration of occupational confounders

Respirable silica (mg/m³-year)	Tungsten (OR*, 95%CI)	Potteries (OR*, 95%CI)	Tin (OR*, 95%CI)	Iron/copper (OR*, 95%CI)
Non-exposed	Reference	Reference	Reference	Reference
1. quintile (0.1–1.1)	2.0 (0.97 – 4.19)	0.7 (0.25 – 1.98)	–	0.7 (0.24 – 2.08)
2. quintile (1.1– 2.6)	1.4 (0.64 – 2.81)	0.7 (0.29 – 1.81)	–	1.0 (0.31 – 3.28)
3. quintile (2.6 – 5.4)	0.6 (0.32 – 1.30)	0.7 (0.25 – 2.19)	–	1.4 (0.33 – 5.50)
4. quintile (5.4–10.1)	0.8 (0.42 – 1.51)	0.5 (0.15 – 1.84)	–	– –
5. quintile (10.1–72.4)	1.0 (0.55 – 1.66)	0.9 (0.19 – 4.32)	–	– –
Additionally adjusted for	no	PAH	Arsenic	PAH, Radon

*adjusted for smoking

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Lung cancer risk among silica exposed workers in China

Effects estimated in a pooled analysis (without Iron/Copper)

	OR	95% CI
Arsenic (mg/m³-year)	1.69	1.07 – 2.68
Carcinogenic-PAH (per 100 µg/m³-year)	1.29	1.09 – 1.52
Radon (yes vs. no)	0.81	0.48 – 1.39
Respirable silica (mg/m³-year) per mg/m³-year	1.00	0.98 – 1.02
Non-exposed	Reference	–
1. quintile (0.1 –1.1)	1.22	0.57 – 2.59
2. quintile (1.1 – 2.6)	1.05	0.49 – 2.27
3. quintile (2.6 – 5.4)	0.81	0.36 – 1.79
4. quintile (5.4 – 10.1)	0.73	0.32 – 1.68
5. quintile (10.1 – 72.4)	0.86	0.35 – 2.09
	Trend-Test:	p= 0.17

Adjusted for Smoking, Arsenic, PAH and Radon

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Conclusion

- The observed excess risk of lung cancer among silica exposed workers is probably due to exposure to other occupational hazards (such as arsenic and PAHs) rather than due to exposure to respirable silica.
- Risk classification of silica exposure should be reconsidered because of new epidemiological evidence.

Perspectives

Recommendation of an extended Follow-Up of the Chinese Cohort

- Increased number of lung cancer cases
- Validation of the conversion factors for silica exposure and confounders
- Analysis are feasible despite of colinearity
- Less expensive

RIQUA

Thank you very much

for your attention

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Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers

A summary of the methods and results of the paper by

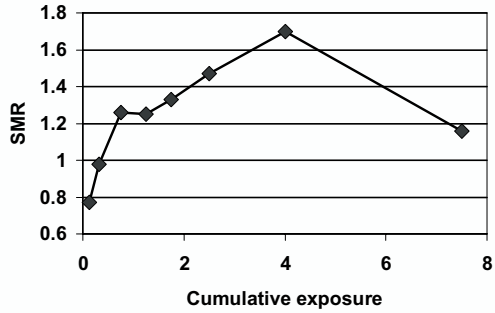
Michael Attfield and Joseph Costello

Am J Ind Med (2004) 45: 129-138

Methods

- 5,414 Vermont granite workers
- Employed in period 1950 to 1982
- Mortality followed up until 1994
- Dust data from six environmental studies
- Job concentrations from Davis et al. 1983
- Cumulative exposures using work histories
- SMRs, SRRs, and Poisson models
- Analyses: Unlagged, lagged (15 yr), untransformed, log transformed, with and without last exposures group

SMRs by cumulative exposure



Results: Predicted LC cases/1000

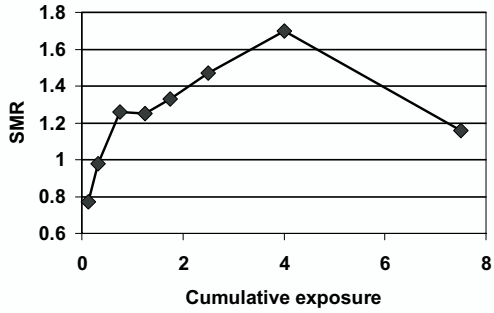
Dust level (mg/m^3)	# LC Cases	95% LCL	95% UCL
0,01	5	2	8
0.02	10	4	16
0.03	15	6	26
0.04	21	8	36
0.05	27	10	48
0.06	34	13	60
0.07	41	15	74
0.08	48	17	89
0.09	56	20	105
0.10	64	22	123

Untransformed exposure, 15 years lag, omitting highest exposure group, external adjustment

Comment

- Exposure-response for lung cancer showed a drop in the highest exposure group
- No clear explanation for this drop – possible reasons could be competing causes, diagnosis issues, exposure assessment
- Up to the highest group, exposure-response was monotonic; the penultimate two SMRs/SRRs were statistically elevated
- If a curvilinear model fitted, predicted risks at lower dust levels would have been similar.

SMRs by cumulative exposure



Weaknesses

- No SSNs for follow-up
- Dust data not company-specific

Strengths

- Quantitative exposures
- Dust data comprehensive (6 studies)
- Wide exposure range
- Long follow-up and large cohort size
- No other occupational confounders

			Exposure			
Work history, job title	Davis et al. [1983], job title	No.	Pre-1940	1940–1950	Post-1950	Note[a]
Cutter/marker/surfacer	Cutter	1,308	0.37	0.22	0.07	1
Channel bar	Channel bar operator	798	0.54	0.54	0.01	2
Lumper	Lumper	610	0.14	0.09	0.04	
Polisher	Polisher	570	0.12	0.10	0.07	
Sawyer/saw-helper/saw	Sawyer	562	0.05	0.04	0.04	3
Sandblaster	Sandblaster	451	0.06	0.05	0.04	4
Crane	Cranemen	255	0.14	0.09	0.03	5
Boxer	Boxer	247	0.14	0.09	0.03	
Draftsmen/designer	Office worker	179	0.01	0.01	0.01	
Foremen (shed)	Foremen (shed)	170	0.06	0.04	0.01	
Derrick (quarry)	Other quarry	161	0.06	0.04	0.01	6
Maintenance/repairman	Maintenance	121	0.14	0.09	0.03	
Plug drill	Plug drill operator	113	0.54	0.34	0.02	
		5,545				

[a]Respirable free silica measurements in mg/m^3. From personal and area measurements compiled from various studies 1924–1977 by Davis.
[b]1, 99% Of these are cutters (based on the examination of a 10% sample of these jobs); 2, includes Leyner bar operator and driller; 3, includes wire, diamond, carbo, gang, and circular saw; 4, includes sandblaster shaper and stencil sandblaster; 5, includes shed derrickmen; 6, includes quarry cranemen.

Conclusions

- Exposure-response relationship detected between cumulative respirable free silica and lung cancer (and TB, non-malignant respiratory disease and pneumoconiosis)
- 45 years exposure to silica at 0.05 mg/m^3 associated with 27 cases per 1000 (93/1000 using log model). At 0.1 mg/m^3, 64 cases per 1000 predicted.

Statistics for highest exposure group

- 19% were >=60 years old, 48% >50 years
- 21% of deaths in highest exposure group were associated with TB or silicosis

Results: SMRs and SRRs by exposure group

Cumulative exposure* mg-yr/m^3

Exposure level	0-	0.25-	0.5-	1.0-	1.5-	2.0-	3.0-	5.0-
SMR	0.77	0.98	1.26	1.25	1.33	1.47 a	1.70 b	1.16
SRR	1.00	0.91	1.28	1.32	1.32	1.38 a	1.76 a	0.86

* Time to first exposure = 15 years or more
a One-sided p<0.05
b One-sided p<0.01

The Vermont Granite Industry and Control of Disease
William G.B. Graham

Pre-1940: severe problem with early silicosis and deaths from silicotuberculosis. Average stone shed air was 20 mppcf, and pneumatic tool operators exposed to 60 mppcf.

1940: Vermont adopted standard of 10 mppcf (0.1mg/cubic meter). Twice yearly inspection of dust control. Annual chest films offered to workers.

1940-1955: Gradual reduction of dust due to improved industrial hygiene. Dust levels stabilized by 1955 to levels of 5-6 mppcf (0.05-0.06 mg/cubic meter).

1940-1970: No cases of radiographic silicosis apparent in workers hired after 1940.

1970: NIOSH established. Research by Peters et al concluded that an average year of dust exposure of 523 micrograms/cubic meter caused 2 ml. loss of FVC. Later papers suggested losses of 50-70 ml. in FEV 1.0 and 70-80 ml in FVC (Musk et al).

1974: Based on above studies, NIOSH criteria document adopted recommended exposure limit of 0.05 mg/cubic meter.

1981: Severe technical problems with estimated lung function loss became apparent. Workers predicted to have 350 ml LOSS of function actually GAINED 500 ml in FVC after a 5 year interval. Short expiratory effort and spirometer leak responsible.

1988: 8 year longitudinal lung function study showed loss only in relation to aging and smoking history. No loss in relation to granite dust exposure.

1991: Survey of 972 granite workers averaging 40 years in age and 20 years of exposure showed only 0.7% radiographic abnormalities suggestive of silicosis (small rounded opacities in upper lobes). Opacities of low grades of profusion. No large opacities.

2000: Study of retired workers. 26% of men (average age 77; tenure 43 yrs) beginning work before 1940 had radiographic abnormalities. Only 5.7% of men (average age 66, tenure 30 yrs) beginning work after 1940 had abnormalities. 19 of 20 of the latter began work before 1955.

2004: Follow-up of mortality study of 1988: for workers hired after dust control: no deaths from silicosis; SMRs for TB and respiratory disease, not elevated. SMR for lung cancer was elevated at 1.18 (C.I. 1.03-1.3) for all workers.

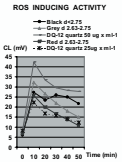
When workers hired before and after 1940 with similar latency (40 yrs) and tenure (30 yrs) were compared, the SMRs for lung cancer were similar (1.63** and 2.17*), despite great differences in quartz dust exposure and in SMRs for silicosis.

Conclusion: Control of quartz dust below the current OSHA PEL of 0.1 mg/cubic meter eliminated quartz related disease. Deaths from lung cancer appear not to be related to quartz levels. All cancer deaths occurred in smokers when smoking habits were known.

FINNISH GRANITE WORKERS
Riitta-Sisko Koskela

a. Exposure

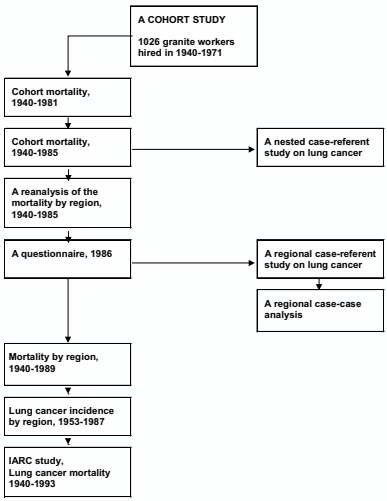
- Quarring, crushing, block processing
- Three main granite areas
  - red, grey, black
- Dust measurements
  - quartz and total dust
- Work histories
  - employers' records
  - questionnaires
- Quantitative exposure estimates
  - by job and calendar time
- Mineral composition
- In vitro experiments with fractionated dusts
  - cytotoxity tests
  - production of ROS



Mineral composition of the three types of granite.

Mineral	Types of granite		
	Balmoral red Vehmaa (%)	Grey Kuru (%)	Black Viitasaari (%)
Feldspar	41	38	0
Quartz	36	31	0
Plagioclase	16	20	60
Mica	7	9	0
Amphibole and pyroxenes	0	2	0
Augite	0	0	20
Fluorite	0	0	15
Hornblende	0	0	5
All	100	100	100

A flow-chart of the epidemiological cancer study



HEALTH AND CONFOUNDING DATA

OBTAINED DATA

* SYMPTOMS	1980-1992	QUESTIONNAIRE
* DIAGNOSED DISEASES	1980-1992	QUESTIONNAIRE
* REGISTERED DISEASES	1969-1992	MEDICINE REGISTER
	1953-1992	CANCER REGISTER
* CAUSES OF DISABILITY	1969-1992	DISABILITY REGISTER
* CAUSES OF DEATH	1940-1992 1993-2003	DEATH CERTIFICATES

* CODED ACCORDING TO ICD 8TH REV.

CONFOUNDING & MODIFYING

VARIABLE	DATA FROM	CONTROL
CARCINOGENIC OCCUPATIONAL EXPOSURE	EMPLOYERS' RECORDS QUESTIONNAIRE MEDICAL RECORDS	STRATIFYING EXCLUSION MATCHING
SMOKING	QUESTIONNAIRE MEDICAL RECORDS	STRATIFYING EXCLUSION MATCHING
REGION	REGIONAL REGISTERS ON POPULATION AND CANCER	STRATIFYING
OTHER DISEASES	QUESTIONNAIRE REGISTERS	EXCLUDING-COMORBIDITY
CALCULATION OF PERSON-YEARS	QUESTIONNAIRE REGISTERS	SEVERAL ANALYSES

RESULTS

EXCESS LUNG CA MORTALITY
EXCESS LUNG CA INCIDENCE

- AMONG SILICA EXPOSED

NO CONCOMITANT CARCINOGENS

LONG EXPOSURE TIMES AND LATENCY

SILICOSIS RARE

EXCESS MORBIDITY
- GI-CANCER
- RA
- RESP. DISEASES

Lung cancer morbidity in 1953–1987

Latency, years	Balmoral Red Obs.	Exp.	SMR	Grey Obs.	Exp.	SMR
≥10	25	12.3**	203	17	7.8**	218
≥15	19	9.8**	194	15	6.4**	234
≥20	17	6.9***	246	11	4.8*	229
≥25	13	4.4***	295	6	3.2	188
≥30	9	2.4***	375	3	1.8	167
Total	25	15.4*	162	17	9.4*	181

* P<0.05, **P<0.01, *** P<0.001, Poisson distribution

Observed and expected lung cancer deaths in 1940–1989

Area	Latency (years) <20 Obs.	Exp.	≥20 Obs.	Exp.	Σ Obs.	Exp.
Balmoral red						
<10 years of exposure	1	1.8	4	2.7	5	4.6
≥10 years of exposure	0	1.1	13	9.8	13	10.9
Σ	1	2.9	17	12.5	18	15.4
Grey						
<10 years of exposure	1	1.6	3	2.5	4	4.1
≥10 years of exposure	4	0.6*	9	5.1	13	5.6**
Σ	5	2.2	12	7.5	17	9.7*
Both						
<10 years of exposure	2	3.4	7	5.2	9	8.6
≥10 years of exposure	4	1.7	22	14.9#	26	16.5*
Σ	6	5.1	29	20.1*	35	25.1*

P=0.05, * P<0.05, ** P<0.01, Poisson distribution

Exposure to silica dust and lung cancer risk in Germany

a) Case-control study among nonsilicotics (Thorax , 1999)

b) Cohort study among silicotics
(Int Arch Occup Environ Health, 2004)

Ulm et al. Institute for Medical Statistics and Epidemiology,
University of Technology, Munich (Germany)

with the help of the insurance institutes of the
stone & quarry industry
glas- and ceramics industry (only study a)

a) Case-control study among nonsilicotics (Thorax , 1999)

Cases with lung cancer: n = 247 (stone: n = 133; ceramic:n = 114)

Controls: n = 795 (stone: n = 231; ceramic:n = 564)

Controls matched by age and smoking habits.

All workers with exposure to silica dust **and** without silicosis

*Table 5 Odds ratios with 95% confidence intervals for the different measures of exposure**

Type of exposure	*Stone and quarry*	*Ceramics*	*Both industries*
Time weighted	0.81 (0.37 to 1.77)	1.03 (0.49 to 2.16)	0.91 (0.57 to 1.46)
Cumulative	0.86 (0.38 to 1.95)	1.05 (0.59 to 1.86)	1.02 (0.67 to 1.55)
Peak	1.25 (0.58 to 2.69)	0.75 (0.46 to 1.24)	0.85 (0.58 to 1.25)

*Adjusted for age at onset of exposure, year of first exposure, duration of exposure, latency, and additional exposures in the work place.
Each index is divided into two levels (low and high): time weighted and peak exposure, low ≤ 0.15 mg/m^3; cumulative exposure, low ≤ 2.88 mg/m^3 • years.

*Table 6 Relative risk for lung cancer by time weighted average and cumulative exposure**

Exposure	*Cases*	*Controls*	*OR*(95% CI)*
Cumulative exposure (mg/m^3 • years)			
<1.56	63	195	1.00
1.56–2.88	54	197	0.95 (0.48 to 1.53)
2.89–4.68	52	212	0.92 (0.44 to 1.61)
>4.68	78	191	1.04 (0.53 to 1.89)
Σ	247	795	
p for trend = 0.69			
Time weighted average exposure (mg/m^3)			
<0.04	64	194	1.0
0.04–0.07	45	207	0.74 (0.42 to 1.27)
0.08–0.11	62	209	0.96 (0.56 to 1.71)
≥0.12	76	185	0.82 (0.47 to 1.44)
Σ	247	795	
p for trend = 0.87			

*Adjusted for the same factors as listed in table 5.

b) Cohort study among silicotics
(Int Arch Occup Environ Health, 2004)

Workers from the stone & quarry industry (n= 440)

Selection criteria: compensation between 1988 – 2000 (x-ray ≥ 1/1; MDE ≥ 20%)

Follow-up period: date of compensation until death or 31.12.2001

Exposure: recording of all job with and without eposure to silica dust
characterisation of the level in 6 categories

Phase 1: dust measurements (25 %)
or exposure assessment by industrial hygienists

Phase 2: Job-Exposure matrix (based on the data of phase)

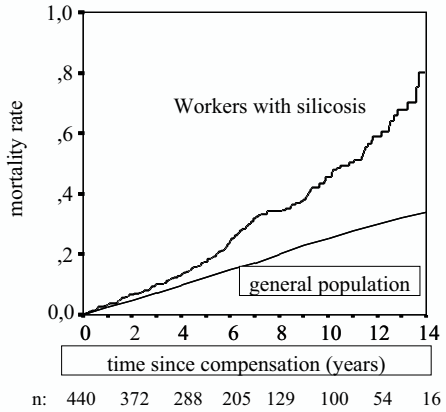
Other variables (e.g. smoking) from already existing files

Cause of death assertained by death certificates

SMR for selected causes of death for male silicotics (n = 440)

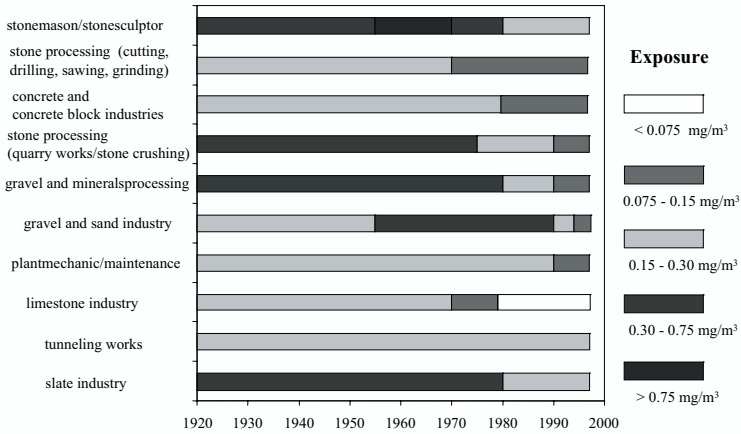
	ICD	Obs.	Exp.	SMR	95% CI		p-value
all causes	000-999	144	74,35	1,94	1,63 -	2,28	0,000
all tumors	140-208	37	22,73	1,63	1,15 -	2,25	0,004
.lung cancer	162	16	6,67	2,40	1,37 -	3,90	0,001
.all other tumors		21	16,06	1,31	0,81 -	2,00	0,184
tuberculosis	010-018	6	0,08	75,00	26,99 -	164,33	0,000
NMRD	460-519	55	5,43	10,13	7,63 -	13,19	0,000
pneumoconioses	500-508	48	0,23	208,70	153,83 -	276,87	0,000
disease circ. system	390-459	29	32,64	0,89	0,59 -	1,28	0,702
isch. heart disease	410-414	9	16,47	0,55	0,25 -	1,04	0,966

*) NMRD = non malignant respiratory diseases



Eurosil; NewYork 5. - 6.8.2004 7

relation between job and exposure



Eurosil; NewYork 5. - 6.8.2004 8

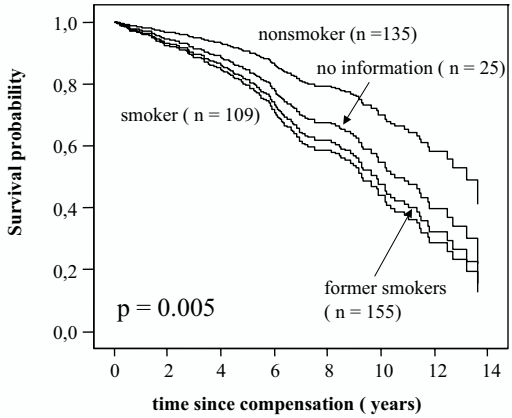
Level of exposure (n = 440 workers)

exposure	min	5%	10%	25%	50%	75%	90%	max.
average (mg/m³)	0,10	0,18	0,21	0,39	0,58	0,85	1,10	1,50
cumulativ (mg/m³ · years)	0,79	3,72	5,25	8,78	18,90	30,90	34,28	55,50
duration (years)	3	13	16	23	33	39	43	58

SMR for total mortality within different jobs

jobs	n	Obs.	Exp.	SMR	95% CI	p-value
stonemason/stonesculptor	262	79	42,29	1,87	1,48 - 2,33	0,000
stone processing (cutting)	16	2	2,47	0,81	0,08 - 2,98	0,706
stone processing (crushing)	29	13	7,87	1,65	0,88 - 2,83	0,058
gravel and mineral	14	9	2,81	3,20	1,45 - 6,11	0,002
gravel and sand industry	26	7	3,38	2,07	0,82 - 4,29	0,056
concrete industries	24	8	3,88	2,06	0,88 - 4,08	0,044
underground workers	12	5	2,06	2,43	0,77 - 5,71	0,058
slate industry	39	18	7,43	2,42	1,43 - 3,84	0,001
other jobs	18	39	2,19	1,37	0,26 - 4,05	0,375
total	440	144	74,35	1,94	1,63 - 2,28	0,000

Survival rates for total mortality (age at comp = 62.5 years)



Summary of both studies:

-no or low lung cancer risk für nonsilicotics
-increased mortality rate for silicotics (SMR ≈ 2)
-increased lung cancer risk for silicotics (SMR ≈ 2 – 2.5)

Prevention avoiding silicosis:

-exposure limits:

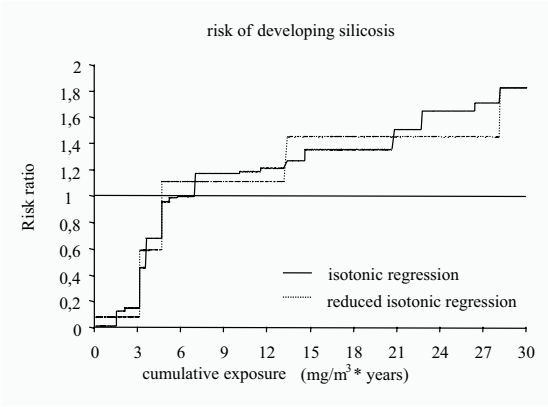
-peak < 0.15 mg/m^3

-cumulative < 3 mg/m^3* years

-average < 0.10 mg/m^3

Prevention reducing mortality risk among silicotics:

Smoking prevention


risk of developing silicosis
Risk ratio
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0 3 6 9 12 15 18 21 24 27 30
cumulative exposure (mg/m3 * years)
isotonic regression
reduced isotonic regression

UK Pottery Workers

Nicola Cherry
Gary Burgess
Sue Turner
Corbett McDonald

Epidemiological Perspectives
on Silica at Work

New York, 5-6 August 2004

Cohort definition

- Card index of all workers seen in Stoke on Trent by the Silicosis Medical Boards (and successors)
- Male, born 1916 – 1945, no minimum period of employment **(N=7064)**
- Exclusions- any recorded work with asbestos, foundries ≥ 1 year with coal or “other dusts”, first seen outside the Stoke on Trent area **(N=5115)**

Data available

- On hire and every two years (since 1931)
  - Medical examination with standard medical record forms
    - Job or process
    - Duration of previous dust-exposures (asbestos, foundries, etc)
    - Smoking habit
- On hire and every four years (since 1948)
  - Chest radiograph (posterior – anterior)
  - Classification on ILO system

First follow-up (to June 30, 1992)

Outcomes

- Mortality (vital statistics, cause of death)
- Pneumonicosis (chest radiograph)
- [rheumatoid arthritis]

Exposures

- JEM using exposure data from government agencies with "representative" (not worst case) sampling strategies

First follow-up (to June 30, 1992)

Tracing – through DSS using National Insurance Number

- 5057/5115 (98.9%) traced
- 705/5057 (13.9%) dead
- 681/705 (96.6%) death certificates obtained
- 88/681 (12.9%) ascribed to lung cancer

Analysis

Mortality

- person years (SMR) analysis against all England and Wales, and Stoke on Trent
- Nested case-referent
  - Cases (lung cancer) matched to 3-4 referents on date of birth and first hire

Pneumonicosis

- Prevalence of radiographic change ($\geq$ 1/0)

Person years analysis: deaths 1985 – 1992

	Against rates for			
Selected Causes	**England and Wales**		**Stoke and Trent**	
All malignant disease	1.44	(1.22 - 1.69)	1.12	(0.95 – 1.32)
Lung cancer	1.91	(1.48 – 2.42)	1.28	(0.99 – 1.62)
Non-malignant respiratory disease	2.87	(2.17 – 3.72)	2.04	(1.55 – 2.65)
Heart disease	1.36	(1.16 – 1.58)	0.98	(0.83 – 1.13)
All causes	1.46	(1.33 – 1.60)	1.15	(1.05 – 1.26)

Prevalence of small parenchymal opacities (> 1/0) by cumulative exposure

Exposure ($\mu g/m^3 y$)	Prevalence	N
<2000	0	109
2000 – 3999	2.0	449
4000 – 5999	6.4	257
$\geq$ 6000	16.0	225
Overall	5.9	1080

Related to intensity (OR=2.66 95% CI 1.94-3.66)
rather than duration (OR=1.06 95% CI 0.83-1.40)

Case-referent analysis

Small opacities	Cases	Referents
(≥ 1/0)	3/44 6.8%	10/170 5.9%

Relation* to	OR	95% CI
Intensity	1.66	1.14 – 2.41
Duration	0.75	0.48 – 1.18

*Lagged 10 years and adjusted for smoking

Second follow-up (to June 30, 2002)

- Tracing – through ONS using name and date of birth
- Now being finalized – vital status for 94.8%
- Lung cancer deaths (in records retrieved to date) 79/640
- Renal disease?

Strengths

- **Exposed cohort (not compensation cases)**
- **Absence of intrinsic confounders (e.g., radon)**
- **Smoking data**
- **Contemporary information on prior exposures**
- **Exposure matrix from representative sampling strategy**
- **Near complete establishment of vital status and cause of deaths**

Weaknesses

- Gaps in information (smoking, small opacities) for workers with short duration
- Possible destruction of record cards prior to 1985
- Extrapolation of exposure (rather than direct measures within each company)

Italian refractory brick workers: Lung Cancer Mortality (1954-20000) by length of employment

Length of employment (years)	Period of hire					
	<=1957			>1957		
	Obs.	SMR	95%CI	Obs.	SMR	95%CI
<=24	10	118	56-216	19	70	42-110
25-34	12	203	105-354	0	0	0-546
>=35	0	0	0-238	-	-	-

Italian refractory brick workers: Respiratory tract mortality (1954-2000) by length of employment

Length of employment (years)	Period of hire					
	<=1957			>1957		
	Obs.	SMR	CI 95%	Obs.	SMR	CI 95%
<=24	19	203	122 - 316	14	80	44 - 134
25-34	21	307	190 - 469	0	0	0 - 1267
>=35	5	354	115 - 825	-	-	-

Italian refractory brick workers: Silicosis mortality by year of hire: Analysis restricted to 1970-2000 (available death rates)

	Period of hire			
Length of Employment (Years)	<= 1957		>1957	
	Obs*	SMR	Obs*	SMR
<= 24	6	2224	7	949
25-34	6	2587	0	
>=35	1	2363	0	
* 20 out of 29 deaths from silicosis				

A mortality cohort study among workers in a graphite electrode production plant in Italy

D F Merlo, S Garattini, U Gelatti, C Simonati, L Covolo, M Ceppi, F Donato

Occup Environ Med 2004;**61**:e9 (http://www.occenvmed.com/cgi/content/full/61/2/e9)

Background: Graphite electrode manufacturing workers are exposed to coal tar and its volatiles containing a variety of polycyclic aromatic hydrocarbons (PAH), silica and graphite dusts, and asbestos.
Aims: To investigate mortality from cancer and other diseases among workers in a graphite electrode production plant in Italy.
Methods: A total of 1291 males actively employed between 1 January 1950 and 31 December 1989 who had worked at the plant for at least one year were studied. The follow up extended from 1950 to 1997. Standardised mortality ratios (SMR) and their 95% confidence intervals (CI) were computed using mortality rates for the Italian and regional male population.

Survivors followed by Local Health Unit (surveillance)

Table 1 Mortality from specific causes among graphite electrode manufacturing workers

Cause of death (ICD 9th)	Observed deaths	Expected deaths	SMR	95% CI
All causes (001–999)	541	376.19	1.44	1.32 to 1.56
Infectious and parasitic diseases (001–139)	6	7.11	0.84	0.31 to 1.84
Malignant neoplasms (140–208)	141	110.95	1.27	1.07 to 1.50
Lips, mouth, and pharynx (140–149)	8	3.8	2.10	0.91 to 4.14
Oesophagus (150)	6	2.74	2.19	0.8 to 4.77
Stomach (151)	17	13.36	1.27	0.74 to 2.04
Colon (153)	4	5.89	0.68	0.18 to 1.74
Rectum (154)	–	3.35	0.00	0.00 to 0.89
Liver (155)	24	5.73	4.19	2.68 to 6.23
Pancreas (157)	3	4.06	0.74	0.15 to 2.16
Larynx (161)	5	3.8	1.32	0.43 to 3.07
Lung (162)	32	32.89	0.97	0.67 to 1.37
Pleura (163)	–	0.63	0.00	0.00 to 4.73
Bone and articular cartilage (170)	2	0.9	2.22	0.27 to 8.04
Connective tissue (171)	1	0.2	5.04	0.13 to 28.1
Melanoma (172)	1	0.73	1.37	0.03 to 7.63
Prostate (185)	10	5.6	1.78	0.86 to 3.28
Bladder (188)	5	4.61	1.08	0.35 to 2.53
Kidney (189)	4	2.19	1.83	0.50 to 4.68
Brain (191)	2	2.28	0.88	0.11 to 3.16
Lymphomas (200–202)	3	3.13	0.96	0.20 to 2.80
Leukaemia (204–208)	1	3.39	0.30	0.01 to 1.65
Diseases of the circulatory system (390–459)	126	143.08	0.88	0.73 to 1.05
Diseases of the respiratory system (460–519)	108	26.75	4.04	3.31 to 4.87
Silicosis (500, 502)	79	1.19	66.39	52.56 to 82.74
Diseases of the digestive system (520–579)	49	30.15	1.63	1.20 to 2.15
Liver cirrhosis and other chronic diseases (571)	36	19.22	1.87	1.31 to 2.59
Injury and poisoning (800–999)	35	26.34	1.33	0.93 to 1.85

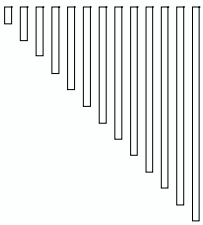
SMR, standardised mortality ratio point estimate; 95% CI, 95% confidence interval of the SMR.

5

Table 3 Mortality from selected causes by age at death

	Age at death								
	<45 years			45–59 years			>59 years		
Cause of death (ICD 9)	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
All causes (001–999)	58	1.83	1.39 to 2.37	192	1.86	1.61 to 2.14	291	1.21	1.07 to 1.35
Malignant neoplasms (140–208)	2	0.33	0.04 to 1.21	54	1.55	1.16 to 2.02	85	1.21	0.97 to 1.50
Cancer of the liver (155)	1	7.69	0.19 to 42.86	7	4.46	1.79 to 9.19	16	4.00	2.29 to 6.50
Lung cancer (162)	0	0.00	0.00 to 2.66	17	1.51	0.88 to 2.42	15	0.73	0.41 to 1.21
Diseases of the respiratory system (460–519)	10	9.09	4.36 to 16.72	45	9.05	6.60 to 12.12	53	2.56	1.92 to 3.35
Silicosis (500, 502)	10	333.33	159.8 to 613.0	39	121.88	86.66 to 166.6	30	35.71	24.10 to 50.9
Liver cirrhosis and other chronic diseases (571)	8	1.29	0.56 to 2.54	17	2.36	1.37 to 3.78	11	1.89	0.97 to 3.39

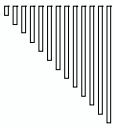
O, observed deaths; SMR, standardised mortality ratio point estimate; 95% CI, 95% confidence interval of the SMR.



Expert Workshop: Epidemiological Perspectives on Silica and Health

- *Exposure Assessment*

Dirk Dahmann, IGF, Bochum



Key Issues

- **Occupational Settings**
- **Sampling and Measurement Procedures**
- **Sampling Strategy**
- **Plausibility Checks**

Occupational Settings

- Description of the settings:
  - Exactly what species of crystalline silica did the exposure consist of?

Species of crystalline silica

- Cristobalite (diatomaceous earth industry, possibly potteries)
- Different quartz species (see section on physico-chemical properties)
- Amorphous silica (containing fibrous particles?)

Occupational Settings

- Description of the settings:
  - Exactly what species of cristalline silica did the exposure consist of?
  - What types of technical processes were used?

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Types of technical processes

- Examples:
  - Complete description of the mining processes (blasting or cutting etc.), the minerals (geological formation), the dust prevention techniques applied (wet drilling or not) for mining.
  - Description of the temperature ranges applied in kilns, the raw material used and the processing of materials and products for potteries.

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Occupational Settings

- Description of the settings:
  - Exactly what species of cristalline silica did the exposure consist of?
  - What types of technical processes were used?
  - How did these processes develop over time?
  - What „relevant“ species of co-exposures (workplace confounders?) were present?

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Co-exposures

- Examples:
  - Asbestos from thermo insulation of heating processes.
  - Radon in relevant minerals (granite?).
  - Heavy metals in some mining processes.
  - PAHs from fuel in heating processes.
  - Diesel particulates in some mining processes.

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Occupational Settings

- Description of the settings:
  - Exactly what species of cristalline silica did the exposure consist of?
  - What types of technical processes were used?
  - How did these processes develop over time?
  - What „relevant“ species of co-exposures (workplace confounders?) were present?
  - How do the settings differ (similar ones and different ones)?

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Differences of Settings

- In all cases where data are pooled the homogeneity of the data needs to be discussed and guaranteed before pooling! Examples:
  - Industrial sand
  - Granite
  - Chinese tin mines
- Different exposure levels of similar industries in different studies need to be discussed!

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Different exposure levels of similar industries (from Mannetje et al. 2002)

Study	Average median of respirable silica exposure (mg/m³)	Median of cumulative exposure (mg/m³years)
US granite	0.05	0.71
Finland granite	0.59	4.63
US gold mining	0.05	0.23
Australia gold mining	0.43	11.37

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Sampling and Measurement Procedures

- Sampling
  - Which type of sampler(s) were used (complete description of the technical equipment/processes)?

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Type of samplers - examples from Mannetje et al. 2002

Units given	Description of sampling process	Study
mppcf	Millions of particles per cubic feet, light microscopy of impingersamples	Diatomaceous earth, US granite, US sand-, US gold
Particle/milliliter	Konimeter („Witwatersrand“)	RSA gold
Particle/milliliter	Konimeter (which one?)	Australia gold
mg/m³ total dust	Gravimetric, open faced filter casettes, person carried	Diatomaceous earth
mg/m³ total dust	Gravimetric (original publication not available to this author)	Finland granite
mg/m³ total dust	Gravimetric open faced filters, „Chinese total dust sampler“	China tin
mg/m³ respirable dust	Respirable dust, cyklone-preseparator	Diatomaceous earth, US sand

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Sampling and Measurement Procedures

- Sampling
  - Which type of sampler(s) were used (complete description of the technical equipment/processes)?
  - How do these samplers comply to modern standards (respirable dust)?

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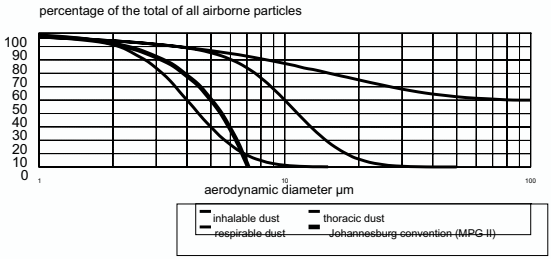
We DO have standards:



Sampling and Measurement Procedures

- Sampling
  - Which type of sampler(s) were used (complete description of the technical equipment/processes)?
  - How do these samplers comply to modern standards (respirable dust)?
  - If they don't, can „conversion" be done (or do the actual samplers behave „erratically")?
  - If conversion is possible, how was it done in the studies?

This conversion is the core of the scientific process in most studies and needs special attention. It is however never the only problem!

Sampling and Measurement Procedures

- Sampling
  - Which type of sampler(s) were used (complete description of the technical equipment/processes)?
  - How do these samplers comply to modern standards (respirable dust)?
  - If they don't, can „conversion" be done (or do the actual samplers behave „erratically")?
  - If conversion is possible, how was it done?
- Analytical procedures
  - How has the content of crystalline silica been determined (especially the content in the respirable fraction)?
  - How have the historical data been converted into modern (correct?) ones?

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Sampling Strategy

- Was a complete description of the actually applied sampling strategy given?
- How could that strategy be converted into eight hour shift data?
- How could these data be converted into lifetime exposure doses (number of shifts per year, actual shift lengths)?

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Problems

- Short time measurements (Total dust in China for 20 minutes, konimeter measurements in a second)!
- Compliance measurements or not? (What consequences will a “high” result have had?)
- “Worst case” strategies (Germany), or random approach (e.g. UK).
- 240/a shifts then, 180/a shifts now!
- 10 h shifts then, 7.5 h shifts now!

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Plausibility Checks

- Have efforts been made to check plausibility of the exposure assessment?
- How was the plausibility of the exposure levels checked during the process?
- How well are the steps of exposure assessment documented (***ALL THE STEPS***)?
- Would “an educated reader” be able to perform a plausibility check by using the published exposure data?
- ***Could the published data be used for a sensitivity analysis during the mathematical modeling (estimation of data uncertainty!)?***

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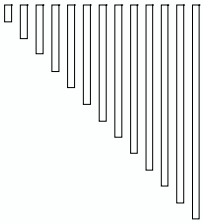


Thank you for your attention!

Bice Fubini
Dept of Chemistry and Interdepartmental Centre "G. Scansetti" for Studies on Asbestos and other Toxic Particulates, University of Turin, Italy

Physicochemical features of the dust

(which are of particular relevance to the design of silica studies)

Overview of the basis of the "Variability of Crystalline Silica Hazard"

Expert workshop: Epidemiological Perspectives on Silica and Health
New York 5-6 August 2004

*Carcinogenicity in humans was not detected in all ...circumstances ...**IARC 1997***

inherent characteristics

particle dimensions
particle micromorphology
state of the surface: freshly fractured, hydrophilic…

} *determined by the origin of the silica dusts*

external factors

metal ions (e.g. Al, Fe) contaminants,
associated minerals (clay)
impurities acquired during processing
deposited macromolecules, polymers, etc

} *great variability*

to chemistry the task of finding out which silica sources are pathogenic…

Since the IARC classification…

new studies addressed | Variability of crystalline silica hazard

Physico-chemical properties
Cellular responses
Animal studies

Crucial role of the particle surface

Large variety of "surface states"

Inhibitory effects obtained by acting on the surface

Inconsistence of epi studies may reflect differences in silica sources

Only some silica particles, when inhaled, are pathogenic

open questions

What makes a silica particle toxic?

How to predict toxicity of different sources of silica dusts?

Does variability concern in similar ways fibrogenicity and carcinogenicity?

epidemiological studies may confirm mechanisms while mechanisms may suggest new aspects to consider in experimental studies

Present overview

What we know in terms of adverse physicochemical features from experimental studies

Which physicochemical features should be considered, if possible, when examining exposures in epidemiological studies

Not all silica dusts are equal…

different polymorphs — *e.g. quartz vs stishovite or amorphous forms*

same polymorph, different origin — *e.g. cristobalite: ex mineral, ex heated quartz dust, ex diatoms*

same polymorph, different source — *e.g various industrial quartz dusts*

same sample — *e.g. variously heated, surface modified, ground in different jars, aged vs freshly ground…*

variability among surface modified samples may even exceed variability among different polymorphs

Achievements in the past few years…

Large variety of different kinds of cell responses all inhibited by old antidocts, Al or PVNO
(Borm&Donaldson labs)

Freshly ground surfaces more bioreactive & pathogenic
(Castranova et al., NIOSH; Fubini lab)

Different surface sites or contaminants regulate the various free radical generation, reaction with antioxidants, H-bonding potential…
(Fubini lab)

"European Commercial Quartz"
Various cell responses to a quartz particle are not regulated by the same physico-chemical factors
(Bruch, Borm, Fubini lab)

European commercial quartz dusts project
(Bruch, Borm, Fubini labs)

16 samples of commercial quartz dusts of different origin

in vitro test (98-99% SiO_2)
Guinea pig alveolar macrophages

Toxicity ROS Glucuronidase TNF α

Four non-correlated cell responses to AM activation by silica

⇩

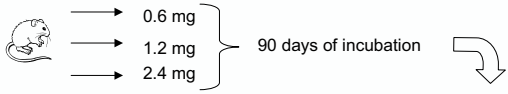
Each response governed by different particle features

4 samples selected on the basis of macrophage responses

	Qz 2/1-c	Qz 3/1-c	Qz 11/1-c	Qz 5/1-c
•ROS	+	+	-	-
•Glucuronidase	+	-	+	-
•TNF	++	++	+	-
•Toxicity/viability	++	++	-	+

In vivo test

Inflammatory, fibrogenic and genotoxic activity examined in a rat lung model.(*intratracheal injection*)



	Qz 2/1-c	Qz 3/1-c	Qz 11/1-c	Qz 5/1-c
Proliferation (Ki-67)	+	+	+	+
Fibrosis (90d)	++	++	+	+
8-OH-dG	++	-	-	-
Mutation (90d)	+	-	-	-
Inflammation (90d) (total cells, PMN)	+++	++	+	+
	pathogenic		inert	

The most active on macrophages ⟹ the most pathogenic in vivo

Level of contaminants of the 4 samples

quartz	**Al** ppm	K ppm	Ca ppm	Mg ppm	Na ppm	Ni ppm	Mn ppm	Fe ppm	**C** ppm	SiO_2 %weight
Qz 2/1-c	**1049**	112.9	68.6	41.0	32.6	21.8	6.3	380	**79**	99.6
Qz 3/1-c	**1110**	72.2	100.7	39.2	87.6	133.0	23.0	1359	**81**	99.6
Qz 5/1-c	**2993**	954.7	90.0	80.2	34.9	26.0	7.6	430	**83**	99.0
Qz 11/1-c	**2509**	600.2	167.9	68.1	49.7	103.0	17.2	960	**283**	98.9

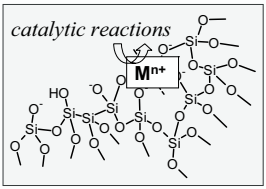
two non-toxic dusts

These amounts are sufficient, if dispersed, to cover all the surface

Aluminium is renown to inhibit quartz pathogenicity, quartz from clay or coal mine is less pathogenic…

Silica peculiarities: role of contaminants

surface associated metal ions: a new chemical entity



1% in weight, spread at the surface, may fully cover it

All theories taking into account just one chemical feature failed…

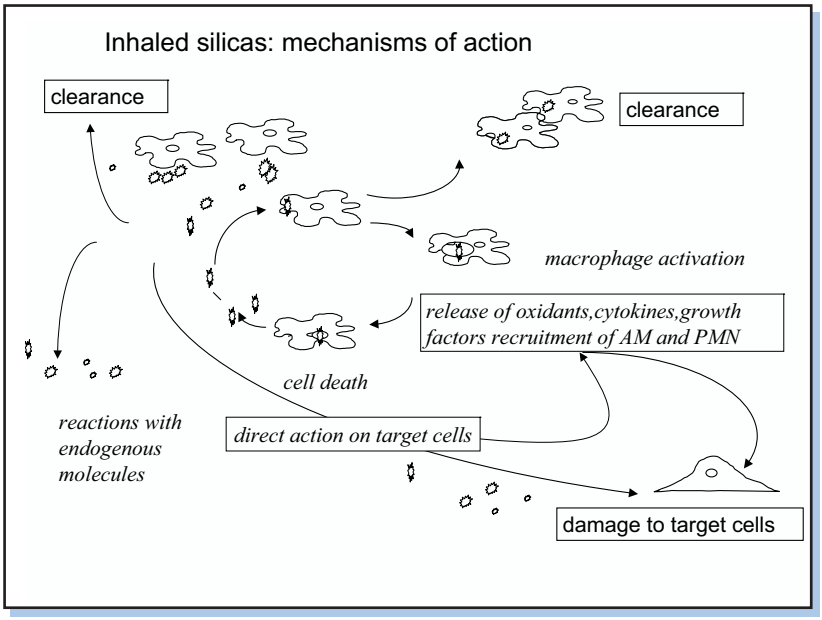
not a single physico chemical property but a set of features impart pathogenicity to a given dust

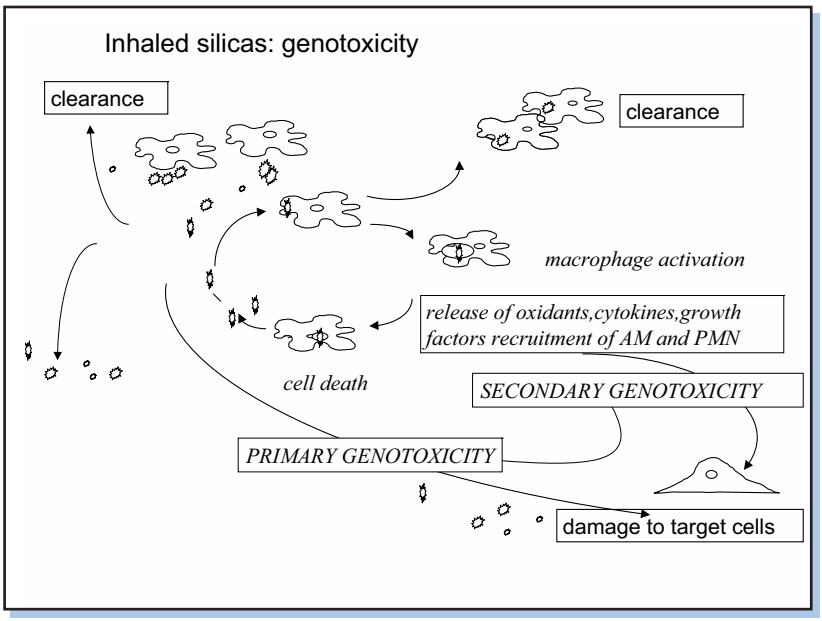
• several physico-chemical properties involved

• multiple cellular responses and signalling pathways activated

⇨ *intensity of the adverse reaction*

Even if a complex interplay exist between cell responses and physico chemical features, one single surface modification may inhibit several biochemical reactions generated by different surface sites


Inhaled silicas: mechanisms of action
clearance
clearance
macrophage activation
release of oxidants,cytokines,growth factors recruitment of AM and PMN
cell death
reactions with endogenous molecules
direct action on target cells
damage to target cells


Inhaled silicas: genotoxicity
clearance
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release of oxidants,cytokines,growth factors recruitment of AM and PMN
cell death
SECONDARY GENOTOXICITY
PRIMARY GENOTOXICITY
damage to target cells

Physicochemical properties relevant to toxicity

Freshly fractured vs aged

Particle generated free radicals

Iron ions as contaminants

Association with clay

Pure silica surface vs aluminium covered

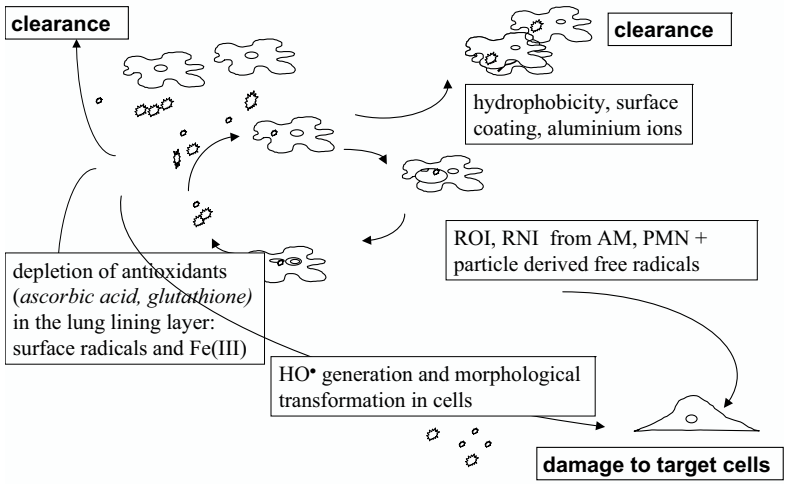
Polymer coating e.g. PVNO

Hydrophobic vs hydrophilic surfaces

H-bonding to membranes

mostly confirmed in vitro & in vivo

Association between surface properties and cellular responses



Which physicochemical features should be considered, if possible, when examining exposures in epidemiological studies?

All kind of silica sources

- Crystallinity
- Respirable size
- Origin of comminution and procedure
- Extent of exposure to freshly fractured respirable particles
- Associated minerals and chemical compounds
- Average chemical composition of the dust up to 1%

Miners

gold	*US* *South Africa* *Australia*
tin	*China*
miners & pottery	*China*
coal	*Scotland*

info

Associated minerals
Chemical composition
Methods of extraction
Exposure to freshly fractured fine dust

Granite and stone workers

Vermont
Finland
Denmark
Ontario
US
China
Germany

info

Kind of granite
Define stones
Assess associated minerals
(clay, iron oxides, aluminium compounds)

Wet or dry grinding
Freshly ground exposure
Quarry workers vs shed workers

Industrial sand and diatomaceous earth workers

Note:
•diatomaceous earth and sands start up as a comminute product
but
•Sands start up as crystalline, diatomaceous earth become crystalline during processing

sands — *US*, *Britain*

DE — *California*, *Iceland*

info

Origin of sand
% Crystalline silica
Chemical composition
Associated minerals
Working procedures

info

Chemical composition
(residual impurities from original diatoms)
% Crystalline silica
Processing procedures
Stages in which exposure occurred

Pottery & refractory workers

Britain
Denmark
China
Italy

info

Kind of pottery, materials employed
Development of crystallinity during processing
Stage at which exposure occurred
Re-grinding failed products customary

conclusion

requirement of a multidisciplinary approach

Expert Workshop: Epidemiological Perspectives on Silica and Health

Confounding Factors

Patrick Hessel, PhD

Exponent®

Why is Confounding Important?

- **Studies are inconsistent**
- **Exposure-response relationships have generally not been found**
- **Smoking is a strong risk factor for lung cancer**
- **Manual workers tend to smoke more and lifestyle may differ from the general population**
- **When risks are elevated, they are generally modestly elevated**

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Smoking and Lung Cancer

- Chan *et al* (2000)
  - Compensated silicotics in Hong Kong
  - SMR (lung cancer) = 1.94
  - RR (smoking) = 1.75

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Smoking and Lung Cancer

- Carta *et al* (2001)
  - Compensated silicotics in Sardinia
  - SMR (lung cancer) = 1.37
  - Lung cancer associated with radon, smoking, airflow obstruction
  - Not associated with silica or severity of silicosis

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Smoking and Lung Cancer

- **Kjaerheim *et al* (2002)**
  - **Rock and slag wool workers in Scandinavia and Germany**
  - **Lung cancer not associated with silica exposure**
  - **Based on smoking levels in controls: expected SMR = 1.3**

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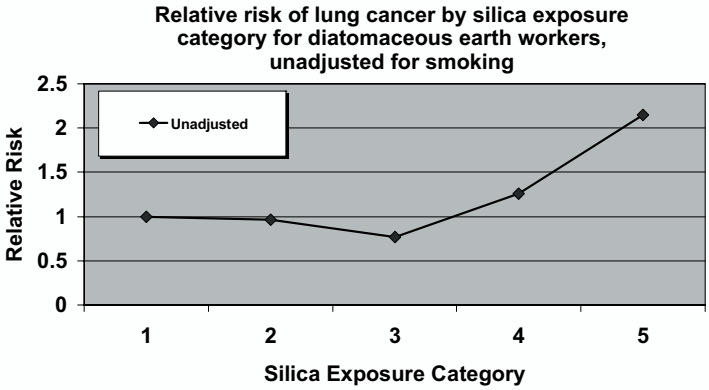
Checkoway *et al*, 1997



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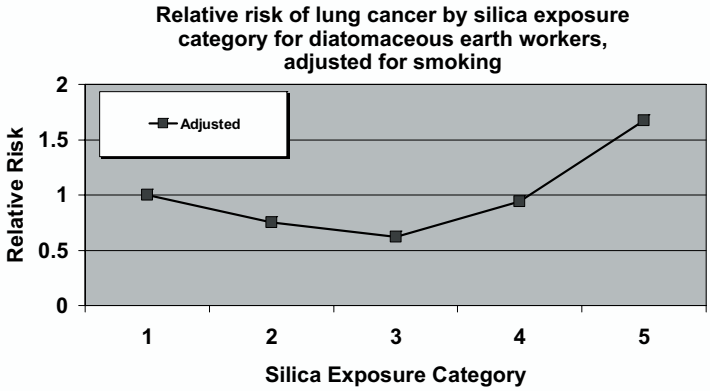
Checkoway *et al*, 1997



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Silicosis and Smoking

- 13 studies
  - 3, positive association (x-ray)
  - 8, populations with positive associations (x-ray)
  - 1, no association (x-ray)
  - 1, negative association (autopsy study)
- Could confound studies of those reported to have radiographic silicosis

(Hessel *et al*, 2003)

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Short-term Workers

- STWs at increased risk of lung cancer (lifestyle)
- Adzersen *et al* (2003)
  - German foundry workers
  - Inverse association: lung cancer and duration
  - *"…unskilled persons are found at 'dirty' workplaces in higher proportion, and…they are simultaneously those employees who tend to change jobs more frequently."*

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Short-term Workers

- Negative E-R Relationships
  - McLaughlin *et al*, 1992 (tungsten miners)
  - Cherry *et al*, 1998 (pottery workers)
  - Brown and Rushton, 2003 (sand workers)
  - Menvielle *et al*, 2003 (population-based)
  - Coggiola *et al*, 2003 (talc miners)
  - Pinkerton *et al*, 2004 (uranium mill workers)

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Socioeconomic Status

- **Soutar *et al*, 2000**
  - **Lung cancer mortality across social strata**

    "These social class differences do not appear simply to reflect the influence of exposures to harmful agents at work, for 80% of the variation of lung cancer SMRs between the major occupational groups is explained by social class."

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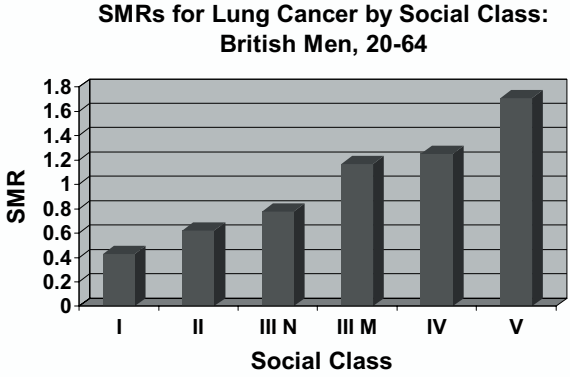
Office of Population Censuses and Surveys, 1986



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Martikainen *et al*, 2000

- Large Finnish cancer prevention trial
- Education as measure of SES
- Controlled for smoking (detailed) and asbestos exposure
- 32% excess of lung cancer in lowest education category

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SES in Studies of Silica & Lung Cancer

- Fillmore *et al*, 1999 (U.S. women)
- McDonald *et al*, 2001 (sand workers)
- Kjaerheim *et al*, 2003 (rock/slag wool workers)
- Kauppinen *et al*, 2003 (road paving workers)
- Adzersen *et al*, 2003 (foundry workers)

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Lung Function and Lung Cancer

- Poor lung function is a risk factor for lung cancer even after controlling for smoking
- Many silicosis registries require respiratory impairment to award compensation
- Respiratory impairment may prompt workers to seek compensation
- Silicosis registries not appropriate for etiologic studies

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Conclusion

- Important to consider confounding factors in studies of occupational lung cancer
- Recent studies of silica, silicosis, and lung cancer have been better at this
- Research efforts should focus on the multiple factors that impact lung cancer risk in workers exposed to silica and other substances

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Statistical/data analysis issues
J. Hughes

- Sufficient sample size and power
- In matched designs, retain matching in analyses
- SMR's - comparison population is important
  - regional (State, provincial?) rates
- Some adjustment for important covariates important
  (smoking and lung cancer)

Outcome can develop after person ceases exposure

Mortality – with sufficient follow-up, straightforward (e.g., NDI).

Morbidity (e.g., silicosis)

Studies of active workers may be inadequate. (insufficient elapsed time for development)

Inclusion of inactive workers (retirees/left):

- difficult to track and obtain participation
- possible bias
- difficult to assess potential bias

Risk in relation to cumulative exposure is not sufficiently informative for setting exposure standards.

Is 40 years' exposure to 50 μg/m^3 equivalent to 20 years at 100 μg/m^3 ?

Need to separate effects of exposure duration and concentration (problems of sample size, follow-up time).

Validating exposure estimates – essential but difficult.

Relationship with known exposure-related outcome validates estimates ordinally.

Generally underestimate exposure → overestimate risk for specified exposure.
Generally overestimate exposure → underestimate risk for specified exposure.

IF crystalline silica is a human lung carcinogen:

Are exposure levels that are sufficiently "safe" regarding development of silicosis also safe regarding lung cancer?

Is exposure-induced lung cancer a consequence of lung fibrosis?

Edited by EUROSIL *aisbl*

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