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Special issue

Second international symposium on silica, silicosis and cancer

Guest editors

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Preface

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The Second International Symposium on Silica, Silicosis, and Cancer, held 27—30 October 1993 in San Francisco, California, was convened to address research and risk assessment issues surrounding the toxicity and carcinogenicity of crystalline silica. The Second Symposium followed the First by 10 years and was designed to highlight the progress made in the past decade. In so doing, the papers in this special issue of the *Scandinavian Journal of Work, Environment & Health* from the 1993 Symposium have accomplished the following two major objectives: 1) expanded knowledge about silica from the fields of medical toxicology, industrial hygiene, epidemiology, and tumor biology and 2) described new areas of research in physicochemistry, biological mechanisms, mineralogy, risk assessment, and prevention.

The contents of this issue are the result of the submission of 56 manuscripts from the 102 presentations from the San Francisco Symposium. Included in this group are two papers requested by the Editors from Amandus and his co-workers and Partanen and his colleagues to summarize occupational epidemiology studies conducted in North Carolina and Finland. All the manuscripts were peer-reviewed by at least two scientists using a standard review format and were rated for acceptability. These reviews were transmitted to the Editor in Chief of the special issue and, when there was disagreement, a third opinion was sought. Through this process, the editors accepted 28 papers for publication and added a last summary paper. The accepted papers have been organized into the following five sections: 1) Physico-chemistry, Tumor Biology, Cellular Mechanisms (pages 5—34), 2) Silica Sampling, Industrial Hygiene and Modeling (pages 35—54), 3) Epidemiology of Silica, Silicosis and Cancer (pages 55—86), 4) Environmental and Workplace Risk Assessments (pages 87—107), and 5) Future Research Directions and Areas of Focus (pages 108—117).

Section 1 (pages 5—34) consists of seven papers describing the physical and chemical properties of silica dusts and their differential ability to produce fibrogenesis and carcinogenesis.

Section 2 (pages 35—54) includes several interesting papers on methods for collecting quartz samples and applying silica dust levels. Of note are the contributions describing dust levels in Chinese industries, North Carolina soils, and the application of physiological models to estimate dust levels in the respiratory system.

Section 3 (pages 55—86) extends the literature linking industrial silica exposure to silicosis and the roles silica exposure and the presence of silicosis play in cancer risks. Some highlights include silicosis surveillance in Ontario, Canada, the follow-up of Chinese silica brick workers, health risks among Italian silicotics and ceramic workers, and lung cancer findings from Michigan and New Jersey silicotics.

Section 4 (pages 87—107) is a new contribution to this field — a description of risk assessment research focusing on silica-related health risks among workers and people potentially exposed from ambient sources. The research in this section derives from previous work in epidemiology, toxicology, pulmonary medicine, industrial hygiene, and bio-statistics.

Section 5 (pages 108—117) provides a guide for future research in this field, with particular attention drawn to biogenic amorphous silica and compensation issues. The editors of the special issue conclude by summarizing the growth in silica, silicosis, and cancer knowledge over the past 10 years, suggesting fruitful areas for new endeavors.

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Many scientists generously contributed to the quality and content of the special issue by their willingness to be peer reviewers for both the Symposium abstracts and the contributed manuscripts. However, the publication of this volume was a result of hours of review, writing, rewriting, and good advice by and from my co-editors: Gregory Wagner, Umberto Saffiotti, Jean Rabovsky, and James Leigh. Special thanks are due to Jim Leigh for his diligent work on behalf of this special issue.

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Mineralogical characteristics of silica polymorphs in relation to their biological activities

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Guthrie GD Jr, Heaney PJ. Mineralogical characteristics of silica polymorphs in relation to their biological activities. *Scand J Work Environ Health* 1995; suppl 2:5—8.

Numerous aspects of silica polymorphs can affect their biological activities, including periodic structures, compositional variations, dissolution characteristics, surface properties, and particle size and shape. For an understanding of mineral-induced pathogenesis from a mechanistic perspective, the links between these properties and biochemical processes must be elucidated. This paper presents some strategies for designing assays to evaluate these properties.

Key terms cristobalite, coesite, keatite, quartz, toxicity, tridymite, stishovite.

Each day, we are exposed to respirable mineral particulates derived from soil and rock. Numerous minerals, including several varieties of silica, have been studied with respect to pulmonary disease, and many appear to be toxic. Biological activities of minerals vary extensively, irrespective of particle morphology (1). This variation in biological activity reflects factors, such as structure, composition, and surface properties, that influence the interactions between inhaled minerals and living tissues and cells. Unfortunately, little attention has been given to the mineralogical aspects contributing to pathogenesis or to the development of occupational and environmental regulations for mineral particulates.

In this paper we present the basic mineralogical aspects of quartz and discuss how they relate to biological activity. Important underlying concepts of this discussion include mineral species and particles, structure, and composition. The major variables for predicting bioactivity are silica structure and metal ion impurities. Surface properties are also important in pathogenesis, and they have been reviewed in the mineralogy field (2, 3).

Mineral structures

One of the primary qualities of minerals is structure. Minerals exhibit translational periodicity (ie, their structures repeat over large atomic distances); therefore they are said to be crystalline. Noncrystalline or amorphous materials, such as glass, are not defined as minerals because their structures do not repeat in a regular fashion.

Silica is a chemical term for silicon dioxide (SiO_2). This general term describes a range of structures and properties. Silica can crystallize as one of at least eight polymorphs (α-quartz, β-quartz, cristobalite, tridymite, stishovite, coesite, moganite, and keatite), each of which occurs in nature. (See reference 3 for illustrations of these polymorphs.) In addition, silica can occur in noncrystalline forms, and several amorphous materials are composed chiefly of silica with smaller amounts of other constituents (eg, water, cations, anions). Some of these polymorphs are not abundant. The diversity in structures exhibited by silica (including the structures of the rare polymorphs) must be exploited by future biological studies so that relationships between mineral structure and biological activity can be elucidated. Heaney & Banfield (3) provide a review of most of the structures of silica. It is critical for scientists to understand that silica does not refer to a single substance; therefore this term has limited utility for health studies or regulatory debates. Use of the more exact terms for the mineral species is essential in any discussion of biological activity or health effects.

Quartz. Numerous studies have demonstrated that samples of quartz can be biologically active, and under some conditions exposure to quartz appears to result in fibrosis or tumors or both (4—7).

Of the silica polymorphs, quartz is by far the most abundant because it is thermodynamically the most stable polymorph under ambient conditions. Quartz occurs in numerous rock types, soils, and beach sands, and quartz particles from these sources can be respirable. Quartz occurs as one of two polymorphs: α-quartz (or low quartz) and β-quartz (or high quartz). β-Quartz is stable only at temperatures above ~573°C, and it readily converts to α-quartz upon cooling.

The structure of α-quartz consists of corner-sharing tetrahedra linked to form double helices that coil along the c-axis. The cores of these helices form open, ditrigonal tunnels, which can accommodate extra cations in interstitial (nonframework) sites, as will be discussed later.

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Tridymite and cristobalite. The biological activities of tridymite and cristobalite have been studied extensively, and generally they appear to have activities comparable to quartz (5).

Tridymite and cristobalite are high-temperature, low-pressure polymorphs of silica. They form stably above ~870°C (tridymite) and ~1470°C (cristobalite) and metastably in some low-temperature environments. For example, these polymorphs often form during the devitrification of siliceous volcanic or synthetic glass. The tridymite → quartz and cristobalite → quartz transformations require the breaking of bonds. Hence even tridymite and cristobalite crystallized at high temperatures can remain metastable under ambient conditions. Tridymite and cristobalite occur as fine-grained crystals, often intimately intergrown with glass or other minerals, including each other.

Both the tridymite and cristobalite structures are based on polymerized sheets of tetrahedra (8), where the tetrahedra point alternately up and down. These sheets can be bonded by stacking in two ways. In one stacking scheme, alternate sheets are rotated by 60° or 180° to allow the joining of tetrahedra between the sheets producing tridymite. In the other stacking scheme, alternate sheets are shifted slightly, thus forming cristobalite. The similarities between these two structures allow them to intergrow extensively, and this type of intergrowth is referred to as a stacking defect (8).

Coesite and stishovite. The biological activities of coesite and stishovite have been studied much less than those of quartz, tridymite, and cristobalite (9—11). However, a few studies have indicated that these two silica polymorphs are much less biologically active and, in the case of stishovite, perhaps biologically inert.

Moganite and keatite. Two silica polymorphs (moganite and keatite) have structures similar to quartz. Consequently, the possibility exists that these polymorphs could intergrow with quartz on a fine scale, particularly in disordered silica samples. In fact, moganite has been reported in many natural, microcrystalline quartz specimens in concentrations ranging between 20 and 85% (12). Intergrowths of these polymorphs could significantly alter the properties of a quartz specimen, even if present in relatively minor amounts. The structure of moganite is similar to that of quartz (ie, tetrahedra are linked to form double helices that coil along the c-axis). Whereas in quartz each double-helix tube is linked to six others, in moganite each tube is only linked to four others.

Keatite has no demonstrated stability field. However, keatite can be synthesized over a range in pressure (350—1250 atmospheres) and temperatures (380—585°C). Keatite can appear as an intermediate phase during the hydrothermal crystallization of quartz (2), and it occurs with high altitude, atmospheric dusts (13) that are believed to originate from volcanic sources. Keatite has a structure similar in some respects to the structure of α-quartz. When viewed down the [110] axis, "double helices" are clearly visible in the keatite structure. However, some of the tetrahedra are shifted out of the double helices and into the ditrigonal tunnels. Thus one difference between keatite and quartz is that the ditrigonal tunnels are not continuous, which would affect the diffusion of cations into and out of the framework.

Noncrystalline silica. Synthetic and natural occurrences of noncrystalline silica are common. Most descriptions of silica glass address the nature of the short-range order, which can be probed using several techniques. Such studies suggest that silicon is dominantly in fourfold (tetrahedral) coordination with oxygen (14). The relative abundances of coordination environments for silica at surfaces of glasses have not been reported; however, calculations of dissolution mechanisms for quartz in water have suggested that 5-coordinated silica surface sites are formed as intermediate steps. The nature of silica sites at the surface may affect biological activity in as much as it alters the charge density or distribution (ie, the proton donor-acceptor characteristics of oxygens in fivefold coordination with silica differ from those of oxygens in fourfold coordination).

Noncrystalline silica is less stable relative to the crystalline varieties. However, the transformation to a crystalline polymorph is generally sluggish because it requires the breaking of Si-O bonds. Transformation is often facilitated by the presence of H_2O. The relative instability of silica glass also results in higher solubilities, which in turn can result in lower biopersistence. However, no solubility data have been published to allow a comparison of the solubilities of crystalline and noncrystalline silica in physiological fluids.

Varietal types of silica. Some species of crystalline silica are described with varietal names — for example, chert, chalcedony, flint, and agate — and they consist predominantly of fine-grained α-quartz.

Stuffed derivatives. The stuffed derivatives constitute a group of minerals in which trivalent or divalent cations can substitute for some of the silica. This substitution creates a negative charge on the framework that can be compensated by a cation in an interstitial position. Eucryptite ($LiAlSiO_4$), nepheline ($KNa_3Al_4Si_4O_{16}$), and carnegieite ($NaAlSiO_4$) are examples of stuffed derivatives of quartz, tridymite, and cristobalite, respectively. By comparing the activities of the stuffed derivatives with those of their parent structures, one can isolate the biological effects specifically associated with these characteristics.

Mineral surfaces

Ultimately the surface cells of silica particles interact with cells. Some evidence suggests that quartz surfaces may be largely amorphous (15—16). Furthermore, most surfaces become protonated in air, particularly in aqueous environments. Nevertheless, for the silica polymorphs, the structure at the surface is influenced by the structure of the bulk material. Work by Fubini and her colleagues and by Shoemaker and his co–workers (in this volume) demonstrates that biological activity increases when silica surfaces are either heated or freshly fractured.

Chemical variability

Although the major chemical component of the silica polymorphs is silicon dioxide, other elements (principally cations) can be present in trace amounts. The four most important are aluminum, alkali cations, iron, and titanium. (See reference 2 for more details.) Aluminum readily substitutes for silica in a tetrahedral framework. In general, the transformation is coupled with the substitution of a monovalent cation into a vacancy site: $Si^{4+} + \square \rightarrow Al^{3+} + X^+$, where $\square$ represents a vacancy and X^+ is generally an alkali cation. Substitutions with divalent cations also occur: $2Si^{4+} + \square \rightarrow 2Al^{3+} + Y^{2+}$, where Y^{2+} is generally Ca^{2+} or Mg^{2+}. These substitutions occur frequently within numerous silicate mineral groups and account for most of the chemical variability in the feldspars and stuffed derivatives. Generally, aluminum is present in low amounts in the silica polymorphs (ie, $< \sim 10^{-3}$ wt%) (2). At

the other extreme, stuffed derivatives can contain aluminum substituted for up to one-half of the Si.

Alkali cations such as K^+, H^+, Li^+, and Na^+ can occur in silica minerals to offset charge imbalances created by other substitutions (eg, the Si ~ Al substitution), but their concentrations are generally low (ie, < 0.01 wt%) (2). These cations are generally too large to substitute for Si in the framework structure but instead occur in the open cavities within the framework.

Iron can be present in the silica polymorphs in amounts up to a few tenths of a weight percent. The presence and nature of iron may have a strong influence on the biological activity of a sample. Asbestos studies have suggested that mineral-derived iron can catalyze the production of oxygen radicals via a Fenton-type reaction ($Fe^{2+} \leftrightarrow Fe^{3+} + e^-$) (17—18). However, quartz contains significantly less iron than the amphibole asbestos minerals do.

Titanium can be present in silica polymorphs in amounts up to a few hundredths of a weight percent (2). However, the silica polymorphs typically accommodate much less titanium (< 0.01 wt%), due to the relatively large size of the titanium atom compared with the size of the silicon atom. However, the substitution of titanium in silica polymorphs may have a minimal affect on the biological properties of quartz.

Linking mineralogical properties to biological activity

Structure, composition, surface periodicities, and dissolution properties of silica are among the factors likely to affect biological activity. Nolan et al (19) argued that the hydrogenated surface silanol groups are responsible for the hemolytic toxicity of the silica polymorphs. In support of this possibility, the activity of quartz can be diminished (19) by treating silica dusts with polyvinyl-pyridine-N-oxide (PVPNO), a polymer that binds to proton donor sites.

Mineral species is clearly an important factor in determining biological activity, inasmuch as polymorphs vary in their cytotoxicity. It is relevant that regulatory distinctions are made between crystalline and noncrystalline silica. In fact, numerous researchers have noted differences in the biological activities of silica polymorphs (9—11). Variations in the biological activities of silica polymorphs may relate to structural differences. An additional complication arises from the possible presence of amorphous material on the surfaces of some specimens. For example, Min-U-Sil 5 (α-quartz) may have up to 10—15 wt% amorphous material on particle surfaces (15, 16), and the amount of amorphous material on a sample is affected by sample preparation (16). Future studies of biological activity must thoroughly characterize the nature of particulate surfaces of each sample.

Limited data on the biological activity of coesite and stishovite suggest that they are less active than quartz, cristobalite, or tridymite (9, 11). However, for at least some samples or assays, coesite appears to be as fibrogenic as quartz (10). Interestingly, most samples of rutile (structurally related to stishovite but with titanium in place of silicon) appear to be biologically inert in a variety of in vitro and in vivo assays (20), although at least one rutile sample is more cytotoxic than quartz (Saffiotti, National Cancer Institute, Bethesda, MD, personal communication).

Concluding remarks

Linking mineralogical properties with biological processes is an essential step in the understanding of the mechanisms underlying mineral-induced disease. Experiments can be constructed such that the differences are exploited to allow mineralogical properties to be compared. For example, by comparing the biological responses of less well known polymorphs with quartz, one can assess differences in toxicity due to crystal structure. This type of approach leads to the recognition of mineralogical features that are important in pathogenesis, such as trace-element composition, specific surface periodicities, and freshness of fracture. Once these features are identified, the biological activity of a sample can be evaluated by determining their presence or abundance. From a practical perspective, this possibility could lead to procedures for neutralizing potentially hazardous samples by altering the specific properties that are pathogenic (eg, leaching a trace metal from the surface or binding a polymer to the active surface of the sample). From a risk perspective, the result may be an elimination of some mineral samples from lists of potentially hazardous minerals, a procedure which would lead to more rational regulations.

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Physicochemical properties of crystalline silica dusts and their possible implication in various biological responses

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Fubini B, Bolis V, Cavenago A, Volante M. Physicochemical properties of crystalline silica dusts and their possible implication in various biological responses. *Scand J Work Environ Health* 1995;21 suppl 2:9—14.

The effect of grinding, heating, and etching was investigated on polymorphs of silicon dioxide exhibiting different biological responses. Diatomaceous earths were converted into cristobalite at 1000°C. Dusts obtained by grinding crystalline minerals exhibited different micromorphology and a propensity to originate surface radicals which decrease in the sequence cristobalite → quartz → coesite → stishovite. The production of surface radicals was suppressed by grinding in the presence of water. Thermal treatments selectively quenched the radicals and decreased surface hydrophilicity. Quartz treated with aluminum lactate exhibited higher surface acidity when compared with pure quartz, with a reduction in fibrogenicity. Etching by hydrofluoric acid smoothed the particles with loss of specific surface. Adsorption of water on three cristobalite dusts of different origin (ground mineral, ex-diatomite, heated quartz) indicated a loss in heated quartz (1300°C) that was relatable to the corresponding reduction in fibrogenicity.

Key terms cristobalite, diatomite, fibrogenicity, ground silica, hydrophilicity, membranolysis, particle size, quartz, stishovite, surface radicals.

In spite of extensive work since the early 1950s on the pathogenicity of silica-related diseases, the molecular basis for the mechanism of action of silica is still unknown. Two reasons may account for this: (i) experimental silicosis studies have often been carried out with ill-defined silica specimens, while epidemiology has been more concerned with the quantitative aspects of exposure than with the qualitative ones, such as the physicochemical characteristics of the inhaled dusts, and (ii) once inhaled, several particle-cell interactions take place whereby the silica surface elicits a specific biological response. It is well known that alveolar macrophages play a role in the particle ingestion cycle. Adsorption of endogenous matter, cell adhesion, oxidative burst, and membranolysis occur via different reactions. The molecular mechanism governing each step involves different particle surface functionalities so that there are likely to be multiple pathways influencing the overall pathogenicity.

The surface chemistry of crystalline silica dusts has been studied in detail so that each of the biological responses elicited in cells and tissues may be linked to a specific chemical feature of the particle. In an attempt to compare toxicities found with dusts having nominally the same chemical composition, the effect of heating, grinding, and etching has been studied for several crystalline polymorphs — quartz, cristobalite, coesite, stishovite — comparing pure samples with mineral and industrial ones.

Attention was focused on the following properties: (i) the hydrophilicity and propensity for hydrogen bonding, determined by the abundance and geometric arrangement of surface silanols (SiOH) and evaluated from the heat of adsorption of water vapor; (ii) Lewis and Brönsted surface acidities, the former relatable to cation impurities and the latter to silanols acting as proton donors; (iii) strained siloxane and peroxo bridges, Si-$(O)_n$-Si, evaluated from their reactivity with water and ammonia; (iv) surface radicals and charges, originated by grinding and evaluated from the electron spin resonance (ESR) spectrum of the dusts. Although not strictly related to chronic fibrogenicity, surface charges may be implicated in acute cell damage, free radical release, and possibly also carcinogenicity.

The possible role played in vivo by the various surface sites is depicted in figure 1. Several factors — origin, crystallinity, thermal and mechanical history, and contaminants — determine the presence and abundance of the various surface sites, hence also the peculiarity of each silica specimen.

The aim of the present paper is to outline the influence of these factors on some surface properties that may be related to the biological response to silica.

Materials and methods

The following materials were used: pure quartz chips (99.999%, Atomergic) (QRZ-p), Madagascar quartz (QRZ-md), Min-U-Sil 5 and DQ12 (Pennsylvania, Glass Sand Co) (1); cristobalite: ground mineral (C&E Minerals, King of Prussia, PA) (2, 3) (CSR-m), pure quartz chips ground and heated (1300°C) (CSR-q), heated diatomaceous earth (CSR-d) (4); stishovite and coesite: purified dusts from Meteor Crater (Arizona) (5); and commercial amorphous silicas: biogenic "silica earth" and "celite 545" Merck amor-

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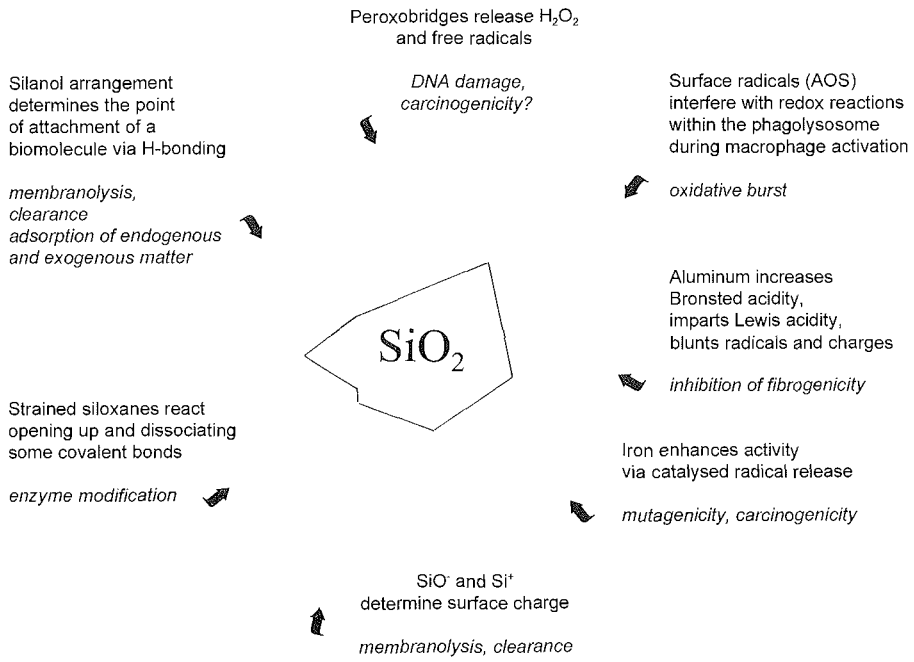

Figure 1. Possible role in the pathogenicity of chemical functionalities at the silica surface.

phous Aerosil 50, A-50, Degussa, an amorphous diatomaceous earth sample.

The set of samples was chosen to compare well-established pathogenic silicas (quartz and cristobalite) with less or nonpathogenic polymorphs (coesite, stishovite and amorphous silica); to investigate surface properties of three cristobalites of different origin: ground cristobalite mineral (CSR-m), quartz dust transformed into cristobalite by heating above 1300°C (CSR-q), and calcined diatomaceous earth (CSR-d); and to contrast samples largely used as standard dusts for in vivo and in vitro tests (Min-U-Sil and DQ12).

The crystal structures were investigated by X-ray diffraction (Philips diffractometer, Co k_α radiation) and (micro)morphology by transmission electron microscopy (TEM) (Jeol JEM 2000EX). Particle-size distributions were evaluated by means of a Coulter LS 130 with a fluid module.

Surface areas were measured with the BET method (nitrogen adsorption at –196°C, "Quantasorb," Quantachrome).

Hydrophilicity, propensity for hydrogen bonding, surface acidity, and the reactivity of strained bridges were all evaluated from the heat of adsorption of appropriate probe molecules (water, ammonia) using a Tian-Calvet microcalorimeter (Setaram) connected to a volumetric apparatus, according to previously described techniques (6—8). Surface radicals and charges were measured by electron spin resonance spectroscopy by means of a Varian E 109 spectrometer as previously described (9, 10).

Results and discussion

The interaction of a mineral particle with living matter depends upon its form and its surface reactivity. The term "form" comprises the crystal structure, size, shape, and micromorphology of the crystallites, while "surface reactivity" is any surface arrangement or site liable to react at the liquid-solid or air-solid interface.

Form

All crystalline samples of mineral origin exhibited the expected XRD pattern. TEM images (omitted from this paper but available from the authors) of some of them revealed substantial differences that may be ascribed to the different crystal structure and to the origin of the mineral. The heated diatomaceous earth CRS-d was fully crystalline, retaining the diatom morphology, and it exhibited only the cristobalite crystalline structure. It is noteworthy that these products are sold under commercial names that do not indicate their crystalline nature. They have been prepared from amorphous diatomaceous earths calcined below 1000°C (ie, in a temperature range in which cristobalite is thermodynamically unstable with respect to quartz). Such a low-temperature material should be regarded with great concern, being in the respirable size range and in the most toxic crystalline form. The transition temperature of any lot of biogenic silica to cristobalite will depend on its particle size and impurities. It is possible, however, to set up ad hoc chemical treatments for displacing the transition at higher temperatures.

Calcined diatomaceous earth represents one of the few cases in which a crystalline form of silica is directly obtained in a finely divided form. Usually quartz and other crystalline dusts are obtained by grinding bulk pieces of the mineral. In such cases fresh reactive surfaces are created during the grinding process (11). The single silica particles exhibit sharp and protruding edges but are absent in stishovite. The particles tend to stick together, the smaller ones covering the larger ones, because of surface charges. The latter have been supposed to play a role in particle-tissue interaction (12, 13). This stickiness may somehow distort particle size measurements. (See the following discussion.)

In the evaluation of size distribution, the question of parameter arises. Figure 2 illustrates data obtained with a quartz dust finely ground for biological tests. In the number or diameter representation few bigger particles escape detection, even if they represent a

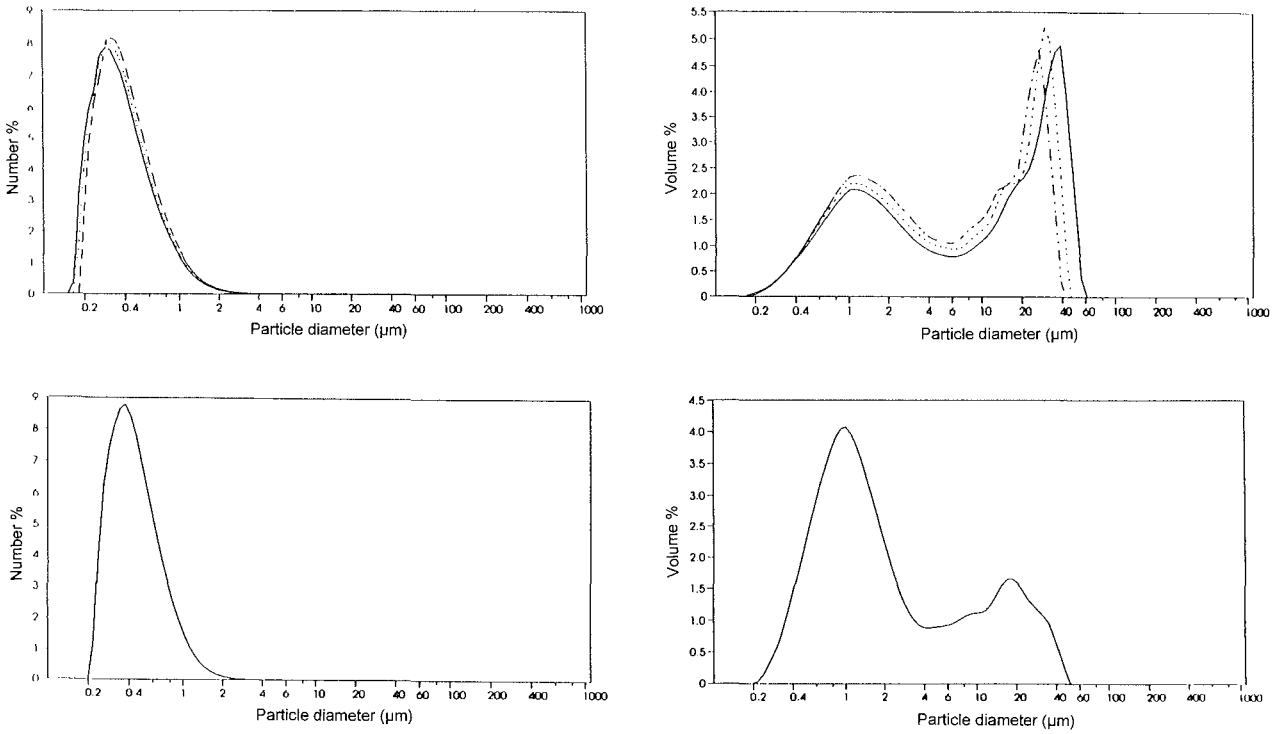

Figure 2. Evaluation of particle size distribution. (left side: number (%) of particles as a function of particle diameter; right side: volume (%) of particles as a function of particle diameter; upper graphs: bold lines, no sonication; dotted and dashed lines, sonication of particle suspensions with ultrasounds from the Coulter LS Fluid Module applied for 2 and 5 min, respectively, before the measurment; lower graphs: ultrasounds from a stronger external bath applied for 5 min before the measurement)

consistent part of the weight of the sample. Depending on the kind of test (eg, inhalation, injection, cytotoxicity, or cell transformation) big particles may be involved. In experiments in which results are compared by the weight of dust, this effect may be a source of error. The dotted lines in the figures show the effect of sonicating the dust suspensions, a process which somehow detaches particles held together by surface charges within the aggregates. Clearly, when tightly held particle aggregates such as quartz are being dealt with, the intensity of the ultrasound influences the results.

Surface reactivity

Grinding. Freshly ground silicas have shown a higher degree of toxicity ascribed to the peculiar reactivity of newly created surfaces. Grinding cleaves the silicon-oxygen bond via an homolytic or an heterolytic path (figure 3), with consequent formation respectively of dangling bonds ($Si^{\bullet}$, $SiO^{\bullet}$: reactive surface radicals with an impaired electron in a *p* orbital) and surface charges (Si^{+}, SiO^{-}). Once formed, these very reactive species tend either to recombine with the formation of strained reactive bridges [Si-O-Si; Si-$(O)_n$-Si] or to react with atmospheric components, yielding active oxygen species at the surface and in subsurface layers. The ESR spectra of the dusts, largely reported in previous papers (9, 10, 11, 14), revealed the identity and abundance of the various radical forms. The potential role of radicals in silica toxicity has been previously reported (9, 11, 14, 15). Some radicals underwent a relatively rapid decay in the first hours after grinding (11, 16—18), and this decay was related to acute damage in workers involved in mining, drilling, or sandblasting and exposed to freshly ground dusts in the respirable range. The most stable surface radicals, also visible in aged dusts (14), did not seem to be involved in the pathogenic process; still they appeared to be a good marker of reactivity and hence also of the potential toxicity of a given dust. The ESR spectrum of the solid revealed the amount and the chemical features of the radicals formed. We compared the spectra obtained for quartz, coesite, and stishovite before and after a very mild grinding in a ball mill. It is noteworthy that with coesite, whose pathogenicity in experimental silicosis is still under debate (19, 20), a structured spectrum similar to quartz appeared after grinding. By contrast, stishovite was nonpathogenic (5) and did not develop any radical when ground. In comparison with previous results the overall number of radicals decreases in the series cristobalite → quartz → coesite → stishovite (ie, upon increasing density of the SiO_2 polymorph).

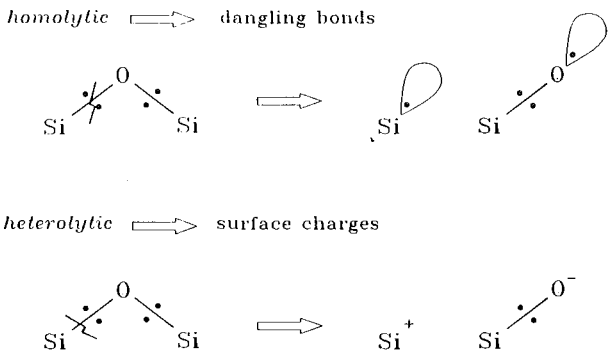

Figure 3. Cleavage of the silicon-oxygen bond after mechanical grinding.

Table 1. Uptake and molar heat of adsorption [H_2O = water, NH_3 = ammonia, n = number of moles adsorbed, q = molar heat of adsorption (H_2O at p = 5 torr; NH_3 at p = 40 torr)]

	Reversible		Irreversible	
	n (μmol · m^{-2})	q (kJ · mol^{-1})	n (μmol · m^{-2})	q (kJ · mol^{-1})
H_2O adsorption				
Aged quartz (unheated Min-U-Sil)	8.50	52	0.00	0
Freshly ground quartz (unheated QRZ-p)	7.20	57	1.00	50
NH_3 adsorption				
Untreated quartz (QRZ-md heated at 500°C)	9.50	68	1.50	20
Aluminum-treated quartz (QRZ-md heated at 500°C)	8.00	56	3.00	67

Comparisons, however, are not straightforward, as the number of radicals formed depends not only upon the grinding procedure (time, weight of the balls), but also upon the environment. A dry atmosphere favored the formation of radicals and distorted bridges, while a wet one inhibited radicals because water assists surface reconstruction (21). When mineral is ground wet, the dust loses its capability to originate radicals when compared with dust from mineral ground while dry, even if previously heated. Differences in the pathogenic potential of dusts are a function of their mechanical history, and they govern the release of active oxygen species involved in an oxidative burst and in lipid peroxidation.

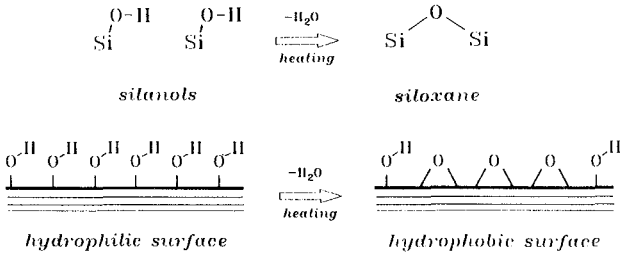

Figure 4. Progressive conversion, upon heating, of a hydrophilic surface into a hydrophobic one, after the condensation of silanols into siloxanes.

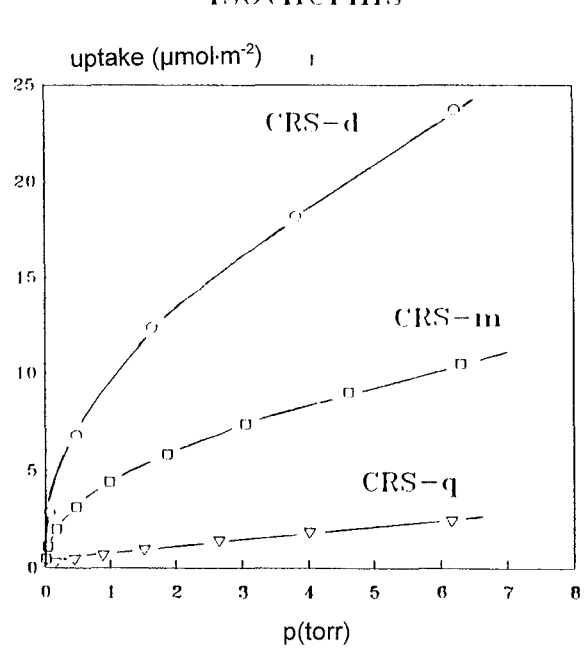

Figure 5. Adsorption of water vapor on three cristobalites of different origin: CRS-d (45 kJ · mol^{-1}) = calcined diatomaceous earth; CRS-m (58 kJ · mol^{-1}) = ground cristobalite mineral crystal; CSR-q (25 kj · mol^{-1}) = pure quartz dust converted into cristobalite by heating up to 1300°C. Adsorption isotherms (uptakes versus pressure) and average molar heat. (molar heat at p = 3 Torr)

Other manifestations of the reactivity of freshly ground dusts include (i) oxygen being absorbed at –196°C and yielding an "ozonide" radical O_3^- whose abundance parallels the fibrogenic potential (10), (ii) only freshly ground dusts release H_2O_2, following the hydrolysis of the surface peroxide bridges (Si-O-O-Si) reported by Kolbanev et al (22), and (iii) irreversible uptakes of water (table 1) on freshly ground QRZ-p revealing strained siloxane bridges (Si-O-Si), absent on Min-U-Sil, which readily dissociate the molecule and form a couple of vicinal silanols.

Heating. When silica is heated, surface radicals are healed and disappear (9), while silanols are condensed into siloxanes (figure 4) and the hydrophilic surface is progressively converted into a relatively hydrophobic one (8). This change apparently does not modify the ultimate fibrogenicity of the dust, as long as some hydrophilic patches persist on the surface, but it does markedly lower the membranolytic potential of the dust and affect transport properties. More heated than unheated cristobalite particles are found in cells in bronchoalveolar lavage and are transported to lymph nodes in exposed rats (3, 23). Hydrophilicity thus determines the fate of inhaled particles.

The extent of hydrophilicity was measured from the amounts of adsorbed water vapor and its energy of interaction: the higher these values, the more hydrophilic the surface. The results of the adsorption of water on the three cristobalite samples of different origin, CSR-m, CSR-q, CSR-d, are shown in figure 5. Both the adsorption isotherms and the heat of adsorption reveal remarkable differences between the three samples. CSR-m and CSR-d are very hydrophilic, whereas CSR-q is fully hydrophobic. The figure clearly demonstrates how the surface reactivity may differ, even within a set of samples of similar size and identical crystal structure. CSR-m has been shown to be highly pathogenic in inhalation studies (2), while, in the same intratracheal injection study, CSR-d provoked a typical silicotic response and CSR-q only elicited alveolar lipoproteinosis (4, 24). A remarkable reduction in fibrogenicity upon heating quartz and cristobalite at a high temperature has been also found by Więcek (25).

A possible explanation for the heat effect is that unheated ground dusts or mildly heated ones still retain the active surface sites prerequisite to determining the biological responses leading

to silicosis, whereas, when dusts are heated at a very high temperature, surface irregularities, radicals, and charges are healed, and silanols are wholly eliminated to form stable unreactive siloxanes, with consequent loss of the pathogenic potential. The higher hydrophilicity of CSR-d compared with that of CRS-m may be simply due to metal oxide contaminants.

Etching. Crystalline silicas were etched by three chemical agents, hydrofluoric acid, alkaline hydroxides and catechol. By attacking the silica framework, these chemicals destroyed the external surface layers and progressively eliminated surface radicals. However silanols and charges were maintained or reformed after etching (10). With hydrofluoric acid the external surface is smoothed, while the specific surface decreases. As a consequence of the dissolution of smaller particles the size distribution reveals a higher proportion of bigger particles.

Etching also eliminates impurities which modulate silica toxicity and to some extent substitute fluoride for hydroxyl, with consequent variations in the overall hydrophilicity. It has been reported that membranolysis was decreased (26), but in some cases fibrogenicity increased (27).

Impurities. Silica particulates obtained from mineral ores may contain some impurities that impart their chemical properties to the dust and may modify the pathogenic responses either by enhancing or decreasing intensity. The results obtained from the simple adsorption of water on two of the quartz dusts primarily used in animal and cell experiments, Min-U-Sil and DQ12, are shown in figure 6. Both the adsorbed amounts and the heat of interaction are higher for DQ12, for which 5% of the dust is not silica and the adsorption kinetics reveal a very slow reaction on DQ12 that does not take place with Min-U-Sil. If these surface properties have something to do with the molecular mechanisms predictive of the pathogenic process, the biological tests performed with these dusts may yield different results. It is noteworthy that Muhle et al (28) found the steepest cancer potency slope with DQ12, whereas Dagle et al (29), with Min-U-Sil, found the shallowest. The two tests are not fully comparable however because the maximum tolerated dose was exceeded by Dagle et al and different rat strains were used. Surface properties may, however, also account for some of the differences in carcinogenicity.

The metal ion contaminants most commonly found in silica specimens are iron and aluminum. They both decrease membranolysis (26, 30, 31), and, while aluminum may also inhibit the development of silicosis (32), iron impurities may act as a potential source of active oxygen species (33), causing DNA damage (34) with an increase in the carcinogenic potential of the dust.

In order to detect any surface modification brought about by aluminum, we measured the adsorption of ammonia, a Lewis and Brönsted base, on a quartz dust (QRZ-md) before and after treatment with aluminum lactate, according to the protocol used by Bégin and his associates (32), to prevent silicosis. The most remarkable differences between the two samples were found in the irreversible interaction with ammonia in the partially dehydrated samples (500°C), which evidenced a much higher surface acidity on the treated than on the untreated sample (table 1). Aluminum in a silica framework substitutes for silicon in a tetrahedral position, acts as a Lewis acid (electron acceptor), and also enhances Brönsted acidity (proton donor) by facilitating hydrogen ion donation from nearby silanols. A higher acidity may affect surface affinity for biomolecules, membranolytic potential, and the overall reactivity of the surface.

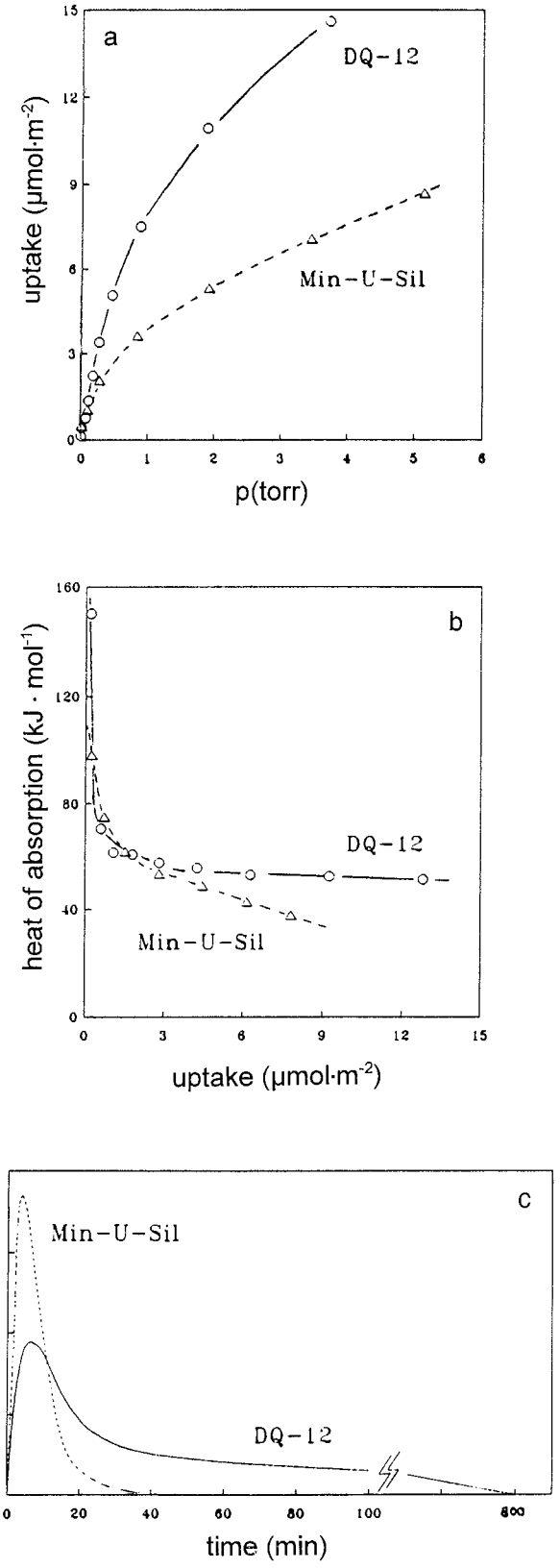

Figure 6. Adsorption of water vapor on two types of quartz, Min-U-Sil and DQ12, widely used in biological tests: a: adsorption isotherms (uptake versus pressure); b: heat of adsorption as a function of coverage; c: kinetics of the heat emission of the first adsorbed dose of water, heat emission (au), versus time.

Concluding remarks

Grinding, heating, and etching strongly influence surface properties of silica dusts. Furthermore, contaminants and the presence of water and other ions alter surface properties. Our data strongly suggest the need to expand comparisons to explain biological differences in the toxicity and carcinogenicity of silica particulates.

Acknowledgments

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Particle activity and in vivo pulmonary response to freshly milled and aged alpha-quartz

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Shoemaker DA, Pretty JR, Ramsey DM, McLaurin JL, Khan A, Teass AW, Castranova V, Paiks WH, Dalal NS, Miles PR, Bowman L, Leonard S, Shumaker J, Vallyathan V, Pack D. Particle activity and in vivo pulmonary response to freshly milled and aged alpha-quartz. *Scand J Work Environ Health* 1995; 21 suppl 2:15—8.

This study examined the possibility of freshly fractured α-quartz being more toxic and inflammatory in vivo than aged quartz of the same composition and particle size. Fresh quartz was generated by a jet mill, and used immediately, while aged dust was stored for two months before use. Both the production of hydrogen peroxide and hydroxyl radicals and the analysis of surface radicals verified the enhanced surface activity of fresh quartz. Male Fischer 344 rats were exposed to fresh or aged α-quartz by inhalation (20 mg · m^{-3}, 5 h per day, 5 d per week, for 2 weeks) and their pulmonary responses were determined 1—3 d postexposure. Exposure to aged quartz resulted in an increase in cytotoxic and inflammatory parameters. In comparison, the inhalation of freshly cleaved quartz resulted in dramatically greater increases in all of the pulmonary responses. This finding suggests that exposure to freshly machined quartz may result in a greater risk of pulmonary disease.

Key terms aged, freshly fractured silica, inhalation, pulmonary inflammation, silicosis, surface activity.

Exposure to quartz dust is an occupational hazard affecting many workers, including miners, sandblasters, and glass workers. Occupational and environmental monitoring for quartz, as well as the exposure limits, are all concerned with the concentration of the dust. However, quartz that has been recently fractured has been shown to have increased surface activity. Hoenig (1) has shown that grinding quartz (and other materials) causes an exo-electron current. Göthe et al (2) found that disintegrated quartz dust causes an increase in the lung weight and collagen content of rats in comparison with rats exposed to "standard quartz" of comparable particle size. Conversely, Bar-Ziv & Goldberg (3) suggested that the lack of fibrosis in the lungs of Bedouins in which siliceous dust was present was due to the age of the inhaled particulate. More recently, fracturing has been shown to enhance the ability to cause membrane damage, the peroxidation of membrane lipids, and activation of alveolar macrophages in vitro (4—7). These results and previous suggestions imply that workers exposed to freshly fractured silica may be at increased risk of developing pulmonary injury.

To investigate these questions, an inhalation exposure study involving 900 rats has been planned. The study requires the exposure of 300 rats, each to equivalent concentrations of freshly fractured and aged respirable quartz dust, with an additional 300 rats as controls. In this context, aged silica is milled quartz of the same particle size that has aged in air for at least two months. At the end of 2, 4, and 26 weeks, rats from each exposure group will be sacrificed and a series of biochemical and pathological tests performed to determine alveolar damage, cellular inflammation, and alveolar macrophage activation.

To evaluate the entire experimental protocol adequately, a two-week pilot study was performed. All of the procedures planned for the full exposure were evaluated, including the quartz aerosol generation systems, sampling procedures, aerosol analyses (concentration, particle size), dust activity analyses, animal care and handling, and biochemical and pathological analyses. This report summarizes the experimental protocol and presents the results of the two-week pilot study.

Methods

Exposure. In brief, aerosols of quartz dust (20 mg · m^{-3}) were generated in two chambers, each housing 20 male Fischer 344 rats. Quartz sand was air-jet milled, passed through a cyclone, and immediately directed into the "fresh" chamber. The aerosol of previously milled quartz dust that had aged two months was prepared by dropping the dust onto a revolving plate and resuspending the dust through aspiration. This aerosol was

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introduced into the "aged" chamber after passage through a cyclone. The control rats were housed in a chamber into which only filtered air passed. The exposures were performed 5 h each workday for two weeks, and pulmonary responses were determined 1—3 d postexposure. The aerosols were monitored by gravimetry and particle counters for concentration by scanning electron microscopy for particle size and by electron spin resonance (ESR) and the chemical methods for activity levels (hydrogen peroxide, hydroxyl and surface radicals).

The quartz used in this study was Iota standard quartz sand (Unimin Corporation, New Canaan, Connecticut, United States) with a mass median diameter of 193 μm. An optical microscopic examination revealed that the material was at least 99% quartz.

Since metals can greatly influence surface activity and radical production, proton-induced X-ray emission spectroscopy was performed for 72 trace elements, both before and after the milling. The elements that were consistently detected in all of the samples are shown in table 1. These contaminants are a result of the aerosol generation systems. The carbon is assumed to come from the abrasion of the polyurethane liner of the air-jet mill. The iron, chromium, nickel, and manganese are from the stainless steel screws feeding the generation systems. An examination of filter samples collected from the exposure atmosphere by scanning electron microscopy revealed discrete particles of stainless steel agglomerated with several quartz particles. Steps have been taken to reduce the amount of metal contamination for the larger study.

The quartz aerosol generation systems worked well. The time-weighted average concentrations were 22.4 (range 19.9—36.2) mg · m^{-3} for the fresh chamber and 19.3 (range 17.1—20.7) mg · m^{-3} for the aged chamber. The temperature, humidity, and ammonia concentration remained in control and were not significantly different in the three chambers. The count median of the circular-area equivalent diameter for the fresh dust was 0.46 μm with a geometric standard deviation of 2.1; for the aged dust the corresponding values were 0.53 μm and 2.2, respectively.

Measurement of particle activity. The peroxidase-catalyzed oxidation of 4-hydroxyphenylacetic acid (PHPA) by hydrogen peroxide yields a strongly fluorescent dimer of PHPA (8). In our application, the quartz-laden filter was placed into a buffer solution (pH 7) and sonicated for 1 min to remove the dust. The suspension was agitated at 25°C for 30 min to allow efficient transfer of hydrogen peroxide into the solution. The supernatant was combined with PHPA and peroxidase and adjusted to pH 10 after 30 min (to allow) for reaction. The analysis was carried out with a flow injection with a fluorescence detector (excitation 320 nm, emission 420 nm).

Table 1. Elements consistently detected in the quartz dust analyses.

Elements	Bulk[a] (μg · g^{-1})	Milled[b] (μg · g^{-1})
Carbon[c]	54	1654[d]
Chromium	<1.2	58
Iron	7.0	222
Manganese	0.93	6.6
Nickel	0.56	25

[a] Based on an analysis of three samples.
[b] Based on an analysis of six samples.
[c] Carbon was analyzed with an induction furnace method.
[d] Based on an analysis of seven samples.

For determining hydroxyl radical, the dust was scraped from the filter into the 2-deoxyguanosine solution, agitated for 1 h to allow generation of the hydroxyl radical and the production of 8-hydroxy-2-deoxyguanosine, and then centrifuged. The supernatant was then analyzed by high-performance liquid chromatography with electrochemical detection at +0.3 V (9, 10).

The surface reactivity of freshly milled and aged quartz was determined with ESR spectroscopy. On three days, the quartz dust from triplicate filter samples from the exposure chambers was transferred to 5-mm quartz nuclear magnetic resonance tubes and analyzed for free radicals with a Varian E-109 ESR spectrometer at X-band (~9.52 GHz). All of the measurements were made at a receiver gain of $1 \cdot 10^4$, a microwave power of 50 mW, a time constant of 1 s, modulation amplitude of 2 gauss, and a scan time of 120 s with a field amplitude of 3380 (SD 200) gauss. Three scans were integrated for all of the samples, and the scaling and analysis of the spectra were made with an electron paramagnetic resonance DAP 2.0 program. The silicon-based surface radicals of freshly fractured and aged quartz were typically centered around 2.0015 g, and the surface activity was determined from the peak intensities relative to a standard sample of diphenylpicrylhydrazyl (4, 11).

Pulmonary responses. Pulmonary responses were determined 1—3 d postexposure. Briefly, rats were anesthetized and then killed, and bronchoalveolar lavage was performed. The lavage samples were separated into acellular, for the determination of lavage protein, phospholipid, albumin, and N-acetyl-β-D-glucosaminidase (NAG), and cellular, for the determination of cell differentials and macrophage activity fractions. Another set of rats was also killed, and lung slices were analyzed for lipid peroxidation.

The protein content of the acellular lavage fluid was measured by the method of Lowry et al (12). The total phospholipid concentration was determined as the phosphorus present in the lipid extract (13). The phospholipid content was calculated by multiplying the lipid phosphorus values by 25 (14). Albumin was measured with Sigma Diagnostic reagents and procedures. NAG was determined by measuring the release of 3-cresolsulfonphthalcin from the substrate 3-cresolsulfonphthalcin-N-acetyl-β-D-glucosaminide at 580 nm according to the method of Yakada et al (15).

Bronchoalveolar lavage cells were collected, washed, and resuspended in HEPES-buffered medium (145 mM NaCl, 5 mM KCl, 10 mM of HEPES, 5.5 mM of glucose, and 1 mM of $CaCl_2$; pH 7.4). Cell counts and differentials were obtained with an electronic cell counter equipped with a cell sizing attachment (16). The chemiluminescence generated from the pulmonary phagocytes was measured with a Berthold LB953 luminometer at 37°C in the presence of 8 μg% luminol and 2 mg · ml^{-1} zymosan.

The lipid peroxidation potential of the lungs from the animals exposed to filtered clean air, aged quartz, or freshly fractured quartz was monitored by measuring the malondialdehyde generated during the incubation of lung slices for 1 h in a buffered medium without any other stimulation. Frozen lung tissue slices (300—450 mg) were incubated in phosphate-buffered medium at pH 7.4 for 1 h at 37°C in a shaking water bath. The reaction was terminated by the addition of 0.3 ml of 5N hydrochloric acid and 0.625 ml of 40% trichloroacetic acid. After being mixed, the reaction was treated with 0.625 ml of thiobarbuturic acid, mixed, and heated in a water bath at 95°C for 20 min. The substances reactive

to thiobarbuturic acid developed a color which was measured at 540 nm after cooling according to the method of Hunter et al (17). Malondialdehyde production was calculated from a standard graph made with the same reagents and known concentrations of malondialdehyde. Control experiments were carried out without lung tissues, with inactivated lung tissue, and in the presence of an antioxidant, butyl hydroxytoluene, to inhibit lipid peroxidation.

Results

As we expected, the activities of the quartz in the two aerosols were significantly different (figure 1). The hydrogen peroxide levels (95% confidence intervals) were 0.256 ± 0.018 nmol · mg^{-1} for the freshly fractured quartz and 0.114 ± 0.026 nmol · mg^{-1} for the aged samples, a 125% difference. The hydroxyl radical level produced in 1 h by the fresh quartz was 27.13 ± 4.07 pmol · sample^{-1}, while the aged quartz produced 19.04 ± 3.43 pmol · sample^{-1}, a 43% difference. The ESR measurements showed that fresh quartz produced $1.46 \pm 0.17 \times 10^{13}$ spins · mg^{-1} in comparison with $0.96 \pm 0.11 \times 10^{13}$ spins · mg^{-1} for the aged quartz, a 52% difference.

The inhalation of aged α-quartz (20 mg · m^{-3}) caused significant cytotoxicity and pulmonary inflammation (table 2). Damage at the alveolar blood-air barrier was indicated by increased lavage levels of red blood cells, albumin, and protein. Damage at the cell and membrane level was shown as an elevation of the lavage levels of NAG and by an increase in the lipid peroxidation of lung tissue. A lipidotic response to aged quartz was evidenced by elevated levels of phospholipid in lavage fluid, while inflammation was demonstrated as an increase in lavage leukocytes and an enhanced generation of zymosan-stimulated chemiluminescence from alveolar macrophages. In comparison with aged dust exposure, the inhalation of freshly milled quartz resulted in significantly greater reactions for all of these cytotoxic and inflammatory parameters.

Discussion

Recent reports indicate that crushing silica particles results in the generation of silicon-oxygen radicals on the cleavage planes (4, 18). In addition, freshly ground silica can react in aqueous media to generate hydroxyl radicals (19). The present investigation describes an air-jet mill system capable of generating sufficient quantities of freshly cleaved α-quartz for inhalation studies. The enhanced activity of this freshly milled dust, compared with milled dust which was stored for two months, was verified by the increased production of hydrogen peroxide and hydroxyl radicals and by an enhanced ESR signal indicative of silicon-based surface radicals.

In vitro studies indicate that freshly crushed silica is more cytotoxic and is a more potent activator of oxidant release from alveolar macrophages than ground silica which has been aged to allow the decay of these surface radicals (4, 5). Therefore, the hypothesis has been advanced that freshly machined particles would be more fibrogenic than aged dust. Results of the present inhalation study confirm in vivo the enhanced activity of the freshly fractured silica dust relative to that of aged dust. The freshly machined quartz exhibited greater cytotoxicity than aged particulates, which in turn produced a significantly greater response than that found in the control experiment. This cytotoxicity was demonstrated by elevated red blood cell counts, albumin, and protein in lavage samples, all of which indicated damage at the blood-airspace barrier, and by increased enzyme levels and lipid peroxidation, indicating damage at the cell and membrane level. Likewise freshly milled silica was more inflammatory than aged quartz as evidenced by the greater recruitment of leukocytes into the airspaces and the enhanced potentiation of alveolar macrophage oxidant production.

As shown in figure 1, the activity of the aged silica used on days 9 and 10 of this pilot study was much higher than the

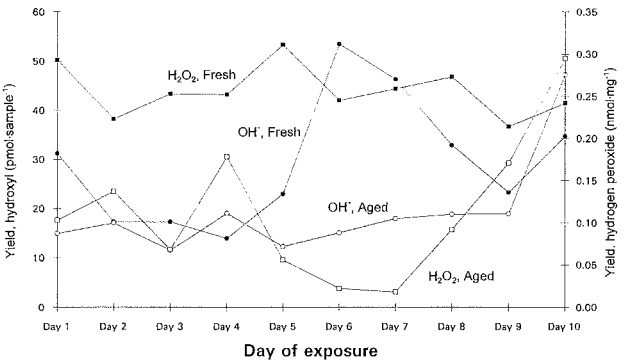

Figure 1. Yields of hydrogen peroxide (H_2O_2) and hydroxyl radical (OH·). Each point is the average of two to five samples taken during each day.

Table 2. Pulmonary responses to the inhalation of fresh versus aged α-quartz. Values are means and standard deviations of four determinations; lavage red blood cells (RBC) and leukocytes in 10^6 cells per rat; albumin in micrograms per microliter of acellular lavage fluid; protein and phospholipid from acellular lavage samples in milligrams per gram of lung; N-acetyl-ß-D-glucosaminidase (NAG) in units per liter of acellular lavage fluid; lipid peroxidation in micromoles of malondialdehyde per gram of lung tissue; and zymosan-stimulated chemiluminescence (Zymo-stim CL) in counts per minute/0.75×10^6 macrophages per 10 min.

Parameter	Air		Aged silica		Machined silica	
	Mean	SD	Mean	SD	Mean	SD
RBC	0.10	0.03	1.48	0.14[a]	5.83	0.74[b]
Albumin	0.3	0.3	0.34	0.09	0.62	0.05[b]
Protein	2.76	0.33	3.93	0.15[a]	4.97	0.03[b]
NAG	35.0	0.0	53.42	10.91[a]	126.52	15.78[b]
Lipid peroxidation	1.01	0.16	2.27	0.37[a]	3.02	0.29[b]
Phospholipid	1.71	0.03	3.66	0.19[a]	5.12	0.15[b]
Leukocytes	0.10	0.01	4.75	0.66[a]	10.70	1.33[b]
Zymo-stim CL	29.34	2.41	277.82	13.08[a]	767.54	79.85[b]

[a] Significantly greater than control ($P < 0.05$).
[b] Significantly greater than aged silica ($P < 0.05$)

dust used the previous eight exposure days (for a variety of technical errors). This increase in activity acts to minimize the differences in the pulmonary responses of the fresh versus aged quartz groups. However, substantial cytotoxic and inflammatory differences were evident that lend support to the hypothesis that freshly cleaved silica may be more pathogenic than aged quartz. These technical errors have been corrected in preparation for the larger study.

In conclusion workers such as sandblasters, rock drillers, and silica flour millers exhibit a significant incidence of silicosis. A factor common to these occupations is exposure to freshly broken or fractured quartz particles. Data from both in vitro and in vivo studies indicate that freshly cleaved silica is more cytotoxic and inflammatory than aged quartz of the same particle size at similar exposure doses. Data suggest that increased disease risk may be related to the unique activity of the fresh cleavage planes of the broken α-quartz crystal.

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Differential pulmonary responses in rats inhaling crystalline, colloidal or amorphous silica dusts

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Warheit DB, McHugh TA, Hartsky MA. Differential pulmonary responses in rats inhaling crystalline, colloidal or amorphous silica dusts. *Scand J Work Environ Health* 1995;21 suppl 2:19—21.

Pulmonary responses in rats were compared after short-term inhalation exposure to polymorphs of silica dust. Groups of CD rats were exposed 6 h a day for 3 d to crystalline silica or amorphous silica. Another group was exposed to Ludox colloidal silica for 6 h a day, 5 d a week for two or four weeks. Thereafter the groups were killed, and the lungs washed at several postexposure times. The crystalline silica produced persistent pulmonary inflammatory responses characterized by neutrophil recruitment and consistently elevated biomarkers of cytotoxicity in bronchoalveolar lavage fluids, and progressive histopathological lesions were observed within one month of the exposure. Amorphous silica produced a transient pulmonary inflammatory response, and Ludox elicited transient pulmonary inflammatory responses at 50 or 150 mg · m^{-3} but not at 10 mg · m^{-3}. After three months most of the biochemical values of the Ludox-exposed animals had returned to the control level. These results demonstrate that crystalline silica dust is more potent in producing pulmonary toxicity when compared with amorphous or colloidal silica particles.

Key terms amorphous, colloidal, crystalline, fibrosis, inflammation, persistent effects, pulmonary, silica, transient effects.

Chronic inhalation of crystalline silica dust causes pulmonary inflammation and the development of fibrosis in experimental animals and exposed humans (1, 2). After acute inhalation exposure of rats, a persistent inflammatory response ensued which progressed to alveolar proteinosis and fibrosis. While it is widely accepted that exposure to the crystalline species of silica dust elicits toxic pulmonary effects, there is limited information regarding lung responses to other forms of silica dust. Accordingly, this report is a compilation of four bioassay studies implemented to compare pulmonary responses in rats after short-term inhalation exposure to several polymorphs of silica dust. The dust comprised two forms of crystalline silica (α-quartz and α-cristobalite), one form of amorphous silica, and one form of colloidal silica particles.

Cells and fluids from groups of sham and dust-exposed animals were recovered by bronchoalveolar lavage (BAL). Lactate dehydrogenase (LDH), protein, and N-acetyl glucosaminidase (NAG) were measured in BAL fluids several times postexposure. The cells were identified, counted, and evaluated for viability. The lungs of additional animals were processed for histopathology, and these results have been reported elsewhere (3, 4). The data generated from these studies provide an interesting comparison of differential pulmonary responses in rats inhaling various forms of silica dust.

Materials and methods

General experimental design. This study was designed to evaluate pulmonary responses in rats after short-term inhalation exposure to two forms of crystalline silica, one form of amorphous silica and one form of colloidal silica particles. Crystalline silica particles, in the form of Berkeley Min-U-Sil-5, were obtained from the Pennsylvania Glass and Sand Corporation (Pittsburgh, Pennsylvania, United States). α-Cristobalite silica was obtained from the C & E Mineral Corporation (King of Prussia, Pennsylvania, United States) and was a generous gift from Dr David Hemenway from the University of Vermont. Ludox colloidal silica was obtained from DuPont Chemicals. Amorphous silica particles (Zeofree 80) were purchased from the JM Huber Co, Havre de Grace, Maryland. These particles are known to be free of crystallinity (Dr David Hemenway, personal communication).

For two of the inhalation toxicity studies, groups of 24 CD rats were exposed for 3 d at aerosol concentrations of either 10 or 100 mg · m^{-3} to either cristobalite or amorphous silica. In another study with Min-U-Sil α-quartz particles, 24 rats were exposed for 6 h a day for 3 d to concentrations of 100 mg · m^{-3}. In the fourth study, rats were exposed to Ludox for 6 h a day, 5 d a week for two or four weeks at concentrations of 10, 50, or 150 mg · m^{-3}. After the termination of the exposures, groups of animals were sequentially killed and their lungs washed several times postexposure.

Inhalation exposure and biochemical assays. The dust generation methods have been previously reported (3, 4). The measured mass median aerodynamic diameter (MMAD) ranges for the various generated silica polymorph particles were the following: cristobalite crystalline silica 3.4—3.6 μm, Zeofree 80

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2.4—3.4 μm, Ludox 2.9—3.7 μm, and Min-U-Sil 3.3—3.5 μm. BAL and cellular quantification procedures were conducted according to previously described methods (5).

Results

The cell differential analyses of rats exposed to Min-U-Sil and cristobalite indicated that inflammation was a prominent feature in the lungs of rats exposed to crystalline silica. Pulmonary inflammatory responses, characterized by the presence of granulocytes (primarily neutrophils) in BAL fluids, persisted throughout a three-month postexposure period (figure 1). In contrast, exposure to amorphous silica produced a transient inflammatory response which was present 24 h postexposure but was abrogated within 8 d postexposure (figure 1). Similarly, exposures to Ludox for two or four weeks at 50 and 150 mg · m^{-3}, but not at 10 mg · m^{-3}, produced increased numbers of lavaged granulocytes ($P < 0.05$), but these numbers were significantly reduced following a three-month recovery period. Extracellular LDH in the BAL fluids was considered to be a sensitive indicator of pulmonary cytotoxicity. Transient increases in LDH were measured in rats exposed to amorphous silica for 3 d. The BAL fluid LDH values increased within 24 h after exposure but returned to control levels by 8 d postexposure (figure 2). In rats exposed to 150 mg · m^{-3} of Ludox, the LDH was significantly increased above the control value at two or four weeks, but was reduced after the recovery period (table 1). No significant differences were measured for LDH at any time postexposure between the rats exposed to 10 or 50 mg · m^{-3} concentrations of Ludox and the controls (table 1). In contrast, the LDH was increased within 24 h after Min-U-Sil and cristobalite exposure, and it remained elevated throughout a three-month postexposure period. Rats exposed to cristobalite for 3 d demonstrated a 12-fold increase in LDH three months after the exposure (figure 2).

The assessments of protein in BAL fluids showed a trend similar to that described for LDH activity. Exposures to Ludox for two or four weeks or to amorphous silica for 3 d produced transient increases in BAL fluid protein (table 1, figure 3). In contrast, exposure to cristobalite or Min-U-Sil produced sustained effects which were substantially increased over those of the controls ($P < 0.05$) three months postexposure (figure 3). Likewise, BAL fluid protein levels were transiently increased in rats exposed to amorphous silica and were sustained in all of the groups of animals exposed to crystalline silica (figure 3).

NAG was significantly increased in BAL fluids ($P < 0.05$) after a 3-d exposure to cristobalite, while the NAG values of rats exposed to amorphous silica did not significantly differ from those of controls by 8 d postexposure (figure 4). Similarly, the NAG values of rats exposed to Min-U-Sil were significantly increased after the 3-d exposure. This increase was sustained throughout the postexposure period (figure 4).

Discussion and concluding remarks

Chronic inhalation of crystalline silica produces pulmonary inflammation and the consequent development of silica-induced pulmonary fibrosis (1, 2). During the acute phase, a pulmonary inflammatory response develops and progresses to alveolar proteinosis and a granulomatous-type pattern of disease in animals.

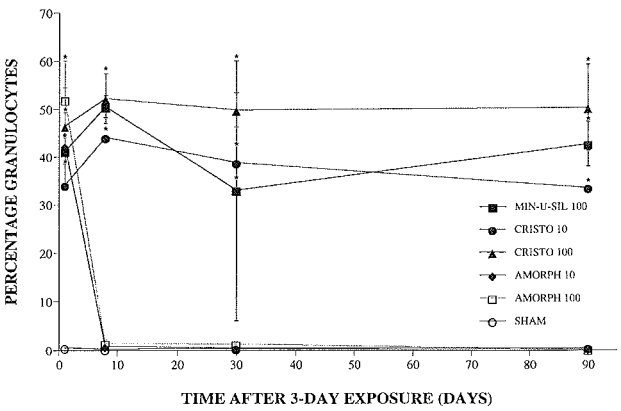

Figure 1. Granulocyte differential percentages for bronchoalveolar lavage fluids of rats exposed to amorphous silica (AMORPH), Min-U-Sil, or cristobalite (CRISTO) ($P < 0.05$).

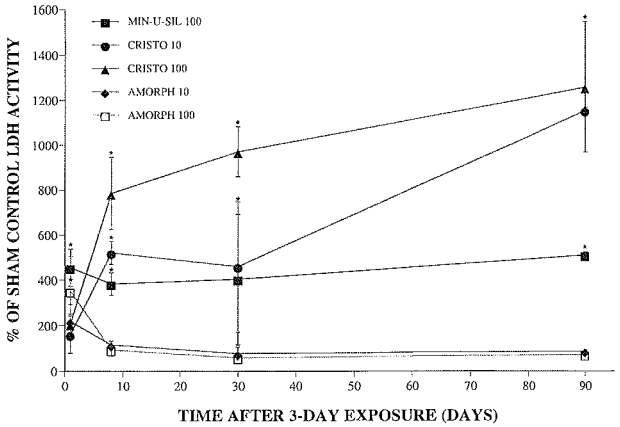

Figure 2. Lactate dehydrogenase (LDH) values for bronchoalveolar lavage fluids of rats exposed to cristobalite (CRISTO), Min-U-Sil, or amorphous (AMORPH) silica ($P < 0.05$).

Table 1. Lactate dehydrogenase and protein in rats exposed to Ludox colloidal silica – percentage of sham control responses.

Ludox	Lactate dehydrogenase						Protein					
	Two-week exposure, no recovery		Four-week exposure, no recovery		Four-week exposure, three-month recovery		Two-week exposure, no recovery		Four-week exposure, no recovery		Four-week exposure, three-month recovery	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
10 mg · m^{-3}	99.1	27.9	108.5	26.5	89.8	11.2	144.9	36.1	89.8	·	91.2	·
50 mg · m^{-3}	110.5		365.9	91.1	159.2	19.8	92.3	19.5	159.2	20.4	75.4	7.5
150 mg · m^{-3}	437	100*	1033	197*	172	72	224	32*	423	104*	125	15

* $P < 0.05$.

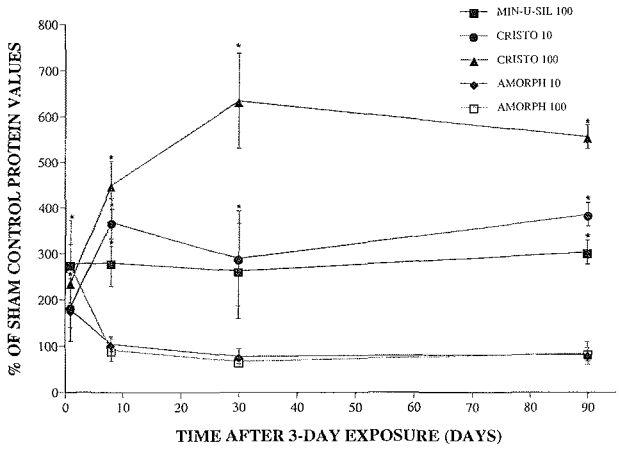

Figure 3. Protein levels of bronchoalveolar lavage fluids in rats exposed to cristobalite (CRISTO), Min-U-Sil, or amorphous (AMORPH) silica ($P < 0.05$).

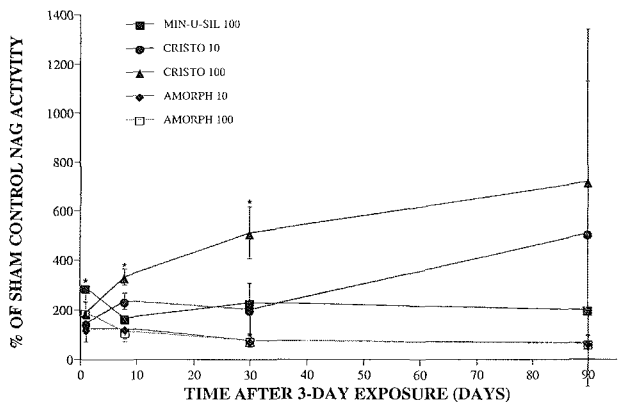

Figure 4. N-acetyl-glucosaminidase (NAG) values of bronchoalveolar lavage fluids in rats exposed to cristobalite (CRISTO), Min-U-Sil, or amorphous (AMORPH) silica ($P < 0.05$).

During the chronic phase, nodular fibrosis occurs in exposed animals and humans. Although the pathological effects of crystalline silica are well known, there is a paucity of information on the pulmonary effects of inhaled amorphous and colloidal forms of silica. The limited toxicologic information available suggests that the pulmonary effects following exposures to amorphous silicates may be reversible in the absence of continuing exposure (6—9). Moreover, in elegant studies presented at the first silica, silicosis and cancer symposium, Hemenway et al (10) exposed rats for 8 d to aerosols of one of three silica species, α-cristobalite, α-quartz or amorphous silica. The greatest measure of lung injury was produced with cristobalite, which caused substantial inflammation and fibrosis. Exposures to α-quartz produced intermediate effects, while amorphous silica produced minimal effects. The authors concluded that amorphous silica particles were less toxic than the different species of crystalline silica polymorphs. In support of the results of Hemenway et al, the results reported in previous studies indicate that Ludox is significantly less active in producing pulmonary effects when compared with Min-U-Sil (3, 4).

In conclusion, brief exposures to two different forms of crystalline silica particles produced a persistent pulmonary inflammatory response, characterized by neutrophil recruitment and consistently elevated biomarkers of cytotoxicity in BAL fluid. Progressive histopathologic lesions were previously observed within one month after a 3-d exposure (3). In contrast, a 3-d exposure to amorphous silica particles produced a transient pulmonary inflammatory response, and two- or four-week exposures to Ludox elicited pulmonary inflammation at 50 or 150 mg · m^{-3} but not at 10 mg · m^{-3}. Most of the biochemical parameters returned to control values after a three-month recovery period. These results demonstrate that the crystalline forms of silica dust are much more potent in producing pulmonary toxicity than amorphous or colloidal forms of silica are.

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Direct interaction between crystalline silica and DNA – a proposed model for silica carcinogenesis

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Daniel LN, Mao Y, Williams AO, Saffiotti U. Direct interaction between crystalline silica and DNA — a proposed model for silica carcinogenesis. *Scand J Work Environ Health* 1995;21 suppl 2:22—6.

Crystalline silica in aqueous buffer produced oxygen radicals that mediated in vitro DNA (deoxyribonucleic acid) strand breakage. The oxidized DNA base, thymine glycol, was also produced. The hydroxyl radical, responsible for most DNA damage, has a reaction distance of about 15 Angstroms, requiring close contact of silica with DNA. Fourier transform infrared spectroscopy of incubations of quartz particles with DNA showed distinct alterations in both DNA and quartz spectra and therefore indicated extensive hydrogen bonding between surface silanol groups and the phosphate-sugar backbone of DNA. Electron microscopy and energy dispersive X-ray spectroscopy of alveolar epithelial cells in fetal rat lung, exposed to quartz in culture, showed localization of quartz particles in the nuclei and mitotic spindles. Direct interaction of crystalline silica with DNA may be important in silica carcinogenesis by anchoring DNA close to sites of free radical production on the silica surface, or by interfering with DNA replication, repair, or the mitotic process.

Key terms carcinogenesis mechanisms, deoxyribonucleic acid, DNA binding, FRLE cell line, electron microscopy, infrared spectra, quartz.

Human exposure to crystalline silica particles causes silicosis (1). Many studies show an increased risk for lung cancer associated with silicosis (2—5). The carcinogenic activity of quartz in vivo has been well established by numerous studies in rats (3, 6—13). In vitro models have also been developed for crystalline silica toxicity (14, 15) and neoplastic cell transformation (16, 17). The physicochemical basis of these effects has not been established, however.

Properties of crystalline silica that have been proposed to account for its pathogenicity include the hydrogen bonding ability of surface silanol groups (18), the negative surface charge produced by ionized surface silanol groups (14), and the generation of oxygen-free radicals at the silica surface (15, 19—22). Crystalline silica produces damage of DNA (deoxyribonucleic acid) in vitro (19, 20), a mechanism which could be involved in its ability to induce neoplastic cell transformation and carcinogenic effects in vivo. However, the hydroxyl radical mediating this type of DNA damage has a reaction distance of approximately 15 Angstroms (23), less than the width of a DNA helix. Adhesion of DNA to amorphous silica, such as glass and silica gel, is well known (24). DNA binding to crystalline silica might also be expected, and this binding could be important in anchoring DNA close to sites of free radical production at the surface of crystalline silica particles. In order to investigate the mechanisms of silica carcinogenicity through direct DNA damage, we addressed the following major questions: (i) what is the mechanism of DNA binding to quartz and (ii) is quartz able to interact with nuclear material in the alveolar epithelial cells — the cell of origin for silica-induced lung carcinomas?

Materials and methods

Silica preparations. A sample of Min-U-Sil 5 α-quartz (MQZ) from the Pittsburgh Glass and Sand Co (now US Silica, Berkeley Springs, West Virginia, United States) was obtained in 1984 through the Illinois Institute of Technology Research Institute (19, 25). Chinese standard α-quartz (CSQZ) (26) was obtained from the Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China. Both samples were characterized for surface area and binding to Janus Green B (25).

The quartz samples were dried in an oven at 110°C for 24 h prior to each experiment, suspended in buffer at 20 mg · ml^{-1} and sonicated for 3 min in a sonicator bath (Branson model 220, Shelton, Connecticut, United States). The suspensions were diluted to the desired concentrations and used immediately to ensure homogeneity.

DNA and chemicals. Calf thymus DNA and chemical reagents were obtained from Sigma (St Louis, Missouri, United States). Phosphate buffers were treated with Chelex resin (Biorad, Richmond, California, United States) and titrated to pH 7.4 by mixing monovalent and divalent stock solutions. One molar stock buffers were diluted to 5 mM by adding H_2O or D_2O. Titration of buffers containing heavy water (D_2O) to pD 7.4 was obtained by adding the value of 0.45 to the pH meter reading (27).

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Fourier transform infrared spectroscopy. The attenuated total reflectance (ATR) Fourier transform infrared (FT-IR) spectroscopic methods used were based on previously published procedures (28, 29). A single-beam FTS-45 FT-IR spectrophotometer (Biorad, Cambridge, Massachusetts, United States) was used with a DTGS detector to obtain spectra (resolution 8 cm^{-1}) at ambient temperatures. For each sample, 1000 scans were taken. The samples were scanned in a liquid ATR cell (Biorad) using a zinc selenide (45°) crystal. Spectral analysis was limited to the range of 1800 to 800 cm^{-1}. All the ATR spectra were recorded under nitrogen atmosphere to minimize water vapor interference. Vibrational signals arising from buffer components were subtracted from sample spectra according to standard subtraction criteria (30, 31). The effects of DNA-silica coincubation were observed by subtracting recorded spectra for DNA or silica from the combination spectrum. In order to obtain correct silica subtraction, distinct silica peaks at 779 and 799 cm^{-1} were used as an internal normalization standard. The criterion for DNA subtraction was a flat base line in the 1750 to 1200 cm^{-1} range (29).

Transmission FT-IR spectra were obtained in a standard fluid cell between parallel zinc selenide windows (Perkin-Elmer, Norwalk, Connecticut, United States).

Cell culture and electron microscopy. The FRLE cell line, derived from fetal rat lung alveolar type II cells (32) (which correspond to the cell of origin for silica-induced rat lung adenocarcinoma) was kindly provided by Dr MA Haralson, Department of Pathology, Vanderbilt University School of Medicine, Nashville, Tennessee, United States, and further characterized in our laboratory (33). Cells at passage 39° were plated at 10^4 cells per 50-mm dish in minimal essential medium (MEM) with 10% fetal bovine serum. At 24 h after the plating the medium was changed to an aliquot containing MQZ or CSQZ (dispersed by sonication immediately before the treatment) at a final concentration of 25 $\mu g \cdot cm^{-2}$. For the electron microscopy, the cultures at 2, 8, and 26 d after silica exposure were washed, fixed in situ with 1.5% glutaraldehyde, postfixed in 1% osmium tetroxide, stained with uranyl acetate, and embedded in pure epoxy resin (LX-112). Thin sections were cut with diamond knives parallel and perpendicular to the cell monolayer. The thin sections were mounted on a formvar film grid and double stained with uranyl acetate and lead citrate. Sections were examined and photographed with a Hitachi H-7000 electron microscope at 100 kV.

Energy dispersive X-ray analysis. Kevex-ray energy dispersive X-ray (EDX) analysis was made in the STEM (scanning transmission electron microscopy) mode on a Hitachi H-7100 microscope operated at 75 kV (TEM mode) and 10 kV (SEM mode). A 68° X-ray takeoff angle detector was used for the silica particle analysis.

Results

Infrared spectroscopy. With the use of transmission FT-IR, consistent peaks were recognizable for DNA (10 $mg \cdot ml^{-1}$) in phosphate buffer (figure 1A) and for quartz in suspension (5 $mg \cdot ml^{-1}$) (figure 1B). MQZ showed a major peak at 1088 cm^{-1} with a prominent shoulder peak at 1163 cm^{-1}. Corresponding peaks were seen at 1095 cm^{-1} and 1161 cm^{-1} for CSQZ (29). Combination spectra obtained by quartz-DNA coincubation produced tracings dominated by the quartz spectrum at the concentrations used. These tracings were characterized by a narrowing of the major peak for quartz and a shift of approximately 9 cm^{-1} (figure 1C). These findings are consistent with a loss of degeneracy in the spectrum due to silicon-oxygen bond alteration on the surface of the silica crystal, presumably as a result of DNA binding to the silanol group.

ATR infrared spectroscopy was performed using 10 $mg \cdot ml^{-1}$ DNA in phosphate buffer, combined with 0.2, 1.0, or 5.0 $mg \cdot ml^{-1}$. The lower silica doses were used in order to increase the ratio of DNA to silica in the combination spectra, which had been dominated by silica in the transmission spectra. DNA spectra were obtained which agreed with previously published spectra (28, 34, 35) (figure 2, dotted lines). When DNA was coincubated with MQZ, the subtraction spectrum [(DNA+quartz)-quartz] showed a major shift in the region of 1053 cm^{-1} of the DNA spectrum (figure 2, upper panel). Both MQZ and CSQZ produced

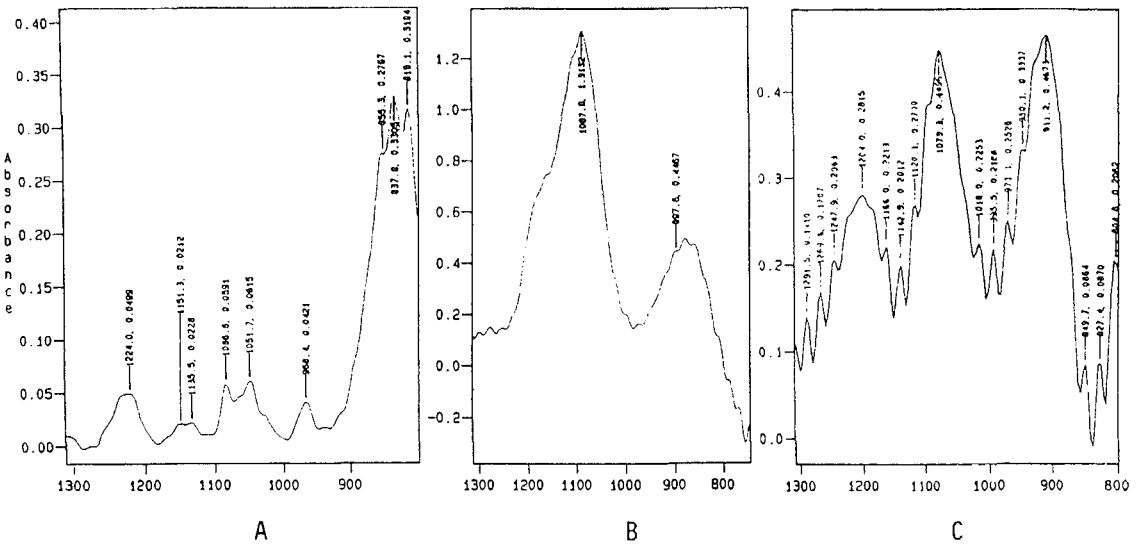

Figure 1. Transmission FT-IR spectra in the region near 1000 cm^{-1}: A = DNA 10 $mg \cdot ml^{-1}$, B = MQZ quartz (5 $mg \cdot ml^{-1}$ suspension), C = DNA plus MQZ. Note the splitting of the broad major peak of MQZ at 1088 cm^{-1} into two narrower peaks at 1204 and 1079 cm^{-1}. The peak at 911 cm^{-1}, which appears to be new, cannot be identified due to strong water absorbance in this region. (Note the different scales of the panels).

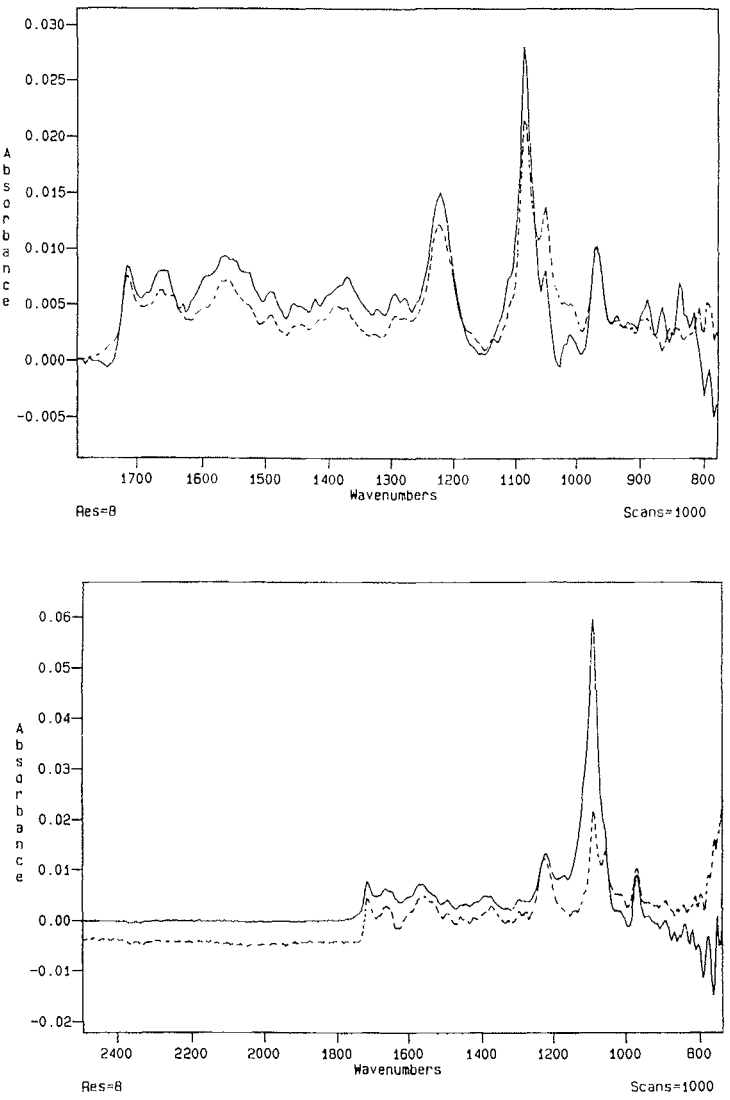

Figure 2. ATR infrared spectra: upper panel = DNA plus MQZ quartz, lower panel = DNA plus CSQZ quartz. Note the different scales of the panels. (- - - - - = DNA alone, ——— = DNA plus quartz after subtraction of the quartz spectrum)

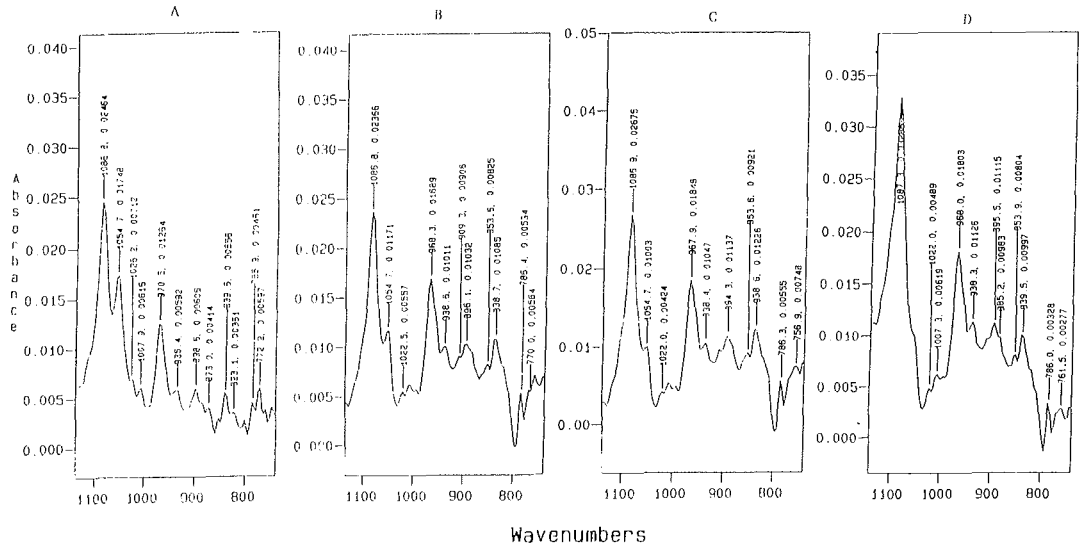

Figure 3. ATR infrared spectra in D_2O: A = DNA (10 mg · ml^{-1}), B = DNA + 0.2 mg · ml^{-1} MQZ quartz, C = DNA + 1 mg · ml^{-1} MQZ, D = DNA + 5 mg · ml^{-1} MQZ. The subtraction factor for normalization is 1.025. (Note the different scales of the Y axes).

marked alterations in the ratios of the peaks at 1086 and 1053 cm^{-1} (figure 2). These peaks correspond, respectively, to symmetric stretching of the PO_2^- in the sugar phosphate backbone of DNA and to either the phosphodiester or the C-O stretch of the sugar ring (28). Since the region below 1000 cm^{-1} could not be accurately measured due to water absorbance, spectra were obtained using D_20 (figure 3). The spectrum for DNA alone (A) was compared with the subtraction spectra obtained from DNA mixed with increasing amounts of MQZ (B,C,D). The effect of increasing amounts of MQZ on the DNA spectrum is evident, with a marked increase in the height of the peak at 1086 cm^{-1} and a progressive loss of the shoulder at 1053 cm^{-1}. Smaller but significant changes were noted in the 1800 to 1500 cm^{-1} region of the DNA spectrum (29). Band alterations observed at 1688 cm^{-1} may indicate a perturbation of the planar base stacking caused by subtle conformational changes in the DNA helix or by bending of the DNA duplex as it wraps around bound silica particles (29).

Electron microscopy and energy dispersive X-ray analysis. A thorough search by electron microscopy for silica particles in the nuclei of FRLE cells, exposed to quartz in culture, revealed that some cells contained small (< 0.5 μm) particles inside the nuclei (figure 4). The intranuclear particles were confirmed as silica by EDX spectrometry (not shown). Quartz particles were also sought in cells undergoing mitosis and were found in mitotic spindles, although not in intrachromatinic locations.

Discussion

Vibrations arising from different parts of the DNA macromolecule correspond to infrared absorptions detectable in different parts of the spectrum (35). The changes in infrared spectra described in this presentation are consistent with an interaction of silica at the phosphate backbone of the DNA molecule. The finding that silica-DNA binding occurs at the phosphate backbone suggests that the proximity of the DNA to the particle surface may be important in the induction of strand breaks by silica through hydroxyl radicals (29). The finding that CSQZ produced more marked effects on the DNA spectrum than MQZ is consistent with the greater surface area of CSQZ (25). The role of the silanol groups on the quartz surface in the DNA binding interaction is supported by evidence obtained by pretreating quartz with poly(2-vinylpyridine-*N*-oxide (PVPNO), a polymer that binds to silanol groups. PVPNO-pretreated quartz did not induce modification of the ATR-FT-IR spectrum of DNA (29).

We propose a model for quartz carcinogenesis, based on the interaction of quartz particles with DNA. Our present and previous results (29) indicate that quartz particles bind DNA in vitro by hydrogen bonding of the DNA backbone to surface silanol groups. DNA damage, induced in vitro by crystalline silica, was found to be mediated by the formation of oxygen radicals on the silica surface (19). The finding of small quartz particles in the nuclei and mitotic spindles of alveolar epithelial cells exposed in culture suggests that a direct contact of quartz and nuclear material is possible in living cells and may occur in vivo. We propose that the binding of crystalline silica to cellular DNA may produce DNA damage in vivo, by anchoring DNA within a few Angstroms of the sites of oxygen-free radical production on the silica surface. This anchoring mechanism enables short-lived toxic radicals, such as the hydroxyl radical, to reach DNA bases and induce DNA damage, which becomes critical for mutagenesis, neoplastic cell transformation, and carcinogenesis. The binding of crystalline

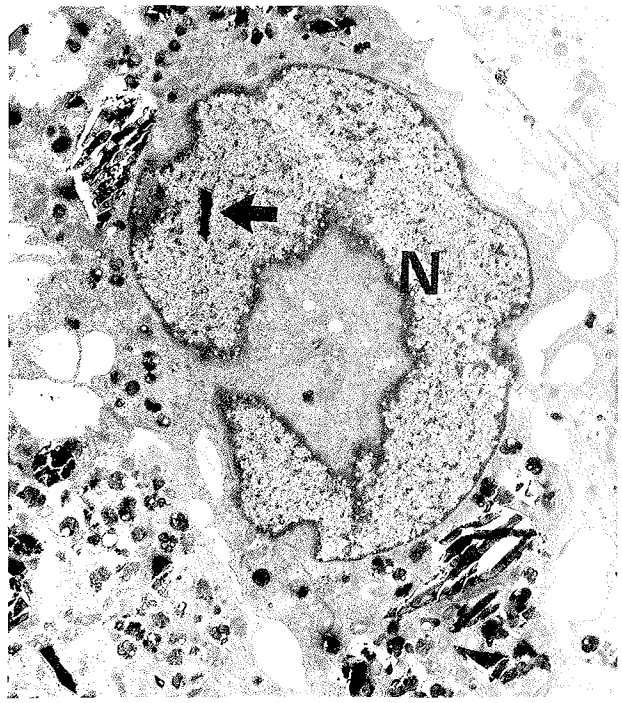

Figure 4. Intranuclear quartz particle (arrow) in a nucleus from FRLE cells exposed to 25 μg · m^{-2} MQZ quartz and sectioned after 26 d. Note two aggregates of silica particles in the cytoplasm of the cell. Energy dispersive X-ray spectroscopic analysis of the intranuclear quartz particle revealed distinct silica peaks (not shown).

silica to DNA may also lead to DNA damage by interfering with the replication, repair, or expression of DNA or by altering the mitotic process.

The mutagenicity of crystalline silica needs to be studied in appropriate systems. Hei et al (36) have demonstrated the mutagenic activity of asbestos fibers (crocidolite and chrysotile) using a target cell system capable of detecting large multilocus deletions. Similar studies with silica have not yet been conducted. Recent studies by Driscoll et al (37) showed that rat lung epithelial cells, harvested from F344 rats 15 months after the instillation of crystalline silica at three different dose levels, had mutation frequencies for the *hprt* gene that were markedly increased in a dose-dependent manner, up to more than 20 times the frequency for untreated controls. The evidence that quartz induced neoplastic transformation and chromosome aberrations in cells in culture (16, 17) further supports the hypothesis that crystalline silica is capable of producing DNA damage in living cells. We do not know how crystalline silica particles come in contact with DNA in vivo, in spite of chromatin packaging. Preferential interaction at sites of DNA unwinding during transcription is a possible hypothesis requiring further investigation.

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Neoplastic lung lesions in rat after chronic exposure to crystalline silica

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Groups of 100 SPF Fischer-344 rats were exposed 6 h a day, 5 d a week for 24 months to crystalline silica (1 mg · m^{-3}, DQ 12 quartz) or titanium dioxide (5 mg · m^{-3}) or air only. The animals were kept without further exposure for an additional 1.5 months. In the group exposed to crystalline silica a significantly increased incidence of 20 primary lung tumors was observed among 19 animals. The distribution of tumor types consisted of 3 adenomas, 11 adenocarcinomas, 4 benign cystic keratinizing squamous-cell tumors, 1 adenosquamous carcinoma, and 1 squamous-cell carcinoma. There were also 13 nodular hyperplasia lesions, which were interpreted to be borderline cases of adenomas. Approximately half of the adenoid tumors and all of the nodular hyperplasia lesions were characterized by moderate central fibrosis. The principal nonneoplastic findings in the silica-exposed group were lipoproteinosis, inflammation, epithelial hyperplasia, and fibrosis. The results can be considered significant due to the increased lung tumor incidence at a relatively low exposure level.

Key terms alpha-quartz, animal, Fischer-344 rats, fibrosis, inhalation, lung tumor.

This investigation was designed as part of a more comprehensive study in which the biological effects of long-term inhalation of a special test toner material, enriched in respirable particles, was evaluated. Two materials, titanium dioxide and crystalline silicon dioxide (silica), were used as positive and negative controls for fibrogenicity. First, results of effects after quartz exposure were published as a brief communication (1). Details of the entire study have been reported separately (2, 3).

Materials and methods

The silicon dioxide (SiO_2), type DQ-12, used in the study originated from Bergbauforschung, Essen, Germany (4). X-ray diffraction analysis indicated 87% crystallinity as α-quartz. The mass medium aerodynamic diameter (MMAD) was about 1.3 µm with a geometric standard deviation of 1.8, and the respirable fraction was 74% according to criteria of the American Conference of Governmental Industrial Hygienists (ACGIH). Titanium dioxide (TiO_2), type "Bayertitan T," was obtained from Bayer AG, Krefeld, Germany. A chemical analysis showed the material was 99.5% rutile TiO_2. The mass median aerodynamic diameter was about 1.1 µm with a geometric standard deviation of 1.6, and the respirable fraction was 78% according to the ACGIH criteria.

A dry aerosol dispersion technique was used (5). Groups of viral antibody-free specific pathogen-free Fischer-344 rats were exposed to crystalline silica (1 mg · m^{-3}) and titanium dioxide (5 mg · m^{-3}) in a two-year study. A third group inhaled filtered air and served as controls. The rats (50 male and 50 female rats per group, 8 weeks of age at the start of the study) were exposed in horizontal flow type whole-body inhalation chambers for 6 h a day, 5 d a week for 24 months under specific pathogen-free (SPF) barrier conditions. The final sacrifices started six weeks after the end of the exposure period. The measured virology, bacteriology, and parasitology parameters were within normal limits or negative during the study (2, 3). The degree of fibrosis was graded according to Wagner (6).

Results

No treatment-related effects on life span or causes of death were observed. The median life span was 750 d after the start of exposure, corresponding to a median life span of 806 d for all the animals.

The wet-lung weight of the silica-exposed animals doubled, while the TiO_2-treated animals had lung weights similar to those of the control group. The mean retained particle mass was 2.72 mg per lung for the TiO_2 group and 0.91 mg per lung for the silica group at the end of the exposure period (pooled data of males and females (3). The fraction of the material retained in the lung-associated lymph nodes of the silica-exposed rats was much higher than that of the TiO_2-exposed group at all time intervals. This finding suggests progressive and massive movement of the crystalline silica from the lung to the lung-associated lymph nodes. Significant cytological changes in the bronchoalveolar lavage fluid and substantial alveolar clearance retardation were observed (2, 3).

The principal nonepithelial findings, which increased with silica exposure, were as follows. Multifocal lipoproteinosis was seen in the silica-exposed group with and adjacent to fibrotic areas, and

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cholesterol clefts were also present. Foamy macrophages containing lipoid substances were observed in 98% of the rats after silica exposure and in only 1% of the rats after TiO_2 treatment. Intraalveolar and interstitial inflammatory cell infiltrates consisting mainly of polymorphonuclear leukocytes were seen in about 70% of the rats after silica exposure. This effect was not observed in the control and TiO_2-exposed groups. A moderate degree of lung fibrosis was observed in 92% of the silica-exposed rats by the termination of the study. The fibrosis was generally multifocal and predominantly located in the subpleural and peribronchiolar region. The lung collagen content was more than doubled. A small but statistically insignificant incidence of fibrosis was seen in the TiO_2-exposed group.

Epithelial alterations. Bronchoalveolar hyperplasia of the alveolar type, characterized by type II pneumocytes, was a rare finding in the control group and occurred in only a few cases in association with alveolar histiocytosis. In the TiO_2-exposed group, this lesion was observed in 9% of the rats. Among the silica-exposed animals, an increase in bronchoalveolar hyperplasia from a slight to a moderate multifocal degree was observed during the exposure period. In these animals, the alveolar walls close to the bronchoalveolar junction (centroacinar region) were lined with a single layer of cuboidal, basophilic cells. At the end of the exposure period, bronchoalveolar hyperplasia was also seen in subpleural areas and in areas of fibrosis and inflammation. In 95% of the silica-exposed rats, bronchoalveolar hyperplasia was also observed.

A focal to multifocal bronchoalveolar hyperplasia of the bronchiolar type, characterized by ciliated cells and Clara cells, was observed in about 80% of the silica-exposed rats. In the females this lesion was medium, whereas in the males the effect was less pronounced.

In the silica-exposed group at the time of death 13 cases of nodular bronchoalveolar hyperplasia were apparent which were interpreted as borderline cases to adenomas. The occurrence of nodular hyperplasia was about equally distributed between both genders. These well-circumscribed lesions had a size of up to 3 mm in diameter and were composed of a single layer of cuboidal to columnar basophilic cells. The alveolar lumina were filled with polymorphonuclear neutrophilic leukocytes and cell debris, and the interstitium was also severely infiltrated by polymorphonuclear neutrophilic leukocytes. Moderate fibrosis was often observed in the center of the nodular hyperplasia. This type of preneoplastic effect was not detected after the TiO_2 exposure.

Keratinizing squamous-cell metaplasias were found in the silica-exposed animals, in 5 of 50 males and 13 of 50 females. Focal or multifocal squamous cell metaplasias were also observed.

Lung tumors. An increased incidence of lung tumors was observed in the silica-exposed group. Altogether 20 primary lung tumors were found in 19 animals. Two tumors, an adenoma and an adenocarcinoma, were observed in separate areas of the lung of one male silica-exposed rat. The distribution of tumor types consisted of 3 adenomas (1 male), 11 adenocarcinomas (3 males, 8 females), 4 benign cystic keratinizing squamous-cell tumors (2 males, 2 females), 1 adenosquamous carcinoma (male), and 1 squamous-cell carcinoma (male). Thus a total of 12 lung tumors were observed among the female rats, whereas among the males 8 lung tumors were found. Details of the results are shown in table 1. With a total number of 15 out of 20 lung tumors, the prevalence of adenoid tumors was surprisingly high. With one exception, all adenoid tumors were located in the large lung lobes (lobus sinister and lobus dexter caudalis). The adenoid tumors can be separated into two different groups: one type with severe, mostly central fibrosis and the other without significant fibrosis. In the group without severe fibrosis (7 cases) a solid appearance of the tumor was found in two cases. In two other cases there was an irregular proliferation on the alveolar septae, and in three cases a central tubular structure was observed. Five of six adenocarcinomas were not clearly demarcated and showed local infiltrative growth. Three of these tumors invaded bronchi, blood vessels, or lymphatic vessels. In two adenocarcinomas, which were classified as being of a nonfibrotic tumor type and which were investigated by electron microscopy, the tumor cells showed signs of type II pneumocytes.

The adenoid tumors associated with moderate fibrosis (8 cases) showed a centrally and usually radially structured fibrosis. The epithelial component either built up small lumina, as in nodular hyperplasia, or showed tubular structures. Usually these tumors were infiltrated by polymorphonuclear neutrophil leukocytes. Two of these tumors showed an invasive growth into blood vessels and bronchi.

Discussion

The incidence of neoplastic changes found in controls and in the TiO_2-treated rats was comparable and not in excess of the historical data (7).

After the exposure of rats to a broad spectrum of tumor types was observed. These tumors were located predominantly in the

Table 1. Principal lung histopathological findings. (A = adenoma, AC = adenocarcinoma, ASC = adenosquamous carcinoma, KSCT = keratinizing cystic squamous-cell tumor, SCC = squamous-cell carcinoma)

	Number of rats investigated (equal number of males and females)	Tumor			Nonneoplastic lesions[a]
		Number of rats with primary lung tumors	Number and type of tumor		Fibrotic foci (21—26 months)
			Benign	Malignant	
Air only	100	3	2 (A)	1 (AC)	1.2 (mild)
Titanium dioxide	100	2	1 (A)	1 (AC)	4.5 (minimal) 1.1 (mild)
Silicon dioxide	100	19[b]	3 (A) 4 (KSCT)	11 (AC) 1 (ASC) 1 (SCC)	7.7 (mild) 92.3 (moderate)

[a] Grading of the degree of fibrosis was done according to the Wagner scale: minimal, mild, moderate, severe (marked fibrosis), and severe (complete obstruction).
[b] Two tumors, an adenoma and an adenocarcinoma, were observed in separate areas of the lung of one rat.

periphery of the lungs. The first tumor after silica treatment was observed after 21 months of exposure. The portion of adenoid neoplasia was relatively high compared with the total number of tumors (15 out of 20 neoplasias). The incidence of this tumor type among the females was double compared with that among the males. Similar observations have been reported by Holland et al (8).

The induction of tumors by crystalline silica has been observed in experimental animals only among rats. Intratracheally injected high doses of silica and inhalative exposure to quartz were negative among hamsters (9). A chronic inhalation study of DQ 12 quartz in hamsters and inhalation experiments with mice were also negative (10—12). Chronic persistent inflammation after quartz exposure was supposed to be an important factor in the carcinogenesis.

The results of our study can be considered significant in that the increased lung tumor incidence was observed at a chronic inhalation exposure concentration of only 1.0 mg · m^{-3}. Tumor induction at similar low doses was recently reported by Spiethoff et al (13). These authors also used DQ 12 quartz. In most previously reported studies the exposure concentration was higher by at least a factor of 10 (9, 14).

These results confirm the classification of the International Agency for Research on Cancer, which stated that there is sufficient evidence for the carcinogenicity of crystalline silica among experimental animals (15).

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Transforming growth factor β1, *ras* and *p53* in silica-induced fibrogenesis and carcinogenesis

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The pathogenesis of mesenchymal and epithelial lung reactions was studied after a single intratracheal instillation of quartz into rats. Relationships between transforming growth factor β1 (TGF-β1) and the *ras* and *p53* genes were investigated in silicosis and associated lung cancer. Immunohistochemical reactivity to mature TGF-β1 was localized intracellularly in fibroblasts and macrophages at the periphery of silicotic granulomas and in stroma adjacent to hyperplastic alveolar type II cells and extracellularly in connective tissue matrix adjacent to hyperplastic alveolar type II cells. TGF-β1 precursor was localized intracellularly in hyperplastic alveolar type II cells adjacent to granulomas and in the cells of adenomas, but not in carcinomas. Hematite-treated controls showed no reactivity to TGF-β1. Immunohistochemical localization of pan-reactive p21 ras protein in quartz-treated rat lungs was increased in hyperplastic alveolar type II cells adjacent to granulomas, but not in adenomas and carcinomas. Foci of nuclear immunoreactivity to *p53* protein were observed in 25% of the carcinomas.

Key terms alveolar type II cells, immunohistochemistry, *p53*, p21 ras, rat, TGF-β1.

Quartz-induced lung cancer in rats was reported in several experiments using exposure by either inhalation or intratracheal instillation (1, 2). Evidence for the carcinogenic activity of crystalline silica also derives from the induction of localized malignant histiocytic lymphomas by intrapleural administration (1), quartz-induced neoplastic transformation of cells in culture (3, 4), and increased lung cancer risk in many, but not all, epidemiologic studies on human subjects with silicosis (1).

A series of experiments in our laboratory (2, 5) investigated the histopathogenesis of lung reactions to crystalline silica in F344 rats of both sexes, as well as in mice and hamsters. Marked species differences were detected. Rats developed silicotic granulomas with fibrosis accompanied by focal hyperplasia of type II cells, adenomatoid proliferation, and eventually high incidences of carcinomas. Mice developed silicotic granulomas with fibrosis, but no epithelial hyperplasia and no tumor induction. Hamsters developed extensive macrophagic silica-storage lesions which did not progress to fibrosis and showed no epithelial hyperplasia. Alveolar type II cell hyperplasia and lung tumors were not found in long-term studies in mice and hamsters exposed to quartz (1, 2). These different host responses offer experimental models to investigate the underlying mechanisms by which silica particles induce the complex mesenchymal and epithelial reactions leading to silicosis or to lung cancer in susceptible hosts.

The rat model resembles the human type of fibrosis-associated lung cancer described as scar cancer, and it lends itself to investigations of the mechanisms of interaction between pulmonary silicosis and hyperplasia of adjacent type II cells leading to the development of carcinoma.

Several cytokines have been shown to play a role in the pathogenesis of experimental silicosis (2). They include interleukin-1, interleukin-6, tumor necrosis factor-α and transforming growth factor β1 (TGF-β1)(2). Their effects on adjacent epithelial cells are still poorly understood. We suggest that cytokines, released by macrophages and other cells during fibrogenic reaction to crystalline silica, stimulate the proliferation of adjacent alveolar epithelial cells, some of which may in turn have undergone direct DNA (deoxyribonucleic acid) damage or chromosome aberrations induced by silica particles. Cytokines are believed to be required for tracheal and bronchial epithelial cell proliferation, differentiation, and growth (6, 7). Alveolar type II cells have been shown in rats to respond to quartz-induced lung injury with early hypertrophy and hyperplasia (8) and with persistent hyperplastic and proliferative changes, eventually giving rise to alveolar cell tumors adjacent to the granulomatous lesions (2, 5).

TGF-β1 is a multifunctional regulatory peptide that plays a major role in the physiological and pathological processes affecting cell growth and differentiation, as well as in metabolic activities, and it is present in a variety of normal human and animal tissues, both benign and malignant (7). TGF-β1 has been shown to play a key role in inflammation and tissue repair, and it is capable of stimulating the formation of collagen and connective tissue (7). Studies in vitro have shown its marked stimulatory effects on the

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formation of collagen in rodent and human fibroblasts. Activated lymphocytes can also stimulate proline incorporation into collagen in rodent fibroblasts (9), which can be partially abolished by specific antibodies to TGF-β1 (7).

In view of the multifunctional roles of TGF-β isoforms, we studied three isotypes of TGF-β1 in three rodent models. We investigated immunohistochemically its location, distribution, and possible roles in the pathogenesis of experimental silicosis and the pathogenesis of associated pulmonary carcinogenesis (5). We also studied the cellular immunolocalization of ras and p53 proteins, which are the proteins of the two most common genes known to be altered in human and rodent lung carcinomas. The relationship between changes in these two genes and TGF-β1 may form the basis for a possible mechanism in silica-associated lung carcinogenesis.

Materials and methods

Lung tissues, fixed in 10% buffered formalin and embedded in paraffin, were obtained from 6 male and 10 female F344/NCr rats, which had received a single intratracheal instillation of 12 mg of Min-U-Sil 5 α-quartz at eight weeks of age. These tissues were chosen to include lesions representative of those observed in a total of 37 male and 36 female rats sacrificed at intervals up to 17 months and 14 male and 6 female rats examined at unscheduled death from 17 up to 26 months. For comparison, lung tissues were also observed from eight mice and eight hamsters (equally divided by sex) that were treated with quartz. Control tissues of all three species were from two male and two female animals treated with hematite and as many untreated animals. Experimental details have been described previously, as were the methods used for the preparation of antibodies to TGF-β1, employed for immunohistochemical studies (5). Briefly, the antibodies were raised in rabbits to the NH_2-terminal 1-30 amino acids of mature TGF-β1 (anti-CC and anti-LC) and to amino acids 266—278 of the TGF-β1 precursor/latency-associated peptide (LAP) (anti-Pre). Anti-CC stained extracellular matrix-associated TGF-β1, while anti-LC and anti-Pre stained intracellular TGF-β1.

Localization of antibodies to ras and p53 proteins on paraffin-embedded tissues was studied with immunohistochemical methods. Mouse monoclonal antibody to pan-reactive p21 ras (Cetus Boston, Massachusetts, and Oncogene Science, New York, New York, United States), monoclonal antibodies to p53 [pAb 421 (ABl) and pAb 240 (Ab3)], and polyclonal antisera to p53 (CM-1) were applied as primary antibodies, using the immunoperoxidase technique. For controls, nonreactive rabbit serum immunoglobulin was used instead of the primary antibody.

Results

Pathology. The histopathological findings from the quartz-treated rats showed the development of silicotic granulomas with progressive fibrosis accompanied by marked hyperplasia of alveolar type II cells, sometimes with adenomatoid pattern, adenomas, and a progressive development of lung carcinomas (2). After the instillation of the same quartz sample, mice developed moderate fibrosis, but no alveolar hyperplasia, and hamsters developed only macrophagic storage lesions without significant fibrosis or epithelial reactions (2). A new schematic of the histopathological events observed at early stages (1—45 d) and late stages (≥ 60 d) among the three species of rodents exposed to quartz is given in table 1.

Immunoreactivity to TGF-β1. The results of the immunolocalization of TGF-β1 in the lungs of quartz-treated rats (5), mice, and hamsters are summarized in table 2, together with the results observed among hematite-treated and untreated controls of all three species. The results, observed for all the rats examined and previously illustrated (5), showed that intracellular mature TGF-β1 was localized in fibroblasts and macrophages at the periphery of silicotic granulomas and in the stroma adjacent to hyperplastic alveolar type II cells. Extracellular mature TGF-β1 was localized in the connective tissue matrix adjacent to hyperplastic alveolar type II cells. TGF-β1 precursor/LAP was localized intracellularly in hyperplastic type II cells adjacent to granulomas and in the cells of adenomas, but not in the carcinomas. Hematite-treated controls showed no reactivity to TGF-β1. Only a few focal groups of macrophages in the silicotic granulomas were immunoreactive to anti-Pre, but their staining pattern was not punctate as observed in type II cells.

Immunoreactivity to p21 ras and p53 proteins. In the silicotic rat lungs, immunoreactivity to pan p21 ras protein was constantly detected in the hyperplastic alveolar type II cells, including those forming adenomatoid patterns (figures 1 and 2). There was no reactivity in the adenomas and carcinomas (figure 3). Nuclear immunoreactivity to p53 was seen in two out of eight (25%) lung carcinomas (figure 4). These findings are summarized in table 3.

Discussion

Chronic lung lesions induced by crystalline silica in rats represent a model for studying the interactions of fibrogenesis, epithelial hyperplasia, and carcinogenesis. Our observations suggest that TGF-β1 is an important factor in the complex cell-cell interactions in the pathogenesis of mesenchymal-epithelial responses to silica (5). Elevated levels of TGF-β1 have been reported in pulmonary fibrosis in rats (10), in murine hepatic fibrosis due to carbon

Table 1. Histopathological findings in quartz-treated lungs of three rodent species. (+ = present, ++ = moderately increased, +++ = markedly increased in numbers, – = not present, early = 1—45 days, late = ≥ 60 days)

Lesions	Rats		Mice		Hamsters		Controls[a]	
	Early	Late	Early	Late	Early	Late	Early	Late
Alveolar macrophages	+++	+++	++	++	++	+++	–[b]	–[b]
Interstitial macrophages	+	+++	+	++	++	+++	–[b]	–[b]
Alveolar type II cells	+	+	+	+	+	+	+	+
Hyperplastic alveolar type II cells	±	+++	+	++	–	–	–	–
Fibrosis	+	++++	+	++	++	–	–	–
Carcinoma	–	++	–	–	–	–	–	–

[a] Controls (untreated and hematite-treated) for all three species.
[b] Increased in hematite controls.

Table 2. Immunohistochemical localization of transforming growth factor β1 (TGF-β1) in quartz-treated rodents. (± = weakly reactive, + = reactive, − = nonreactive, NA = not available, early = 1—45 days, late = >45 days)

	Rats		Mice		Hamsters		Controls[a]
	Early	Late	Early	Late	Early	Late	
TGF-β1 (Anti-LC)							
Intracellular							
Alveolar macrophages	+	+	−	+	−	+	−
Interstitial macrophages	+	+	−	+	−	−	−
Fibroblasts	±	+	−	±	−	−	
Alveolar type II cells	−	−	−	−	−	−	−
Hyperplastic alveolar type II cells	−	−	NA	NA	NA	NA	NA
Carcinoma	NA	−	NA	NA	NA	NA	−
TGF-β1 (Anti-CC)							
Extracellular							
Alveolar macrophages	−	−	−	−	−	−	−
Interstitial macrophages	−	−	−	−	−	−	−
Alveolar type II cells	−	−	−	−	−	−	−
Hyperplastic alveolar type II cells	−	−	NA	NA	NA	NA	NA
Carcinoma	NA	−	NA	NA	NA	NA	NA
Matrix	+	+	±	+	−	−	−
TGF-β1 (Anti-Pre)							
Precursor/LAP							
Alveolar macrophages	−	−	−	−	−	−	−
Interstitial macrophages	+	+	−	±	−	−	−
Fibroblasts	−	−	−	−	−	−	−
Alveolar type II cells	+	+	−	±	−	−	−
Hyperplastic alveolar type II cells	+	+++	NA	NA	NA	NA	NA
Carcinoma	NA	−	NA	NA	NA	NA	NA
Matrix	−	−	−	−	−	−	−

[a] Controls (untreated and hematite-treated) for all three species.

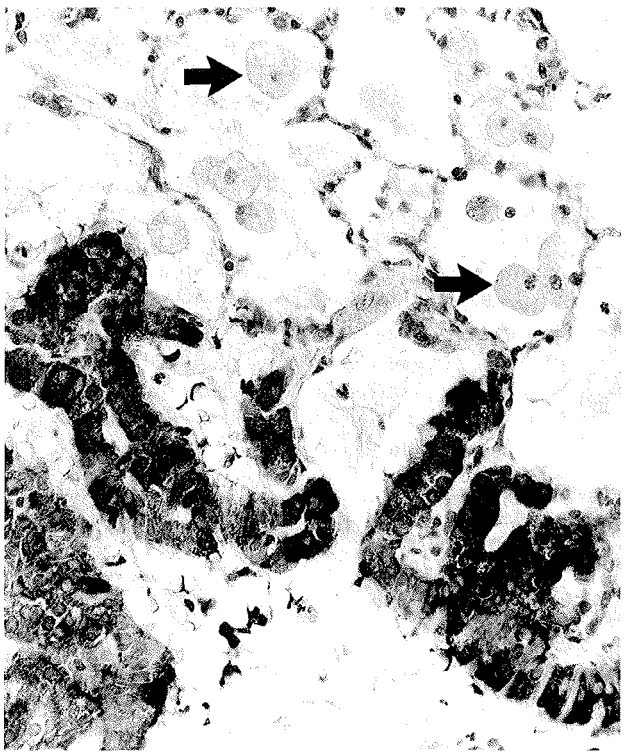

Figure 1. Pan-reactive p21 ras protein immunoreactivity localized in hyperplastic alveolar type II cells in quartz-treated rat lung (dark staining cells). The upper part of the figure shows normal alveolar walls; arrows point to alveolar macrophages.

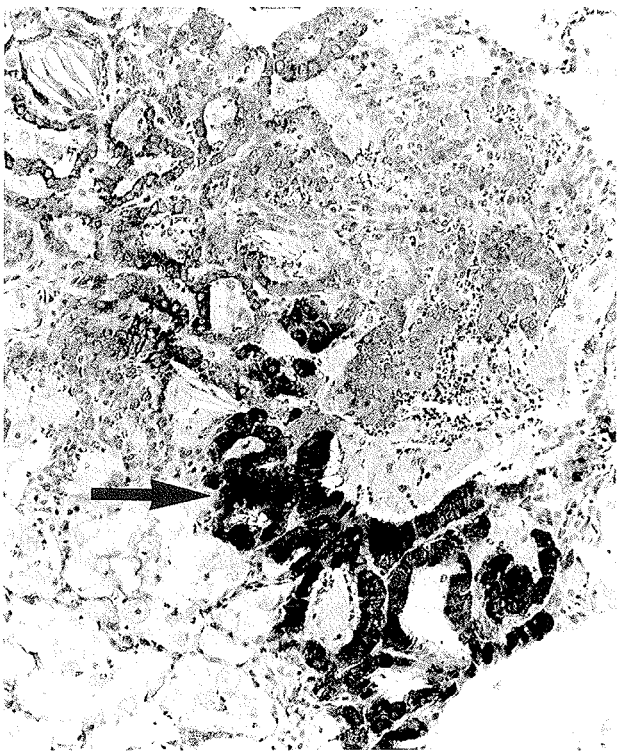

Figure 2. Pan-reactive p21 ras protein immunoreactivity localized in hyperplastic alveolar type II cells in quartz-treated rat lung (dark staining cells). The figure shows nonreactive epithelial cell proliferation in the upper right corner and hyperplastic alveolar type II cells positive for p21 ras protein (arrow).

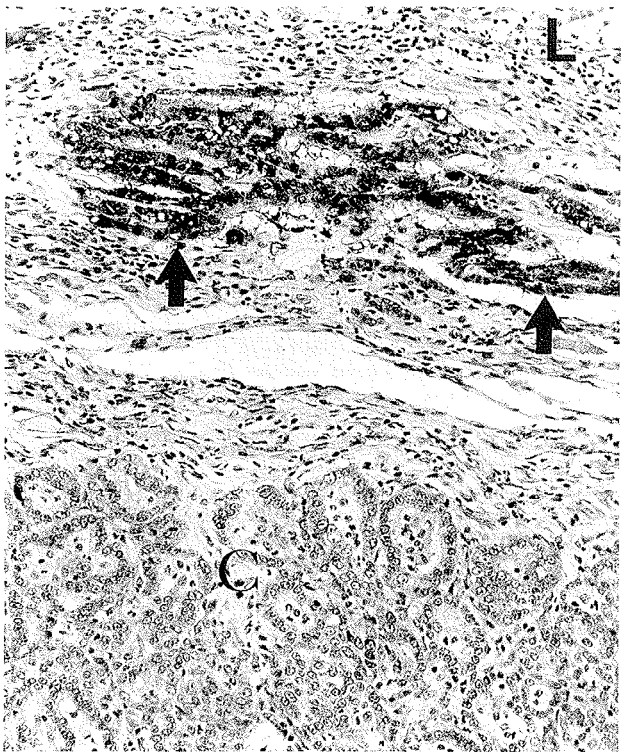

Figure 3. Well-differentiated alveolar adenocarcinoma (C) in the lung of a quartz-treated rat, showing no reactivity to p21 ras protein. Adjacent hyperplastic alveolar type II cells forming adenomatoid patterns (arrows) show reactivity to p21 ras protein (dark staining cells). Uninvolved lung tissue (L) is shown at the top of the figure.

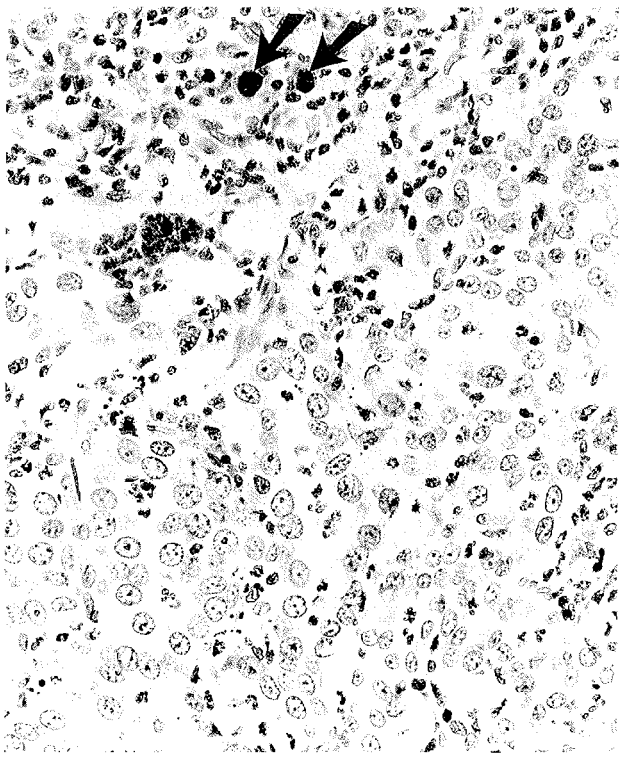

Figure 4. Nuclear immunoreactivity for p53 (arrows) in cells of an undifferentiated carcinoma in a quartz-treated rat lung.

tetrachloride or schistosomiasis, and in humans with the ocular fibrotic disease called proliferative vitreoretinopathy (11). Increased levels of TGF-β1 mRNA (messenger ribonucleic acid) have also been reported in patients with hepatic cirrhosis with regenerative nodules and increased fibrogenic activity (12).

The following mechanisms are suggested for the role of TGF-β in the quartz-induced lesions of rat lung: (i) progressive repair and healing of the silicotic granuloma require an adequate supply of TGF-β1, leading to an increase in the production of TGF-βl precursor in the proliferating alveolar type II cells; (ii) the subsequent activation of the TGF-β1 precursor to mature TGF-β1 stimulates collagen production; (iii) the deposition of collagen and extracellular matrix continues to provide a substrate for repeated cycles of epithelial proliferation (13); (iv) the development of malignancy, which results from malignant transformation of type II cells, in a high proportion of quartz-treated rats may be due to clonal outgrowth during active epithelial proliferation or the escape of cells from the negative regulatory effects of TGF-β1 (7).

The intracellular localization of TGF-β1 precursor/LAP is indicative of its production, first detected in macrophages during the early stages of reaction to silica and then, more conspicuously, in the hyperplastic alveolar type II cells (5). Although the precursor was localized in some hyperplastic epithelial cells at the periphery of carcinomas, it was not detected in malignant cells of the carcinomas. This observation suggests that reactivity to this antibody is lost with progressive loss of cell differentiation. The localization of TGF-β1 precursor can be used to identify the transition between hyperplastic type II cells, which are immunoreactive, and those which have undergone malignant change and have lost their immunoreactivity.

Table 3. Immunoreactivities to transforming growth factor β1 (TGF-β1), ras and p53 in the rat silicosis model. (LAP = latency-associated peptide)

Antibody	Type II cell	Hyperplastic type II cell	Adenoma	Carcinoma
TGF-β1 precursor/LAP	+	+	+	–
p21 ras	+	+	–	–
p53	–	–	–	+ (25%)[a]

[a] Positivity in 25% of the carcinoma cases associated with silicosis.

TGF-β1 is a unique peptide with regard to the regulation of normal and pathological physiology. It is an endogenous cell component that contributes to the healing process (7) and is capable of inducing an inflammatory reaction with the production of granulation tissue. TGF-β1 is likely to be a significant stimulus for the epithelial hyperplasia and proliferation observed in experimental silicosis, as previously observed in other epithelia. The control of cell growth and differentiation by TGF-β1 appears to be coordinated within epithelial cells of various types, in which TGF-β inhibits proliferation and induces terminal differentiation (6, 7). It is noteworthy that, in silicotic rat lungs, TGF-β1 precursor is demonstrable in hyperplastic alveolar type II cells, and in some interstitial macrophages, but not in alveolar macrophages, even though these cell types appear to be capable of internalizing silica particles (Williams et al, unpublished data).

The localization and distribution of TGF-β1 suggests that it plays a role in the pathogenesis of silicotic lesions, and possibly in the development of associated pulmonary carcinomas. It is conceivable that, in the rat silicotic lesions, the synthesized TGF-β1 inhibits further cell proliferation and promotes epithelial differentiation, as suggested for idiopathic pulmonary fibrosis (14). The development of carcinoma from the hyperplastic alveolar type II cells in the rat model may be due to the reduction or failure of TGF-β1 synthesis, leading to uncontrolled proliferation and loss of differentiation.

The immunohistochemical localization of p21 ras protein in hyperplastic type II cells and in their adenomatoid proliferations, but not in the adenomas and carcinomas, suggests its association with phenotypic change. Lack of immunoreactivity to p21 ras antibodies in malignant phenotypes suggests that the *ras* gene may have been activated, but this possibility requires confirmation. The absence of detectable p21 ras protein in the adenomas, which are positive for TGF-β1 precursor/LAP, suggests that the negative regulatory control by TGF-β1 is still maintained after the ras protein is down-regulated. It has been shown in human bronchial epithelial cells, murine skin keratinocytes, and thyroid follicular cells that the down-regulation of TGF-β1 gives rise to an increase of mutant p53, through *myc* transcription (15—17). This mechanism may be pertinent to our observations in the silica rat model, according to which 25% of the observed carcinomas showed nuclear accumulation of p53 protein.

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Methods used by the United States National Institute for Occupational Safety and Health to monitor crystalline silica

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Lorberau CD, Abell MT. Methods used by the United States National Institute for Occupational Safety and Health to monitor crystalline silica. *Scand J Work Environ Health* 1995;21 suppl 2:35—8.

The National Institute for Occupational Safety and Health (NIOSH) in the United States has four methods for monitoring the concentration of crystalline silica dust. They all employ a cyclone for size-selective sampling in the field, but differ primarily in that the laboratory measurement is based on either infrared spectroscopy, X-ray diffraction, or colorimetry. The limits of detection for these methods are similar, but their accuracy is poor, particularly at low filter loadings near the current recommended exposure limit (50 $\mu g \cdot m^{-3}$). Advances in analytical instrumentation have improved measurement precision. Correction techniques to account for X-ray absorption in samples loaded with nonsilica dust have eliminated one source of bias. Direct analysis on collection filters is a convenient technique that should decrease sample manipulation errors, but it has not been shown to improve precision or accuracy significantly.

Key terms dust analysis, exposure limit, infrared spectroscopy, size selective sampling, X-ray diffraction.

Over the last 25 years researchers at the National Institute for Occupational Safety and Health (NIOSH) in the United States have developed and evaluated methods for measuring worker exposure to airborne crystalline silica. The methods are typically described by the instrumental techniques, because they all rely on the same sample collection procedures. Breathing-zone samples are collected using a 10-mm Dorr-Oliver nylon cyclone to remove nonrespirable particles and a polyvinyl chloride (PVC) filter to retain the respirable dust. In the laboratory, all the methods use ashing or chemical dissolution to remove the PVC filter from the collected dust, but final preparation differs for each technique.

The third edition of the *NIOSH Manual of Analytical Methods* contains four methods determining crystalline silica polymorphs (quartz, cristobalite, or tridymite) (1). The approaches are based on three instrumental techniques: colorimetry (COL) (method 7601), X-ray powder diffraction (XRD) (method 7500) and infrared spectroscopy (IR) (methods 7602 and 7603). Each procedure is described below.

Historically, the earliest procedure was the colorimetric method, in which silicates and amorphous silica are dissolved in phosphoric acid, leaving only crystalline silica behind. After washing, the remaining silica is dissolved in hydrofluoric acid. The dissolved silica is reacted with molybdic acid to give a characteristic silicomolybdate blue color, which is measured by visible absorption spectrometry (colorimetry). The advantage of the colorimetric method is the low start-up cost. The disadvantages include the nonspecificity of the phosphoric acid dissolution step and the inability of the method to distinguish the different silica polymorphs.

The X-ray diffraction method involves ashing or dissolution of the filter, suspension of the silica dust in isopropanol, deposition of the dust on a silver filter, and analysis of the contents of this filter by XRD. Ashing is done either in a muffle furnace or a low temperature asher, while dissolution of the PVC filter is done with tetrohydrofuran (THF). Samples can be analyzed for different polymorphs by scanning different diffraction lines characteristic of each polymorph. Although the XRD methods are costly, they are relatively straightforward and less prone to mineral interferences than other methods.

The IR methods also require ashing of the filter and either redeposition of the dust onto an IR-transparent filter (DM 450, Gelman, Ann Arbor, Michigan, United States) from isopropanol suspension (method 7603) or mixing of the dust with potassium bromide and pressing of the mixture into a pellet (method 7602). Samples can be analyzed for different polymorphs by scanning absorption bands characteristic of each. The absorbance bands of the polymorphs significantly overlap, making determinations of mixtures problematic, especially if there are absorbance bands from the matrix present. The IR startup cost is intermediate (dispersive instruments) to high (FT-IR, FT = fourier transform). Sensitivity is slightly better than for the other two methods, but interferences (particularly from silicates) can be a problem.

The goal of NIOSH researchers over the years has been to improve the accuracy of airborne silica determinations. Because

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there were no totally new approaches that might accomplish this goal, efforts consisted primarily of refining existing methods and evaluating their performance. The limit of detection is approximately 5 $\mu g \cdot sample^{-1}$ for each of these methods, but their accuracy is poor, particularly at low filter loadings ($\leq 30 \mu g \cdot sample^{-1}$) typically collected when workplace concentrations of airborne silica approach the current NIOSH recommended exposure limit (REL) of 50 $\mu g \cdot m^{-3}$. The problem is exacerbated when silica is present as more than one polymorph.

Sampler improvements

The performance of the Dorr-Oliver 10-mm nylon cyclone has been studied by numerous investigators (2—6). Early efforts to alleviate sampling errors focused on eliminating sampling pump fluctuations (2). The development of flow-controlled sampling pumps mitigated this source of variability. Experimental work has shown that the 10-mm nylon cyclone closely meets the international respirable cut-size of 4.0 when operated at $1.7\ l \cdot min^{-1}$ (5).

The 10-mm cyclone was examined relative to potential leaks in the sampling train (6), and only major leaks were found to affect its performance. The O-ring at the cyclone's vortex finder was determined to be the most problematic, and a simple field test was proposed as a guide to the integrity of the O-rings: (i) the sampler is complete (no O-rings missing), (ii) the lower adapter O-ring can hold tightly onto a cyclone including the metal clip, (iii) the upper adapter O-ring can similarly hold a cassette, and (iv) the frame O-ring can similarly hold a cassette. Assembled cyclone samplers that met these simple tests were not found to have leaks that resulted in measurable losses in the sampled masses.

Instrumental improvements

Instrumental advances have resulted in improved methods for determining silica. FT-IR instruments have increased optical throughput over dispersive instruments, which only pass a fraction of the total power through to the sample. The lack of slits and absorbing optics further improves the optical throughput of the FT-IR instruments. In addition, the wavelength accuracy of the FT-IR instruments allows for a better subtraction of background (matrix) components and improved accuracy in the resultant spectra. This allows for a more precise IR determination of the silica polymorphs present in the sample.

Sample spinners on X-ray powder diffractometers allow for more crystallites to be properly oriented relative to the detector. The result is an average of the crystallites per unit of irradiated area and a reduction in the error due to the nonuniform deposition of particles on the filter surface, and, therefore, there is also better precision in the diffracted intensity of samples.

Examination of analytical procedure changes

A technique to correct for X-ray microabsorption by the sample matrix in XRD analysis was proposed by Leroux et al (7). The procedure, which was incorporated into method 7500, involves monitoring the attenuation of the diffraction line of the silver filter to arrive at a determination of the matrix X-ray absorption coefficient. The procedure mostly impacts heavily loaded filters where absorption of the diffracted intensity of silica by the matrix is highest.

The elimination of sample preparation steps by analysis directly on the collection filter has been proposed for XRD (8, 9) and IR (10). These "direct-on-filter" techniques would be convenient and would theoretically decrease errors due to sample manipulation. Therefore, on-filter methods were investigated for both XRD and IR analytical techniques (11, 12).

For XRD, direct-on-filter methods were examined with both silver and mixed cellulose ester (MCE) collection filters (11). While the direct-on-MCE filter technique was found to be within 25% of that of method 7500, the direct-on-silver filter technique was only within 30% of the same method. Standard samples prepared from liquid suspension were not found to be equivalent to those obtained by aerosol deposition, which would necessitate the preparation of aerosol deposited standards for direct-on-filter methods (11). The preparation of standards at very low sample loadings (such as ambient silica concentrations) would be extremely difficult due to weighing errors and would hinder any effort to implement a direct-on-filter XRD method.

Limitations of the use of direct-on-filter methods in IR analysis include variations in filters, both within-lot (filter-to-filter) and within-filter (12). Of the filters examined, DM-450 filters were found to be the most consistent with up to 2.4% relative standard deviation (RSD) at 798 cm^{-1}, while DM-800 filters were similar at about 2.8% RSD. A weight-based subtraction of co-added spectra of the filter was found to give a flat base line at the 798—800 cm^{-1} analytical band. However, there were problems at the lower analytical wavelength (695 cm^{-1}) because of carbon monoxide absorbance. The problems were mitigated with a long (20-min) purge of the instrument with nitrogen, but they could not be totally compensated for because of the limited IR source power and detector response at the lower wave lengths. The major problem with direct-on-filter IR methods are absorbance bands of the matrix interfering with the bands employed in the analysis. The presence of 1 mg of coal dust, a broad band absorber, resulted in a negative bias of 7—10% in the determination of quartz at 50 and 200 µg (12). The presence of kaolinite at 100 µg resulted in errors of up to 20% in the quartz determinations, despite the absorbance of other interferences (coal dust) and knowledge of the mass of kaolinite present. The direct-on-filter IR approach was too vulnerable to interferences which might otherwise be removed by pretreatment (ashing) to be a useful approach for assessing exposure to silica.

Improvements in laboratory proficiency

In general, the precision and accuracy of airborne silica determinations have improved over the last 20 years, as shown by a statistical study (13) of the results reported by laboratories analyzing silica samples in rounds 30—101 of the proficiency analytical testing (PAT) program administered by the American Industrial Hygiene Association. Five laboratories participated in the first round of the PAT program in 1972, and participation grew to 130 laboratories before falling to 105 in round 101 in 1990 (figure 1). The objectives of the study were to determine bias between methods, the variability associated with the methods, and any changes in bias or variability due to numerous factors. Because there were so few laboratories participating before round 30 (1974), only data for later rounds were used for this study.

Several models were used to examine bias due to the analytical method and other factors; the conclusions drawn from the models were similar. The colorimetric method has given the lowest results, regardless of sample matrix or particle size, particularly at higher loadings (>100 µg). For sample loadings closer to

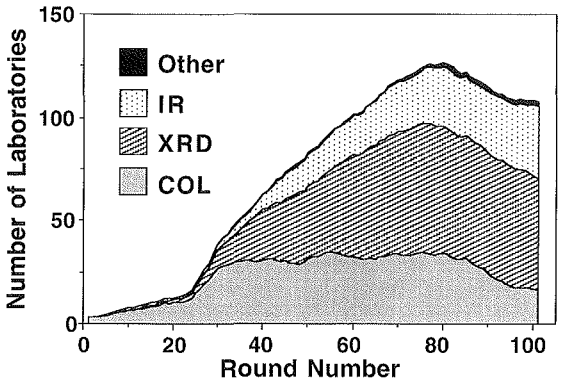

Figure 1. Cumulative number of laboratories using a particular method of silica analysis in the proficiency analytical testing (PAT) program. (IR = infrared spectroscopy, XRD = X-ray defraction, COL = colorimetry)

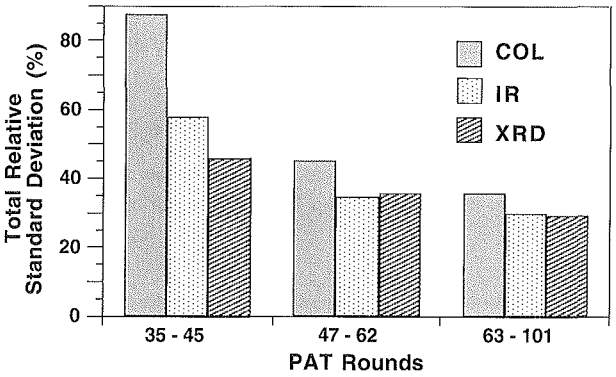

Figure 2. Total variability of silica methods in different periods in the proficiency analytical testing (PAT) program. (COL = colorimetry, IR = infrared spectroscopy, XRD = X-ray defraction)

what would be collected at the REL, however, the bias among methods has been negligible for the last 10 years (rounds 63—101). X-ray diffractometry results were biased higher than IR results during one period, but not in the following period. Between the two periods, the procedures and materials used to prepare PAT samples changed in numerous ways, but the switch to quartz dust with a smaller particle size is a likely explanation for the bias difference (14—16). Generally, silica sampling analyses have improved, and this improvement has taken place for all three of the methods. The colorimetric method has shown the poorest precision of the three methods (figure 2), but, unlike the differences in bias, the differences in precision have diminished considerably over time. The differences in method variability were consistent across the PAT sample matrices (coal dust, talc, calcite, and combinations thereof).

The contribution of within-laboratory variability to the total was of interest; therefore "duplicates" were chosen from rounds that included two samples for which the median results were within 20 µg, as long as each result was greater than 40 µg. The within laboratory variability computed from these data are shown in figure 3, which is similar in appearance to the total variability in figure 2. The within laboratory variability for the colorimetric method was statistically significantly higher than that of the IR method in each of the periods shown in figure 3, and higher than that of the XRD method in the earlier periods, but not in the most recent period.

Precision estimates from other studies were compared with those from this study to learn more about sources of variability. As shown in a collaborative study of silica methods (17), interlaboratory variation remains high (8—14%) even when laboratories employ the same procedures.

Recent developments

All silica methods have relied on the 10-mm nylon cyclone and assembled filter cassette for sample collection. The cyclone, being nonconductive, has been subject to effects of electrostatic charge, as has been described earlier (18, 19). Another design, which is made of (conducting) metal, has been recently evaluated: the Higgens-Dewell (HD) cyclone (5). Experimental work has shown that the HD cyclone closely meets the international respirable cut-size of 4.0 when operated at 2.2 l · min^{-1} (5). This higher sampling rate results in a nominally higher sample load than the 10-mm

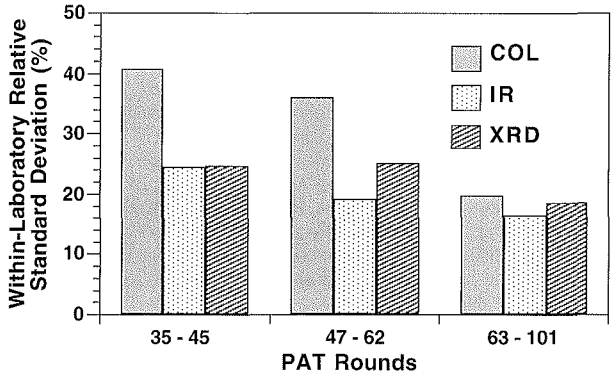

Figure 3. Within laboratory variability of silica methods in different periods in the proficiency analytical testing (PAT) program. (COL = colorimetry, IR = infrared spectroscopy, XRD = X-ray defraction)

nylon cyclone; 53 µg of quartz would be collected when sampled for 8 h at the REL of 0.05 mg · m^{-3} (versus 41 µg of quartz for the nylon cyclone). The HD cyclone is being added as an alternative to the 10-mm nylon cyclone for crystalline silica methods in the fourth edition of the *NIOSH Manual of Analytical Methods*.

Some improvements have been suggested to XRD instrumentation by other researchers (20). High-power X-ray tubes with a rotating anode, capable of about 35 kW versus 2—5 kW for a conventional tube, have been suggested to improve the diffracted intensity. The tubes are very expensive, over USD 100 000 each, and their performance gains have yet to be evaluated. A modification of the XRD goniometer that would allow the sample to be rocked during analysis would allow the diffracted line of more crystallites to be aligned to the detector, but it has yet to be evaluated and is not available commercially. This modification resulted in modest gains (limits of detection to 1 µg · sample^{-1}) but required data collection times of 5—6 h for a single line. Overall, the suggested improvements seem to offer minimal gains that are offset by substantially extra expense and time and result in decreased throughput.

Concluding remarks

In summary, modest improvements in precision and accuracy have been documented for NIOSH sampling methods, presumably as a result of the incremental refinements of the analytical procedures

used by laboratories. Unfortunately, radically new techniques that will allow accurate determinations at significantly lower levels are not anticipated.

Disclaimer

Mention of a company or product name does not constitute endorsement by the US Centers for Disease Control and Prevention.

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Historical total and respirable silica dust exposure levels in mines and pottery factories in China

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Dosemeci M, McLaughlin JK, Chen J-Q, Hearl F, Chen R-G, McCawley M, Wu Z, Peng K-L, Chen A-L, Rexing SH, Blot WJ. Historical total and respirable silica dust exposure levels in mines and pottery factories in China. *Scand J Work Environ Health* 1995;21 suppl 2:39—43.

Historical exposure estimates of total dust and respirable silica were made in a recent nested case-referent study of lung cancer among mine and pottery workers in China. Exposure to total dust and respirable silica was assessed in 20 mines and 9 pottery factories. The average total dust concentration was 7.26 mg · m^{-3}, with a range from 17.68 mg · m^{-3} in the 1950s to 3.85 mg · m^{-3} in the 1980s, while the average respirable silica dust was 1.22 mg · m^{-3}, with a range from 3.89 mg · m^{-3} in the 1950s to 0.43 mg · m^{-3} in the 1980s. The highest respirable silica dust occurred in the underground mining operations (1.43 mg · m^{-3}), particularly for manual drillers (9.03 mg · m^{-3}). Among all facility types, tungsten mines had the highest respirable silica dust exposure (1.75 mg · m^{-3}), while the lowest exposure occurred in copper-iron mines (0.32 mg · m^{-3}).

Key terms Chinese mines and potteries, exposure assessment, industrial hygiene measurements, occupational exposure, retrospective assessment, silica.

Occupational silica exposure is common worldwide (1). The National Institute for Occupational Safety and Health in the United States estimates that approximately 3.2 million workers in 238 000 plants are potentially exposed to crystalline silica (2).

A recent nested case-referent study evaluated the association between lung cancer risk and silica exposure experienced among employees in mines and pottery factories in China (3). The description of the retrospective assessment of exposure to silica carried out in 20 mines (10 tungsten, 6 iron-copper, and 4 tin), and 9 pottery factories has been reported elsewhere (4).

In this report, we present the results of the retrospective assessment of exposure to total and respirable silica dust by operation type (underground mining, surface mining, ore dressing, and pottery making), job title (in 64 mining and 15 pottery making jobs), and facility type (tungsten mines, iron-copper mines, tin mines, and pottery factories) for four decades from the 1950s to the 1980s.

Subjects and methods

The exposure assessment method used in the nested case-referent study has been described in detail elsewhere (4). Briefly, a job-title dictionary specific for the mine and pottery industries (79 specific job titles) was developed and used in both the collection of historical exposure information and work histories of 1668 subjects. A retrospective exposure matrix was developed on the basis of facility, job title, and calendar-year combinations using available historical exposure information and current exposure profiles. The current exposure levels based on the recent measurements carried out in iron and copper mines have been reported elsewhere (5). Information on the amount of respirable and free silica content in total dust was used in estimating exposure to silica. Starting from 1950, 6805 historical estimates were developed for 14 calendar-year periods, using 2.1 million industrial hygiene monitoring data points and other historical exposure information. Exposure indices such as cumulative dust, average dust, cumulative respirable (< 5 μm in particle size) and thoracic (< 10 μm in particle size) silica dust, average respirable and thoracic silica dust, exposure-weighted duration, and the highest or longest exposure were calculated for individuals by merging work histories and the historical exposure matrix for each study subject. In this report, we present the exposure data (for total and respirable silica dust) by four decades starting from 1950, showing the arithmetic mean, the number of estimates at each facility or job title, and the arithmetic standard deviation over time.

Results

Table 1 presents the total dust exposure levels by operation and facility in the mining and pottery industries. The levels of ex-

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Table 1. Historical total dust exposure levels and the number of workers by operation and facility in the mines and potteries.

Operation or facility type	Calender period											
	1950—1959			1960—1968			1969—1980			1981—1987		
	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects
Underground mining	21.06	505	636	4.46	530	665	3.21	852	485	2.52	619	173
Surface mining	11.45	63	149	9.34	82	211	6.62	142	175	5.59	108	77
Ore dressing	14.31	228	246	6.19	256	275	4.18	388	219	2.45	296	92
Others	11.24	85	699	10.01	192	1167	10.19	280	1352	8.78	213	672
Pottery factories	11.82	91	200	11.28	206	277	11.64	300	317	10.44	231	174
Tungsten mines	18.09	533	460	3.49	502	518	2.10	651	549	1.65	486	221
Iron and copper mines	13.61	75	324	7.61	169	430	4.68	418	454	3.11	317	278
Tin mines	21.19	167	375	6.02	165	499	4.22	269	514	2.61	184	257
All facilities combined	17.6	888	1377	6.26	1060	1743	4.91	1662	1853	3.85	1236	940

Table 2. Historical respirable silica dust exposure levels by operation or facility type in the mines and potteries.

Operation or facility type	Calender period														
	1950—1959			1960—1968			1969—1980			1981—1987			All periods		
	Number of samples	Mean ($mg \cdot m^{-3}$)	SD	Number of samples	Mean ($mg \cdot m^{-3}$)	SD	Number of samples	Mean ($mg \cdot m^{-3}$)	SD	Number of samples	Mean ($mg \cdot m^{-3}$)	SD	Number of samples	Mean ($mg \cdot m^{-3}$)	SD
Underground mining	505	4.89	5.3	530	0.84	1.7	852	0.51	0.5	619	0.39	0.4	2506	1.43	3.1
Surface mining	63	1.75	2.3	82	0.83	0.8	142	0.39	0.3	108	0.27	0.3	395	0.67	1.2
Ore dressing	228	3.45	3.4	256	1.19	1.5	388	0.69	0.9	296	0.42	0.5	1168	1.27	2.1
Pottery making	85	0.77	0.7	192	0.70	0.8	280	0.76	0.9	213	0.64	0.9	770	0.71	0.9
Pottery factories	91	0.75	0.7	206	0.69	0.8	300	0.75	1.0	231	0.65	0.9	828	0.71	0.9
Tungsten mines	533	4.99	5.3	502	1.01	1.7	651	0.61	0.7	486	0.46	0.5	2172	1.75	3.3
Iron and copper mines	75	0.75	0.9	169	0.45	0.8	418	0.28	0.3	317	0.20	0.3	979	0.32	0.5
Tin mines	167	3.49	3.2	165	1.03	1.6	269	0.73	0.7	184	0.45	0.3	785	1.31	2.0
All facilities combined	881	3.89	4.7	1060	0.90	1.5	1662	0.56	0.7	1236	0.43	0.5	4839	1.22	2.5

posure to total dust showed a notable decrease over time from 17.68 $mg \cdot m^{-3}$ in the 1950s to 3.85 $mg \cdot m^{-3}$ in the 1980s with an overall average of 7.26 $mg \cdot m^{-3}$. By operation type, the highest average total dust level over all the years (9.87 $mg \cdot m^{-3}$) was observed for the pottery making operations. In the 1950s, the maximum mean dust level (21.06 $mg \cdot m^{-3}$) was determined for underground mining operations. With effective control measures, the total dust level was decreased to 2.52 $mg \cdot m^{-3}$ in the 1980s. By facility type, the highest total dust level was observed in the pottery factories. Among the mining facilities, tin mining showed the overall highest total dust level, 7.83 $mg \cdot m^{-3}$.

Table 2 presents the respirable silica dust exposure levels by operation and facility type in the mining and pottery making industries. Levels of exposure to respirable silica dust showed almost a tenfold decrease over the four decades from 3.89 $mg \cdot m^{-3}$ in the 1950s to 0.43 $mg \cdot m^{-3}$ in the 1980s with an overall average of 1.22 $mg \cdot m^{-3}$ for the 40 years. By operation type, the highest overall respirable silica dust level (1.43 $mg \cdot m^{-3}$) was observed for underground mining operations. In the 1950s, the maximum dust levels were 4.89 $mg \cdot m^{-3}$ and 3.45 $mg \cdot m^{-3}$ for underground mining and ore dressing operations, respectively. For the same operations in the 1980s, the exposure levels were 0.39 $mg \cdot m^{-3}$ and 0.42 $mg \cdot m^{-3}$, respectively, indicating that exposure levels declined in these operations. Among the mining facilities, the maximum exposure to respirable silica occurred in the tungsten mining facilities (1.75 $mg \cdot m^{-3}$).

Table 3 presents respirable silica dust exposure levels by job titles and number of workers in underground mine operations. The maximum exposure to respirable silica was observed among the manual drillers (9.03 $mg \cdot m^{-3}$). This underground job was dominant in the 1950s and 1960s, and its exposure level was dramatically reduced to 0.37 $mg \cdot m^{-3}$ in the 1970s and 1980s. Similarly, among service workers, timber workers had the highest exposure to respirable silica with exposure levels of 7.91 $mg \cdot m^{-3}$ in the 1950s and 0.56 $mg \cdot m^{-3}$ in the 1980s with an average of 2.43 $mg \cdot m^{-3}$ over the four decades. Respirable silica dust showed diverse exposure levels across job titles in the underground mining operations, ranging from 0.04 $mg \cdot m^{-3}$ for water pump workers to 9.03 $mg \cdot m^{-3}$ for manual drillers.

Table 4 presents respirable silica dust exposure levels by the number of workers and occupations in surface mine (open cast) operations. Manual miners (0.92 $mg \cdot m^{-3}$), general transport workers (1.69 $mg \cdot m^{-3}$), road repair workers (1.02 $mg \cdot m^{-3}$), and general service workers (1.26 $mg \cdot m^{-3}$) had higher exposure levels than the other surface jobs. Note that, although samples were collected, there were few or no workers in the manual miner jobs. In the surface mining operations, transport and service occupations generally had higher exposure levels than the mine production occupations, in contrast to the opposite pattern in underground mining operations.

Table 5 presents respirable silica dust exposure levels by job title in ore dressing operations. Higher exposures were observed

Table 3. Historical mean respirable silica dust exposure levels and the number of workers by underground mine job titles.

Underground mine job titles	Calender period													
	1950–1959			1960–1968			1969–1980			1981–1987			All periods	
	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples
Face workers														
Machine driller	7.81	41	80	1.10	49	97	0.73	84	67	0.53	61	12	0.19	235
Blaster	6.58	46	100	0.79	46	63	0.56	76	32	0.45	55	8	1.82	223
Excavator operator	0.50	1	3	0.49	4	3	0.43	8	5	0.37	6	4	0.43	19
Ore sampler	7.12	25	14	1.50	34	18	0.73	60	11	0.56	43	4	1.93	165
Hand shovel worker	6.03	17	11	0.85	14	11	0.27	16	3	0.23	12	1	2.06	59
Roof control worker	5.08	29	13	0.98	26	17	0.56	36	8	0.38	25	1	1.75	116
Manual driller	11.47	37	164	5.70	9	17	0.37	4	1	0.37	3	1	9.03	53
Transport workers														
General transport worker	3.78	7	12	1.65	6	16	0.96	8	15	0.50	6	3	1.74	27
Loader	4.19	29	148	0.53	31	160	0.42	56	84	0.39	40	17	1.13	156
Unloader	3.08	14	3	0.56	16	4	0.28	24	10	0.26	18	3	0.88	72
Railway car driver	2.94	31	129	0.32	41	105	0.28	68	83	0.25	49	16	0.72	189
Pipeline worker	1.75	30	12	0.42	31	19	0.39	52	16	0.32	39	7	0.65	152
Service workers														
Drill rod supplier	5.11	20	8	0.56	16	4	0.37	24	3	0.34	18	1	1.62	78
Timber worker	7.91	46	68	1.36	46	69	0.81	68	35	0.56	49	13	2.43	209
Cement sprayer	0.25	1	0	0.29	4	—	0.25	8	2	0.20	6	2	0.24	19
Maintenance worker	1.18	33	35	0.46	40	58	0.45	68	50	0.32	49	20	0.55	190
Ventilation worker	1.28	25	8	0.51	34	31	0.43	60	25	0.35	43	13	0.56	162
Dust sampler worker	2.32	6	2	0.77	11	3	0.77	16	2	0.65	12	—	0.94	45
Gunpowder mixer	0.95	4	—	0.28	6	7	0.17	8	5	0.17	6	1	0.33	24
Analyst	1.35	4	1	0.54	3	4	0.68	4	2	0.25	3	—	0.75	14
Engineer/technician	1.41	41	45	0.52	45	66	0.48	72	54	0.37	52	26	0.66	215
Signal worker	0.46	4	6	0.34	6	7	0.27	8	6	0.26	6	5	0.32	24
Service worker	0.09	1	14	0.07	3	37	0.22	8	40	0.12	6	16	0.15	18
Water pump worker	0.03	1	11	0.03	3	40	0.03	4	49	0.07	3	31	0.04	11
Elevator worker	0.58	1	7	0.46	3	11	0.13	8	9	0.14	6	3	0.21	18

Table 4. Historical respirable silica dust exposure levels and the number of workers by surface mine job titles.

Surface mine job titles	Calender period													
	1950–1959			1960–1968			1969–1980			1981–1987			All periods	
	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples	Number of subjects	Mean (mg · m^{-3})	Number of samples
Mine workers														
Machine driller	0.73	3	27	0.66	8	23	0.33	19	14	0.24	12	5	0.39	42
Blaster	0.74	2	4	0.50	6	5	0.37	12	5	0.29	9	2	0.40	29
Excavator operator	0.28	4	8	0.28	6	12	0.24	12	10	0.20	9	5	0.25	31
Manual miner	1.91	4	5	0.80	4	2	0.42	4	0	0.42	3	0	0.92	15
Transport workers														
General transport worker	5.11	6	6	1.22	8	9	0.73	11	6	0.65	6	1	1.69	31
Forklift operator	0.47	3	7	0.59	4	5	0.40	8	3	0.21	6	1	0.39	21
Truck driver	0.15	2	15	0.28	4	17	0.31	12	15	0.28	15	7	0.28	33
Service workers														
Road repair worker	1.97	15	38	1.35	18	45	0.47	20	33	0.25	12	15	1.02	65
Maintenance worker	1.26	6	10	0.69	6	16	0.25	12	19	0.08	9	8	0.47	33
Analyst	0.68	2	10	0.52	3	13	0.43	4	14	0.13	3	5	0.42	21
Signal worker	0.15	3	9	0.15	3	12	0.12	8	11	0.09	6	8	0.12	20
Engineer/technician	0.15	3	4	0.15	3	6	0.17	8	7	0.19	9	4	0.17	23
General service worker	2.62	10	2	1.17	9	13	0.75	12	16	0.51	6	6	1.26	40

for the course crusher (2.01 mg · m^{-3}), ore unloader (1.05 mg · m^{-3}), mesher (1.81 mg · m^{-3}), fine crusher (1.31 mg · m^{-3}), ball mill worker (1.05 mg · m^{-3}), grinding worker (1.17 mg · m^{-3}), manual separation worker (1.80 mg · m^{-3}), transport worker (1.79 mg · m^{-3}), package worker (2.12 mg · m^{-3}), sand baker (3.39 mg · m^{-3}), cast cleaning worker (1.56 mg · m^{-3}), and smelter (1.20 mg · m^{-3}) occupations than for other occupations. The majority of these heavier exposures were in the ore pre-

Table 5. Historical respirable silica dust exposure levels and the number of workers by ore dressing job titles.

Ore dressing job titles	Calender period													
	1950–1959			1960–1968			1969–1980			1981–1987			All periods	
	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples
Ore preparation workers														
Ore washer	1.81	3	49	0.51	3	33	0.25	4	5	0.28	3	2	0.68	13
Course crusher	2.47	3	3	2.47	3	17	2.25	4	12	0.79	3	2	2.01	13
Ore unloader	2.57	35	27	1.08	35	22	0.48	48	16	0.33	36	5	1.05	154
Mesher	4.31	26	9	1.35	24	8	1.04	32	5	0.61	14	3	1.81	106
Fine crusher	4.40	44	62	1.05	48	59	0.49	77	47	0.30	60	16	1.31	229
Ball mill worker	3.14	114	4	1.03	12	7	0.52	20	7	0.26	15	3	1.05	58
Grinding worker	3.27	18	4	0.78	21	6	0.66	28	7	0.45	21	3	1.17	88
Ball mill repair worker	1.36	4	1	0.52	6	2	0.32	8	1	0.23	6	—	0.52	24
Ore separation workers														
Flotation worker	·	—	13	·	—	10	·	—	11	0.06	2	2	0.06	2
Magnetic worker	2.25	8	5	0.54	9	3	0.32	16	2	0.17	12	1	0.67	45
Manual separation worker	3.29	8	1	2.44	6	3	0.73	8	3	0.61	6	2	1.80	28
Wet crusher	1.20	1	—	0.55	3	1	0.23	4	1	0.23	3	—	0.40	11
Conveyor operator	0.75	4	7	0.28	6	11	0.22	16	7	0.16	4	4	0.27	38
Service workers														
Maintenance worker	0.43	2	9	0.22	3	21	0.32	8	25	0.15	6	14	0.26	19
Crane operator	·	—	6	·	—	13	0.07	4	17	0.04	3	8	0.06	7
Dust prevention worker	2.05	2	—	0.99	3	1	0.53	4	2	0.37	3	2	0.86	12
Sampling worker	·	—	—	0.15	2	—	0.26	4	1	0.09	3	1	0.18	9
Transport worker	1.88	3	13	2.17	3	12	1.58	4	6	1.58	3	6	1.79	13
Engineer/technician	0.33	2	9	0.13	6	18	0.26	12	14	0.12	9	11	0.19	29
Package worker	4.48	13	11	1.90	12	6	1.55	16	3	0.55	12	—	2.12	53
Sand baker	7.71	18	3	3.28	15	3	1.46	19	2	0.76	15	2	3.39	67
Foundry worker	1.03	12	8	0.88	15	3	0.61	24	4	0.60	18	1	0.74	69
Molder	0.74	1	1	0.74	3	1	0.87	4	1	0.06	3	1	0.60	11
Caster	1.11	5	4	0.75	6	3	0.50	8	2	0.16	6	1	0.60	25
Cast cleaning worker	0.47	1	4	1.63	9	4	1.61	12	4	1.53	9	3	1.56	31
Smelter	0.68	4	2	0.68	3	2	2.52	4	3	0.68	3	2	1.20	14

Table 6. Historical respirable silica dust exposure levels and the number of workers by pottery making job title.

Pottery making job titles	Calender period													
	1950–1959			1960–1968			1969–1980			1981–1987			All periods	
	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples	Number of subjects	Mean ($mg \cdot m^{-3}$)	Number of samples
Mud preparation workers														
Ore crusher	1.55	8	3	1.15	12	5	1.79	16	5	1.30	12	3	1.47	48
Mesher	2.34	4	3	0.54	5	4	0.59	8	4	0.49	6	1	0.86	23
Ore mixer	·	—	11	3.48	5	14	5.14	8	11	5.14	6	5	4.70	19
Other preparation worker	0.76	3	2	0.41	4	4	0.42	16	4	0.42	12	1	0.45	41
Mud forming worker														
Press forming worker	0.05	3	4	0.39	5	9	0.76	8	7	0.55	6	3	0.52	22
Molding worker	0.68	11	44	0.74	22	41	0.64	32	34	0.50	12	3	0.63	89
Fine material worker	0.62	4	5	0.69	6	9	0.39	8	8	0.22	6	4	0.46	24
Finishing workers														
Glazed material worker	0.96	5	4	0.78	19	9	0.76	28	10	0.45	3	12	0.69	73
Furnace loading worker	0.78	11	16	0.72	22	28	0.69	32	33	0.64	24	16	0.69	89
Furnace unloading worker	0.39	5	3	0.39	16	4	0.38	20	8	0.34	15	5	0.37	56
Greenware inspector	0.59	7	2	0.65	17	2	0.67	24	7	0.61	18	6	0.64	66
Fire watcher	0.63	11	19	0.67	22	34	0.55	32	41	0.46	24	25	0.57	89
Boiler worker	0.69	1	1	0.44	4	2	0.37	8	1	0.44	9	—	0.42	22
Service workers														
Maintenance worker	0.30	6	—	0.32	11	3	0.32	16	3	0.32	1	1	0.32	45
Other service worker	0.39	6	11	0.39	16	15	0.38	24	18	0.38	8	8	0.38	64

paration unit or in foundry occupations in the nonmining production unit.

Table 6 presents respirable silica dust exposure levels by occupations in the pottery making operations. High-level exposures were observed for the ore crusher (1.47 mg · m^{-3}) and ore mixer (4.70 mg · m^{-3}). In the pottery making operations, the major source of high exposure to respirable silica dust was found in the mud preparation unit, where the dry raw materials are crushed and mixed for forming pottery mud.

Discussion

We have presented historical exposure levels for total dust and respirable silica dust found in the mines and pottery factories of China. These exposures were estimated using a detailed historical exposure assessment method (4) and were employed in the epidemiologic analysis of a nested case-referent study of lung cancer in China (3).

Although there were 2.1 million monitoring results for total dust exposure, very few (14%) direct measurements were available for the percentage of silica and the respirable or thoracic fraction of the total dust. The quality and quantity of historical measurements of total dust allowed us to employ a detailed job-title specific exposure assessment for total dust concentration. The information on the silica content of total dust and the percentage of respirable dust was, however, limited to recent years and to a few jobs, so that the average percentage of silica and percentage of respirable dust for each facility was used. Mean silica was 32.7%, ranging from 10.6% for the iron-copper mines to 47.6% for the tungsten mines. The respirable portion of the total dust also showed some variation with the mean value of 48.0%, ranging from 25.7% for the pottery factories to 65.1% for the iron-copper mines. These differences in the percentage of silica and the respirable portion have created different rank orders for total dust and respirable silica dust. For example, the highest average total dust exposure was found in pottery factories, while the highest average respirable silica dust exposure occurred in the tungsten mines.

Although several previous reports (6—16) have presented the level of exposure to silica dust in similar or other occupational settings, only four of them (6, 10, 11, 13) were employed in epidemiologic studies. We believe that the results of the exposure levels presented in this report will be helpful for other investigators who assess exposure to silica in epidemiologic studies.

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Potential for respirable quartz exposure from North Carolina farm soils

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Stopford CM, Stopford W. Potential for respirable quartz exposure from North Carolina farm soils. *Scand J Work Environ Health* 1995;21 suppl 2:44—6.

Sandy-loam soils from six active farms in the coastal plains of North Carolina (USA) were analyzed for aerodynamic equivalent diameter and quartz content and compared with results to similar analyses of clay soils of the Piedmont and sandy soils from the sand hills of North Carolina to see whether respirable quartz content varies with soil type. The respirable fraction of sandy loam-soils averaged 0.04 (SD 0.02) versus 0.13 (SD 0.03) for clay soils and 0.04 (SD 0.03) for sandy soils. Quartz content in the 4.25 μm fraction of sandy-loam soils averaged 15.2 (SD 4.1) % versus 2.2 (SD 0.8) % in clay soils and 29.0 (SD 11.1) % in sandy soils. The mass of respirable quartz in sandy-loam soils averaged 0.7 (SD 0.4)% versus 0.3 (SD 0.1)% in clay soils and 1.0 (SD 0.4) % in sandy soils. These results suggest that, during dusty farm activities, there is a potential for greater respirable quartz exposures associated with work with sandy or sandy-loam soils than from work with clay soils.

Key terms agriculture, quartz, respirable fraction, soil analysis.

Exposures to respirable quartz in such industries as hard rock mining, construction, pottery, silica flour mining and milling, and sand blasting carry with them an increased risk of silicosis (1, 2). More recently, several reports have identified a risk of respiratory disease, including pneumoconiosis, among farm laborers. Between 1968 and 1988 in the United States, in multiple cause of death listings where there was any mention of silicosis, farming was mentioned as the third most common occupation (3). The processing of tobacco leaves was the industry with the third highest incidence rate of reported occupational pulmonary diseases for 1989 (3). Sherwin et al (4) described a series of five cases of progressive respiratory failure and death among five nonsmoking California table grape harvesters for whom lung tissue analysis showed chronic inflammation and fibrosis associated with particle deposition. Analysis of the particles disclosed that 5—10% was silicon dioxide. Analysis of the < 5 μm fraction of dirt from the involved fields showed similar elemental distributions to those of the particles found in the lungs. Popendorf et al (5, 6) measured the respirable quartz exposures of California harvesters of citrus, peach, and grape crops. Respirable quartz exposures ranged from 7 to 105 $\mu g \cdot m^{-3}$, and the quartz content of the respirable dusts ranged from 1 to 12%, being highest among the table grape harvesters. Individual cases of pulmonary fibrosis and silicosis have been reported for farmers with quartz levels ranging from 14 to 58% in the mineral dust found in lung tissue (7, 8). Finally, Carlson & Petersen (9) found an excess rate of death from respiratory disease among farm workers compared with farm owners-managers in California.

As part of an effort to define the potential for respirable quartz exposure during farming further, we completed a study of respirable silica in bulk clay and sandy farm soils (10). This study suggested that, for sandy farm soil, quartz exposure can approach the levels found in hard rock mining. We have now extended this study to the evaluation of sandy-loam soils.

Materials and methods

Sandy-loam samples were collected with a stainless steel scoop and stored in polyethylene bags prior to the analysis. No attempt was made to assure that the samples were representative of any particular tilled field. Soils were prepared by drying in an oven at 279°F (137°C) for 2 h. Only clay soils had to be further processed by crushing lumps. Only the particles passing through a 45-μm mesh sieve (and thus likely to be entrained in air) were analyzed further.

Aerodynamic equivalent diameter (AED) is a property of particles that has been directly related to the probability of deposition in the lungs (11). The American Conference of Governmental Industrial Hygienists (12) defines respirable fraction or mass as that portion which penetrates a separator with a size collection efficiency described by a cumulative log-normal function with a median AED of 4.25 μm and a geometric standard deviation of 1.5 μm. Particles settle according to Stokes' Law such that the mass of particles that settle in a given time is proportional to the AED (13). The AED is determined by sampling particle mass at 5 cm below the surface of the Andreasen pipette every 10 min (13—16). The AED is plotted as a cumulative size distribution on log-normal paper with a regression analysis (Quattro Pro, Novell, Utah, United States) from which respirable fraction is determined by interpolation.

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We analyzed samples from six farms growing sweet potatoes or peanuts in three eastern counties of North Carolina's coastal plain. Quartz was analyzed using the carbonate fusion method of Dobreva (17) as modified by Stopford (15). Although crystalline silica and quartz were used interchangeably in the report for convenience, this method does not differentiate between various crystalline polymorphs of silica. Results using this method agree well with the results of analyses by X-ray diffraction (18). This method has the advantage over X-ray diffraction because there are no interferences by silicates, feldspar, or iron (15, 19).

Results

Particle analyses of 45-μm dusts. As can be seen in table 1, the Andreasen pipette analyses of dried dirt that is sieved to 45 μm or less showed that the geometric mean AED ranged from 35.7 to 117.8 (mean 82.6) μm. The samples followed a log-normal distribution with geometric standard deviations of the median values ranging from 4.5 to 7.2 (mean 5.4) μm. The respirable fractions ranged from 0.02 to 0.07 (mean 0.04, SD 0.02).

Quartz analyses. Quartz analyses of ≤ 45-μm particle size dusts (table 2) showed levels ranging from 25.4 to 56.3 (mean 44.6) %. The quartz content in the respirable fraction of these samples was consistently less, ranging from 9.1 to 21.3 (mean 15.2) %. The mass of respirable quartz, calculated by multiplying the respirable fraction times the percentage of quartz in the 4.25-μm fraction, ranged from 0.27 to 1.49 (mean 0.65, SD 0.43) %.

Table 1. Particle size analyses of 45-μm sieve dusts.

Farm	Geometric mean aerodynamic diameter (μm)	Geometric standard deviation (μm)	Respirable fraction
a	35.7	4.5	0.07
b	73.3	4.6	0.03
c	95.7	5.8	0.03
d	106.2	7.2	0.05
e	117.8	5.7	0.02
f	66.8	5.1	0.04

Table 2. Quartz content of 45-μm and 4.25-μm soil dusts.

Farm	Quartz in 45-μm sieve dust (%)	Quartz in 4.25-μm fraction (%)	Respirable quartz (%)
a	56.3	21.3	1.49
b	49.9	9.1	0.27
c	46.2	16.2	0.49
d	54.3	18.5	0.92
e	25.4	14.7	0.29
f	35.8	11.3	0.45

Table 3. Comparison of quartz content of soil dusts according to soil type.

Soil type[a]	Quartz in 4.25-μm fraction (%)		Respirable quartz (%)	
	Mean	SD	Mean	SD
Clay soils (N = 6)	2.2	0.8	0.3	0.1
Sandy-loam soils (N = 6)	15.2	4.1	0.7	0.4
Sandy soils (N = 8)	31.6	9.3	1.0	0.4

[a] N = number of farms.

Discussion

This study has shown that quartz levels in the respirable fraction of sandy-loam soils from farms growing root crops range from 9.1 to 21.3%. These levels are generally higher than the 1 to 12% quartz found by Popendorf et al (5, 6) in dusts generated during the manual harvesting of fruit crops and levels from 0.85 to 17.5% found in tractor air filters at the end of the growing season (20). In the latter study, 50—97% of the dust in the filters had an AED of < 5 μm. This study also suggests that actual entrained dust may include a larger percentage of respirable dust than the 45-μm sieve cut used in our study. As can be seen in table 3, quartz levels in sandy-loam soil are intermediate to those found in clay and sandy soils.

Brantley (16) and Reist & Creed (13) found that measurements of respirable fraction made with an Andreasen sedimentation pipette correlate well with measurements of respirable fraction in a dust cloud. The percentage of respirahle quartz of a soil can thus be used to estimate the respirable quartz levels expected to be found in air under certain work conditions. Total airborne dust levels range from 5 to 70 mg · m^{-3} during manual harvesting activities (6) and from 10 to 200 mg · m^{-3} during mechanized farm activities (21). These values suggest that airborne respirable quartz levels could be on the order of 15 to 600 μg · m^{-3} during the farming of clay soils, 35 to 1400 μg · m^{-3} during the farming of sandy-loam soils, and 50 to 2000 μg · m^{-3} during the farming of sandy soils.

However, the ability of respirable-sized quartz particles in a soil to be aerosolized would likely depend on factors such as the amount of binding to the clay matrix in a soil (22) and the amount of soil moisture. Only clay soil samples require mechanical crushing of particles to produce a dust that could pass through a 45-μm sieve. These soils would also have to be crushed in the field by mechanized farm activities to release respirable-sized quartz particles. Soil moisture would also play a factor; sandy soils would be less likely to retain moisture than clay or sandy-loam soils. In our study soil moisture levels averaged 10.1 (SD 3.9) % for clay soils, 2.5 (SD 3.6) % for sandy-loam soils, and 0.9 (SD 0.5) % for sandy soils.

Our study also found that the percentage of quartz in the respirable fraction of each sample was consistently less than in the 45-μm cut of each soil in that the quartz particles tended to be larger than other associated soil particles. In clay soils respirable quartz was found to make up 0.96 (SD 1.16) % of the total quartz present versus 1.52 (SD 0.70) % in sandy soils and 1.39 (SD 0.66) % in the sandy-loam soils analyzed in this study. This relationship has also been seen by others (23). However, there is no close relationship between total quartz levels in soil and those found in the respirable fraction (5).

Exposure to respirable quartz in soil can also occur during the processing of crops. Farant & Moore (24) found respirable dust levels as high as 12 700 μg · m^{-3}, and the quartz content of the respirable dust ranged as high as 6.1% during the processing of grains. Williams (25) found respirable quartz levels to range from 470 to 1 170 μg · m^{-3} during the processing of tobacco. Barish & Nicas (26) found exposures to respirable quartz as high as 400 μg · m^{-3} among processors of root crops. Since farming is a seasonal activity, farm laborers would have less of a risk of developing silicosis than farmers engaged in the daily processing of crops contaminated with soil or workers exposed to respirable quartz particles in other industries (26).

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Silica exposures in workplaces in the United States between 1980 and 1992

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Freeman CS, Grossman EA. Silica exposures in workplaces in the United States between 1980 and 1992. *Scand J Work Environ Health* 1995;21 suppl 2:47—9.

Between 1980 and 1992, compliance officers of the Occupational Safety and Health Administration in the United States measured respirable quartz in 1655 inspections in 255 industries. In 52% of the 255 industries where respirable quartz was measured, the average severity value was less than one, indicating average exposures below the permissible exposure limit, and in 48% the permissible exposure limit for silica was exceeded. Among industries where more than 10 facilities were inspected, the most severe respirable quartz exposures were found in fabricated structural metal; painting and paper hanging; nonresidential construction; shipbuilding and repair; masonry and other stone work; bridge, tunnel and elevated highway construction; metal coating, engraving and allied services; and special trades contractors.

Key terms brick, clay, construction, foundries, glassware, metal fabrication, permissible exposure limit.

As the need for silica materials has increased in diverse industries, sampling procedures for occupational exposure to silica have improved dramatically and therefore allowed for greater accuracy and precision. New sampling methods can rectify deficiencies in the qualitative and quantitative assessment of airborne silica levels (see Lorberau & Abell, this issue), and efforts to standardize exposure units are underway around the world.

The intensity of peak exposures is often associated with acute health outcomes, while the intensity of cumulative exposure is generally more relevant for diseases with long latency. Depending on the exposure scenario, however, peak exposures may also be etiologically relevant in chronic disease induction (1). For this reason, time-weighted average (TWA) exposures, peak exposures, and, ultimately, permissible exposure limit (PEL) values all need to be accurately quantified, and the adverse health effects associated with excessive silica exposures need to be accurately enumerated.

Regulatory agencies such as the Occupational Safety and Health Administration (OSHA) in the United States need to be able to measure occupational exposures to silica accurately, not only to quantify dose-response relationships, but also to determine compliance with existing standards. The silica-related health effects of concern to OSHA include silicosis and lung cancer among stonemasons, sandblasters, construction employees, and other groups of silica-exposed workers (2). This paper updates and expands earlier reports on industrial exposures to respirable quartz (3, 4). It focuses on the levels of respirable crystalline silica measured during OSHA inspections in all industries and recorded on OSHA's Integrated Management Information System (IMIS).

Collected data

Records in IMIS comprise OSHA's enforcement data base, and it was not designed for research. The contents of IMIS include inspection date, inspection type, employment size, the specific contaminant sampled, the measured level of that contaminant, the job title of the sampled worker, the number of workers similarly exposed, code of the Standard Industrial Classification (SIC), and all other applicable data. The SIC system is widely used for classification and allows industries to be categorized on the basis of the principal product, groups of products, or services performed (3). Because OSHA targets high risk industries for inspection, this data base cannot be considered to be representative of the universe of all workplaces in the United States. Furthermore, it excludes mines and farms because OSHA does not have inspection authority over these industries.

From 1980 to 1989, OSHA's permissible exposure limit (PEL) for quartz was measured as a function of the portion of respirable quartz in the sample. The formula used to calculate the PEL was also used to calculate exposures to respirable mixtures. The PEL, expressed in units of milligrams per cubic meter of air ($mg \cdot m^{-3}$), was given by:

$$PEL = (10\ mg \cdot m^{-3})/(\%SiO_2 + 2),$$

where $\%SiO_2$ is the percentage of free respirable quartz in dust. By making the PEL a function of the portion of respirable quartz in a sample, the PEL was more restrictive for samples with smaller proportions of respirable quartz.

In 1989, a fixed PEL of 0.1 $mg \cdot m^{-3}$ for respirable quartz was incorporated into OSHA's air contaminants standard (29 CFR

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1910.1000, tables Z-1, Z-2, and Z-3). The revised PEL not only appeared to be universally understandable to industrial hygienists, but also comparable worldwide. As the result of a federal legal ruling OSHA's PEL for respirable quartz was returned to the pre-1989 adjustable PEL at the end of 1992.

With these changes in the PEL over time, the routine recording of exposure levels measured during inspections has also changed. This change makes it difficult to compare the occupational exposure levels recorded on the IMIS over time. One way around this problem is to convert exposure levels into comparable units. An alternative solution, however, is to use the severity of exposure instead of the measured exposure level as an indicator of exposure intensity. Severity is reported on the IMIS as the ratio of the measured level of respirable quartz to the "current" PEL (ie, exposure level/PEL). A severity measure greater than 1 indicates exposure above the PEL, and a severity measure less than 1 indicates exposure below the PEL. By expressing exposure levels in terms relative to the PEL, severity takes into account the changes in OSHA's PEL over time.

Table 1. Inspections conducted by the Occupational Safety and Health Administration between 1980 and 1992. (SIC = Standard Industrial Classification, NEC = not elsewhere classified)

Industry	Number	Percentage of total
Gray and ductile iron foundries (SIC 3321)	321	19.4
Copper foundries (SIC 3366)	95	5.7
Steel foundries (SIC 3325)	69	4.2
Aluminum foundries (SIC 3365)	48	2.9
Concrete products except block and brick (SIC 3272)	39	2.4
Brick and structural clay tile (SIC 3251)	35	2.1
Malleable iron foundries (SIC 3322)	30	1.8
Heavy construction NEC (SIC 1629)	29	1.8
Pottery products NEC (SIC 3269)	27	1.6
Steel works, blast furnaces and rolling and finishing mills (SIC 3312)	26	1.6
Clay refractories (SIC 3255)	26	1.6
Special trades contractors NEC (SIC 1799)	26	1.6
Ceramic wall and floor tile (SIC 3253)	24	1.5
Pressed and blown glass and glassware NEC (SIC 3229)	23	1.4
Vitreous china plumbing fixtures (SIC 3261)	23	1.4
All Other Industries	814	49.1
Total	1655	100

Several researchers have reported findings of adverse silica-related health effects using relative exposure measures similar to the IMIS severity measure (4, 5). Evaluating exposures in terms of relative measures allows for the comparisons of possible health effects in industries with similar dust levels. Serious hazards can be distinguished from less serious hazards, rapidly identified, and targeted for intervention. For example, foundry workers cannot only be exposed to respirable quartz, but also to polycyclic aromatic compounds, aromatic amines, and other compounds which have been shown to be carcinogenic (2). Since acute high-level exposures may result in a greater risk of illness and death, OSHA is primarily concerned about such exposures. Thus severity is useful for reflecting exposures of greatest concern.

Findings

The analysis presented herein was restricted to samples collected during inspections where some amount of respirable quartz was measured. It was further restricted to those samples measured as personal, 8-h TWA values and recorded in the IMIS in units of milligrams per cubic meter. Results from follow-up inspections were excluded.

Between 1980 and 1992, federal OSHA compliance officers measured some level of respirable quartz in 6779 personal, 8-h TWA samples collected in 1655 inspections in 255 industries. Table 1 presents the number of inspections conducted in the 15 most frequently sampled industries identified by their four-digit SIC codes. This table shows that half of the inspections were conducted in only 15 industries. Overall, among the 15 most frequently inspected industries, 34% of the total inspections were conducted in foundries (SIC codes 3321, 3366, 3325, 3365, and 3322), 12% in the stone, clay, glass, or concrete products manufacturing industry (SIC codes 3272, 3251, 3269, 3255, 3253, 3229, and 3261), 55 inspections in the all construction industries category, and 26 in steel mills.

Table 2 presents the number of personal, 8-h TWA samples collected in each of the 15 industries presented in table 1, as well as the mean, median, and maximum severity. Table 2 shows that, while the greatest number of samples was collected in the most frequently inspected industry, a large number of samples was collected in some industries with far fewer inspections. For example, 261 samples were collected in 30 inspections of malleable

Table 2. Summary statistics on severity measures in the 15 most frequently inspected industries between 1980 and 1992.[a] (SIC = Standard Industrial Classification, NEC = not elsewhere classified)

Industry	Samples (N)	Mean	Median	Maximum
Gray and ductile iron foundries (SIC 3321)	2442	1.62	.78	153.00
Copper foundries (SIC 3366)	374	1.04	.52	100.00
Steel foundries (SIC 3325)	346	1.19	.83	16.61
Aluminum foundries (SIC 3365)	137	0.76	.44	10.00
Concrete products except block and brick (SIC 3272)	78	1.36	.74	29.70
Brick and structural clay tile (SIC 3251)	143	2.59	1.19	82.19
Malleable iron foundries (SIC 3322)	261	1.42	.64	54.05
Heavy construction NEC (SIC 1629)	62	2.84	1.12	48.22
Pottery products NEC (SIC 3269)	72	1.97	.83	33.17
Steel works, blast furnaces etc (SIC 3312)	136	0.89	.54	7.66
Clay refractories (SIC 3255)	128	0.94	.63	5.84
Special trades contractors NEC (SIC 1799)	60	8.33	1.73	99.00
Ceramic wall and floor tile (SIC 3253)	124	1.80	1.17	14.49
Pressed and blown glass and glassware NEC (SIC 3229)	45	1.39	.53	10.48
Vitreous china plumbing fixtures (SIC 3261)	96	2.19	1.14	18.58

[a] Severity calculated as the measurable level of respirable quartz divided by the permissible exposure limit.

iron foundries, giving an average of 8.7 samples per inspection. By contrast, 95 inspections were conducted in copper foundries, but only 374 samples were collected, giving an average of 3.9 samples per inspection.

The data in table 2 demonstrate that in all but three of the 15 industries (aluminum foundries, steel mills, and clay refractories) the mean measure of severity was greater than one. Therefore the average exposure for 12 of the 15 industries exceeded the PEL. In every case, the mean exceeded the median level, indicating that severity is skewed towards samples in excess of the PEL. Of the 15 most frequently inspected industries, only two (steel works and clay refractories) had maximum levels less than 10 times the PEL. There were silica samples near or above 50 times the OSHA PEL for gray iron foundries, copper foundries, brick and clay tile, malleable iron foundries, heavy construction, and special trades contractors.

Overall, the mean measure of severity was below one for 133 of the 255 industries (52%); however 48% of the industries had average silica exposures exceeding the PEL. Table 3 presents the mean severity for the 10 industries subject to 10 or more inspections which had the most severe exposures to respirable quartz as measured by mean severity. These industries are fabricated structural metal (SIC 3441), painting and paper hanging (SIC 1721), nonresidential construction (SIC 1542), shipbuilding and repair (SIC 3731), masonry and other stone work (SIC 1741), bridge, tunnel and elevated highway construction (SIC 1622), metal coating, engraving and allied services (SIC 3479), special trades contractors (SIC 1799), fabricated plate work (SIC 3443), and heavy construction, not elsewhere classified (SIC 1629). For eight of these ten industries, the mean severity measure indicated average exposure to levels of respirable quartz at least eight times greater than the PEL.

The number of inspections, by year of inspection, is provided in table 4. This table indicates that the number of inspections where samples of respirable quartz were measured has declined over time from 227 in 1980 to 75 in 1992. There are several possible interpretations for the trend observed in table 4. One is that the focus of OSHA inspections has changed during this period. The second is that occupational exposure to respirable quartz has declined over time. Because this study has focused on inspections where respirable quartz was measured and because there is no complete data on the number of times respirable quartz was sampled but not found, it is not possible to determine from these data which interpretation is correct.

Table 3. Most severe 8-h time-weighted average exposures in industries inspected ≥ 10 times where measurable levels of respirable quartz were found. (SIC = Standard Industrial Classification)

Industry	Mean severity
Fabricated structural metal (SIC 3441)	33.11
Painting and paper hanging (SIC 1721)	16.64
Nonresidential construction (SIC 1542)	15.59
Shipbuilding and repair (SIC 3731)	15.27
Masonry and other stone work (SIC 1741)	13.04
Bridge, tunnel, and elevated highway construction (SIC 1622)	10.84
Metal coating and engraving and allied services (SIC 3479)	8.42
Special trades contractors (SIC 1799)	8.33
Fabricated plate work (SIC 3443)	2.96
Heavy construction NEC (SIC 1629)	2.84

Table 4. Number of inspections where respirable quartz, measured as personal 8-h time-weighted averages, was found by year of inspection.

Year	Number of inspections	Percentage
1980	227	13.7
1981	199	12.0
1982	200	12.1
1983	138	8.3
1984	111	6.7
1985	133	8.0
1986	94	5.7
1987	100	6.0
1988	99	6.0
1989	111	6.7
1990	93	5.6
1991	75	4.5
1992	75	4.5
Total	1655	100

Summary

OSHA's IMIS identifies industries that have been inspected for respirable quartz. Information provided on the severity of the exposure can be used, in conjunction with data from other silicosis surveillance data bases, to target industries in which relatively high respirable quartz exposures can be expected. By using different surveillance sources, all gaps in any one system should be identified. In this way, coverage of silica-exposed workers can be improved.

Disclaimer

The views expressed in this paper represent those of the authors and do not necessarily represent those of the US Occupational Safety and Health Administration.

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Mathematical model of phagocytosis and inflammation after the inhalation of quartz at different concentrations

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A mathematical model was developed with several distinctive features to represent the various processes leading to silicosis. It assures the phagocytosis of quartz by the resident alveolar macrophages. It then models the necrosis of macrophages caused by the ingestion of quartz particles and the subsequent release of these clusters onto alveolar surfaces. The inflammatory recruitment of alveolar macrophages and neutrophils in response to the cell necrosis caused by the ingestion of quartz particles is described in a functional form and is included in the model. The model also describes the pathological and other biological reactions to quartz particles in the interstitium. Specifically, once the quartz particles arrive at the interstitium, they can be phagocytozed by interstitial macrophages. The pathological interaction between quartz and interstitial macrophages may lead to quartz particles being sequestered in silicotic nodules, and also cleared to the efferent lymph nodes.

Key terms alveolar macrophage, interstitial macrophage, neutrophil, silicosis.

The function of the immune system of the alveolar region of the lung is to protect its integrity from damage caused by invading pathogens. The first line of the defense is the resident alveolar macrophage (1), the primary function of which is to take up the pathogens and, incidentally, particles and fibers, and neutralize and remove them from the site of injury. The breakdown of these functions is known to be the cause of lung pathologies.

The purpose of this paper is to describe these functions mathematically and to make available the key concepts of the model so as to provide a framework for the analysis and interpretation of data from animal studies involving the instillation or inhalation of cytotoxic quartz particles.

Phagocytosis, clearance and inflammation

The clearance of silica particles depends primarily on the ability of the alveolar macrophages to detect, phagocytoze, and transport particles to the mucociliary escalator, where they are eliminated from the lung. Macrophages can detect particles either by random encounters or by chemotaxis generated by the particles (2). The balance between the rate of macrophage efflux and replacement is maintained in a steady state (3). The ability of macrophages to phagocytose and remove the particles from alveoli becomes impaired as the maximum load capacity (n_{max}) approaches saturation. Impaired phagocytosis and macrophage immobility is known as the "overload" phenomenon (4).

When macrophages are overloaded, they lose their ability to respond to chemotactic gradients and fail to migrate from the alveoli to the mucociliary escalator (5); they die and release particles into the extracellular environment (6, 7).

The difficulty facing local macrophages in eliminating particles is manifested by the release of acute inflammatory mediators by particle-laden macrophages, especially interleukin-1 and leukotriene (LTB_4). Inflammation can occur in "overload" situations, although small doses of toxic particles may not elicit any reaction (9).

Further recruitment of phagocytes is required if inhaled silica dusts are not eliminated. Chronic deposition of dust leads to the necrosis of the macrophages, and the subsequent release of particles ensures that free quartz remains on the alveolar surface. This cyclic capture and release of particles leads to a continuing recruitment of alveolar macrophages and neutrophils, and over time produces "chronic inflammation." A schematic description of the process of inflammation is presented in figure 1.

Modeling phagocytosis

The basic model. Let AM_i be the population of AM cells containing i quartz particles ($i = 0,1,...,n$), AM_0 being the population of particle-free alveolar macrophages, and AM_n the population of macrophages with the maximum load, containing n particles. The total population of macrophages at any time t is $AM(t)$ and is the total sum of all the macrophages belonging to their respective load class:

$$AM(t) \sum_{i=0}^{n} AM_i(t). \qquad \text{equation 1}$$

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Similarly, the macrophage burden at any time t is:

$$X_2(t) = \sum_{i=0}^{n} imAM_i(t), \qquad \text{equation 2}$$

where m is the average mass of a single quartz particle and i is the number of quartz particles representing the load class i. Note that during phagocytosis, macrophages enter the next load class when they ingest additional quartz particles.

The process of phagocytosis by alveolar macrophages can be described as

$$\frac{dAM_0}{dt} = R_{AM} - k_{10}X_0AM_0 - (p_0 + q_0)AM_0$$

$$\frac{dAM_j}{dt} = k_{jj-1}X_0AM_{j-1} - k_{j+1j}X_0AM_j - (p_j + q_j)AM_j, \quad 0 < j < n$$

$$\frac{dAM_n}{dt} = k_{n\,n-1}X_0AM_{n-1} - (p_n + q_n)AM_n, \qquad \text{equation 3}$$

where R_{AM} is the inflammatory recruitment rate of alveolar macrophages, p_j and q_j are respectively the transfer rate to the mucociliary escalator and the death rate of macrophages belonging to class j, X_0 is the number of free quartz particles caused in the alveolar region by inhalation plus release via the necrosis of alveolar macrophages and neutrophils, $k_{j\,j-1}$ is the phagocytosis rate coefficient for alveolar macrophages of class j–1 (ie, the average probability that a given macrophage from load class AM_{j-1} will ingest a free quartz particle in time dt). The system of differential equation 3 is also used to model the process of phagocytosis by neutrophils, and the process is shown diagrammatically in figure 2.

Constraints. As the phagocytosis of silica particles progresses, the cytotoxic effect of quartz on alveolar macrophages renders them less mobile and, consequently, their capacity for further phagocytosis is reduced. If s is the number of quartz particles representing the sublethal dose ingested by an alveolar macrophage, then we can assume that the phagocytosis rates (k) for macrophages with fewer than s particles is the same for all; for alveolar macrophages with more particles than s, the rate of phagocytosis diminishes as the load increases:

$$k_{10} = k_{21} = \ldots\ k_{s\,s-1};\ k_{s+1\,s} > \ldots > k_{n\,n-1}. \qquad \text{equation 4}$$

Similarly, the transfer rates depend on particle load:

$$p_0 = p_1 = \ldots = p_s > p_{s+1} > \ldots > p_n. \qquad \text{equation 5}$$

The death rate of macrophages is also expected to increase with the number of quartz particles ingested once the sublethal number of quartz particles ingested has been reached, and again a similar type of relationship is assumed:

$$q_0 = q_1 = \ldots = q_s < q_{s+1} < \ldots\ q_n. \qquad \text{equation 6}$$

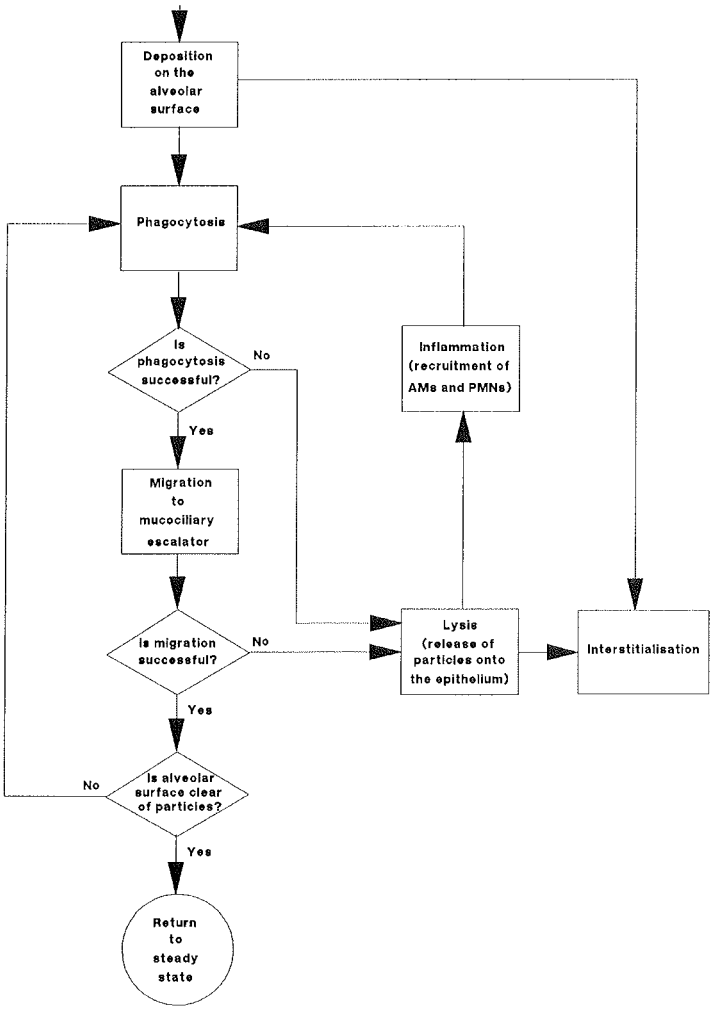

Figure 1. Phagocytosis, migration to the mucociliary escalator, interstitialization, and inflammation. (AM = alveolar macrophages, PMN = neutrophils)

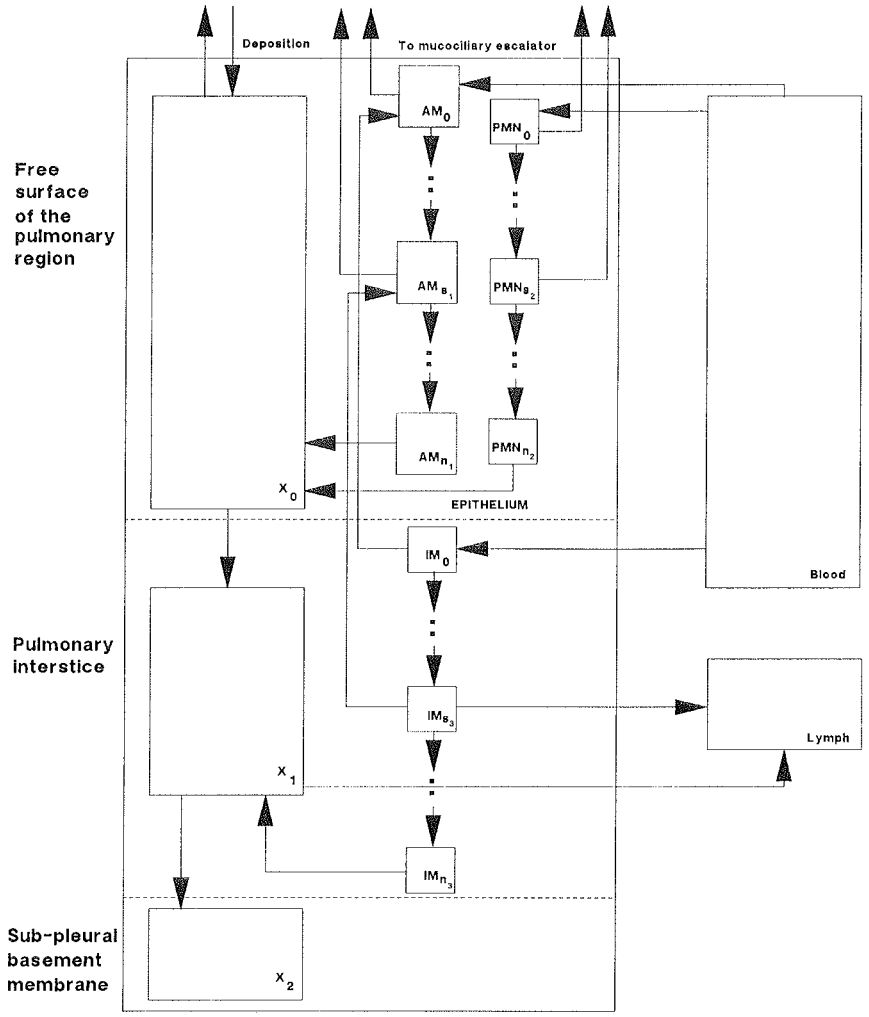

Figure 2. Mathematical model for phagocytosis and inflammation after the inhalation of quartz particles. (X_0 = free quartz particles on the alveolar surface, Am_j = alveolar macrophages of load-class j, $0 \leq j \leq n_1$, n_1 = maximum number of quartz particles ingested per alveolar macrophage, s_1 = critical number of quartz particles ingested per alveolar macrophage, Blood = blood compartment, PMN_j = neutrophils of load-class j, $0 \leq j \leq n_2$, n_2 = maximum number of quartz particles ingested per neutrophil, s_2 = critical number of quartz particles ingested per neutrophil, X_1 = free quartz particles in the interstitium, Im_j = interstitial macrophages of load-class j, $0 \leq j \leq n_3$, n_3 = maximum number of quartz particles ingested per interstitial macrophage, s_3 = critical number of quartz particles ingested per interstitial macrophage, lymph = lymph node compartment, X_2 = free quartz particles in the subpleural basement membrane)

Modeling the inflammatory recruitment of alveolar macrophages and neutrophils. Macrophages and neutrophils with more than their respective sublethal dose of quartz particles will be in distress. The chemotactic signal released by these phagocytes is

$$G = l_1 \sum_{i=s_1+1}^{n_1} AM_i + l_2 \sum_{i=s_2+1}^{n_2} PMN_i, \qquad \text{equation 7}$$

where l_1 and l_2 are the chemotactic signals released by each alveolar macrophage and neutrophil, s_1 and s_2 are the sublethal numbers of quartz particles for alveolar macrophages and neutrophils, and n_1 and n_2 are the maximum numbers of quartz particles ingested by alveolar macrophages and neutrophils, respectively.

The inflammatory recruitment for alveolar macrophages can be described in a functional form as:

$$R_{AM} = \frac{(R_{1\max} - R_{\min})}{[\frac{k_1}{G} + 1]} + R_{\min}, \qquad \text{equation 8}$$

and similarly, for neutrophils:

$$R_{PMN} = \frac{(R_{2\max})}{[\frac{k_2}{G} + 1]}, \qquad \text{equation 9}$$

R_{1max} and R_{2max} are the maximum recruitment rate for alveolar macrophages and neutrophils (10). R_{min} is the minimum recruitment rate for alveolar macrophages required when the AM population is in a steady state. The k's are constants determining how fast the recruitment rate approaches its maximum value. A differential equation for the kinetics of the total alveolar macrophage (AM) population can be derived by adding all the individual equations of the system 3:

$$\frac{dAM}{dt} = \sum_{i=0}^{n} \frac{dAM_i}{dt} = R_{AM} - \sum_{i=0}^{n} (p_i + q_i) AM_i \qquad \text{equation 10}$$

The solution to equation 10 can be compared with data of alveolar macrophage kinetics available from instillation and inhalation studies (11).

Interstitial model

The continuing presence of quartz particles on the epithelium will increase their likelihood of being transferred to the interstitium. As quartz particles are transported, they are confronted by interstitial macrophages. Equation 3 is also used to describe the phagocytosis of quartz particles by interstitial macrophages. Fibroblast

cells (N_f) proliferate while they are activated by the chemotactic signals produced by distressed interstitial macrophages:

$$\frac{dN_f}{dt} = k_3 \sum_{i=s_3+1}^{n_3} IM_i, \qquad \text{equation 11}$$

where s_3 and n_3 are the sublethal doses of quartz and the maximum number of silica particles ingested by an interstitial macrophage and k_3 is the chemotactic signal released per interstitial macrophage cell. These fibroblast cells are also activated to produce collagen leading to interstitial fibrosis.

Results

Experimental rat studies on deposition and clearance were carried out at the Institute of Occupational Medicine (5, 12). The purpose of these studies was to determine the retention and clearance of cytotoxic and inert dusts such as quartz and titanium dioxide and the cellular response from the alveolar region of the lung following the inhalation of these dusts.

The quartz burdens on lungs and lymph nodes (12), together with the alveolar macrophage and neutrophil numbers in the bronchoalveolar lavage (BAL) fluid, were used to test the current model. The strategy for simulation is (i) to obtain as many estimated parameters from the literature as possible (10, 13, 14, 15); (ii) to use one data set of the aforementioned experiments — the exposure of rats to quartz at 50 mg · m^{-3} — to estimate the remaining parameters of the model; (iii) to develop a complete estimated parameter set to be used in simulations of other exposure situations; and (iv) and to compare the results with the experimental data (ie, exposure to 1, 10 and 30 mg · m^{-3}). The aim of this strategy was to reduce the number of parameters to be estimated from the data set to a minimum. Figures 3 and 4 show the inflammatory recruitment of alveolar macrophages and neutrophils after the inhalation of quartz at 10 and 50 mg · m^{-3} and the simulation of this recruitment by the model. Similarly, the results from the simulations and the experimental data for the lung burdens and lymph node burdens are shown in figures 5 and 6. Additional details can be obtained from our earlier work (16).

The simulations of the alveolar macrophage and neutrophil response to the deposition of quartz, as well as the time course of lung and lymph node burden of this dust under different exposure levels, have compared well with the data from experimental studies carried out at the Institute of Occupational Medicine. However, the current model is one of a very complex system; thus the problem of over-parameterization is hard to avoid. Nonetheless the main aims of the model are (i) to offer a mathematical description of the hypotheses regarding the mechanisms of this system (eg, the phagocytosis rate or the inflammatory recruitment rate) which can be refuted, verified, and measured by further experimental investigations and (ii) to identify important areas in the system for which further investigations are needed. Thus it is hoped that this exercise will stimulate further experimental studies aimed at identifying the complete model.

Concluding remarks

The process of phagocytosis of quartz particles by alveolar macrophages and neutrophils is described as a system of differential equations. A Michealis-Menten type of equation is used to model the inflammatory recruitment of alveolar macrophages and neutrophils. The same types of differential equations are also used to describe the movement of free quartz particles to the interstitium and their subsequent phagocytosis by interstitial macrophages. These equations, together with the parameter values found in the literature or estimated from experimental data (10, 13, 14, 15) provide a framework for the simulation of data for the retention and clearance of quartz particles in the alveolar region. This mechanistic model elucidates the effects of impaired phagocytosis and chronic inflammation leading to the development of interstitial fibrosis. The consequences of phagocytosis such as the release of

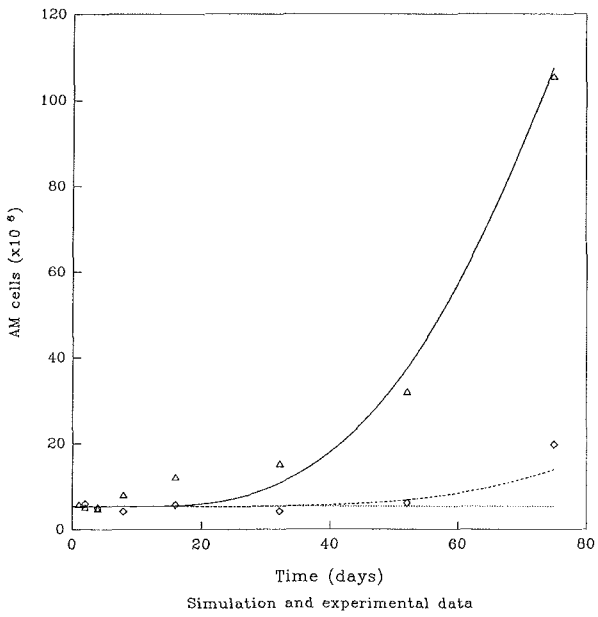

Figure 3. Alveolar macrophage (AM) population following the inhalation of quartz at 50 and 10 mg · m^{-3}. (△ = concentration 50 mg · m^{-3}, ◇ = concentration 10 mg · m^{-3}, — = simulation at 50 mg · m^{-3}, - - - = simulation at 10 · mg m^{-3}, ··· = steady state population)

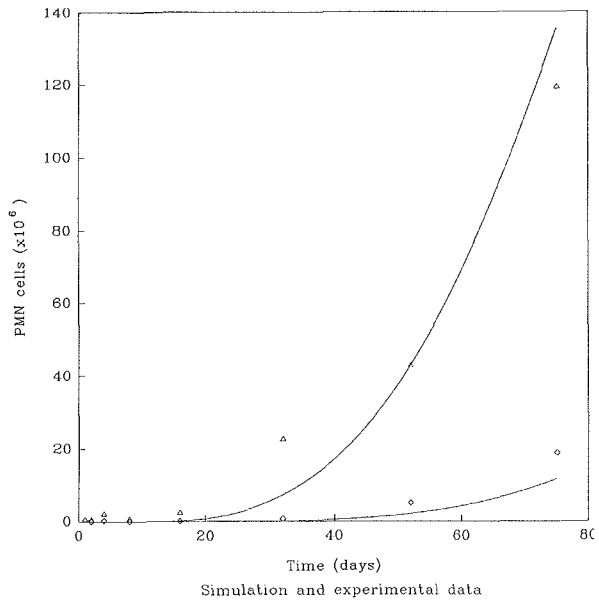

Figure 4. Neutrophil population following the inhalation of quartz at 50 and 10 mg · m^{-3}. (△ = concentration 50 mg · m^{-3}, ◇ = concentration 10 mg · m^{-3}, — = simulation at 50 mg · m^{-3}, ··· = simulation at 10 mg · m^{-3})

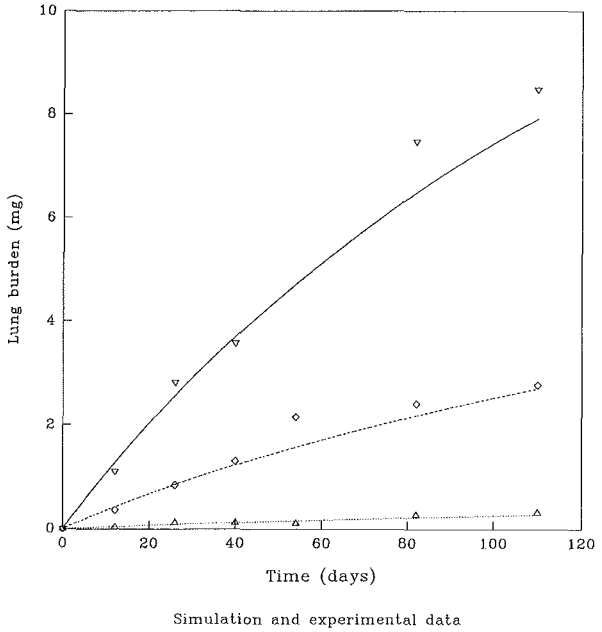

Figure 5. Lung burden following the inhalation of quartz at 1, 10 and 30 mg · m^{-3}. (○ = concentration 30 mg · m^{-3}, ◇ = concentration 10 mg · m^{-3}, △ = concentration 1 mg · m^{-3}, — = simulation at 30 mg · m^{-3}, - - - = simulation at 10 mg · m^{-3}, ··· = simulation at 1 mg · m^{-3})

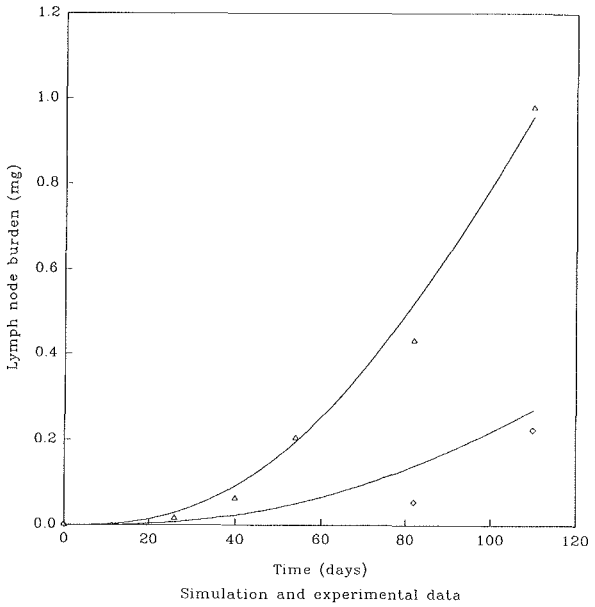

Figure 6. Lymph node burden following the inhalation of quartz at 10 and 30 mg m^{-3}. (△ = concentration 30 mg · m^{-3}, ◇ = concentration 10 mg · m^{-3}, — = simulation at 30 mg · m^{-3}, ··· = simulation at 10 mg m^{-3})

oxidant radicals and proteases can be quantified readily. The damage to type I epithelial cells by oxidant stress and the replacement of these cells by type II cells can also be modeled. Such modeling will form the basis for a mechanistic model of the development of silica-related carcinomas.

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Section 3. Epidemiology of silica, silicosis and cancer

Scand J Work Environ Health 1995;21 suppl 2:55—7

Silicosis surveillance in Ontario from 1979 to 1992

by Murray M Finkelstein, MD[1]

Finkelstein MM. Silicosis surveillance in Ontario from 1979 to 1992. *Scand J Work Environ Health* 1995;21 suppl 2: 55—7.

This paper reports the detection rates of silicosis among silica-exposed persons first exposed to dust in 1950 or later and still employed in 1979 or later in the province of Ontario. The rate varied strongly with latency, being less than two new cases per 10 000 examinations during the first two decades from first exposure, reaching two new cases per 1000 examinations at 27 years from first exposure, and averaging between two and four new cases per 1000 examinations thereafter. A Poisson regression analysis found that the silicosis rate in the interval after 30 years from first exposure was more than 16 times higher than the rate prior to 20 years from first exposure. There was no significant difference in the diagnosis rates among the workers in the mining, primary metal, and nonmetallic mineral industries sectors. The rate of silicosis was higher among smokers than among never smokers (rate ratio 1.54).

Key terms foundry workers, medical surveillance, miners, occupational diseases, screening, silica, smoking.

Exposure to crystalline silica occurs in a variety of industries, including the mining of metal ores, minerals, and coal; the manufacture of stone, clay, and glass products; and iron, steel, and nonferrous foundries. Medical programs to assist in the control of silicosis frequently include periodic chest radiographs and lung function testing. The National Institute for Occupational Safety and Health in the United States, for example, recommends that chest X-rays and pulmonary function testing be carried out prior to employee placement and at least once every three years thereafter (1).

The Province of Ontario, Canada, is one of a few jurisdictions operating a governmental surveillance program for workers in dusty industries. The program has operated for almost 70 years, utilizing both fixed examining stations in the major centers and a mobile service to remote industrial sites and mines. Chest radiographs were the primary screening modality for workers exposed to silica. In the 1960s, pulmonary function testing and a short respiratory questionnaire were added. The frequency of surveillance for silicosis has been determined largely by traditional practice. For many years examinations were carried out in a one- to two-year cycle. The Ontario silica regulation of 1983 specified radiographic examinations at least once every two years. It is the aim of this paper to report on the detection rates of silicosis in the Ontario surveillance program and to discuss the influence of such factors as time from first exposure, industrial sector, and smoking.

Subjects and methods

The Ontario surveillance program has included both miners and workers in dusty surface industries. Some miners attended clinics in the larger mining communities, while others from remote sites were examined by surveillance teams using mobile vans. Surface industry workers were generally surveyed by staff using the vans. Full-sized 14 × 17 inch radiographs have been used in the clinics since 1970. Miniature radiographs were used in the vans until 1980 when they were replaced by full-sized films. Full-sized radiographs were obtained prior to 1980 for workers whose prior radiographs suggested abnormalities. Staff radiologists interpreted radiographs according to the 1930 Johannesburg Conference Report (2). This procedure is a diagnostic, rather than descriptive, coding scheme for pneumoconiosis. The suspicion of possible radiographic pneumoconiosis is recorded as Ontario code 4, sometimes called "dust effects." The definite radiographic diagnosis of silicosis is marked code 5. In the last decade, these ratings have been supplemented by the current codes of the International Labour Organisation (ILO) (3). For the purposes of this report, only the older pneumoconiosis codings were used. Although the radiographs were not reinterpreted for this analysis, a sample of films was reread by two experienced readers. A comparison of their interpretations with those made by the original readers is shown in table 1. Over 98% of the 1584 films not coded as silicosis by the original coders were read as ≤ 0/1 by both readers, and 78% of the films coded originally as silicosis were read as ≥ 1/1 by one or both of the readers. Seven of 46 (15%) films originally coded as silicosis were read as ≤ 0/1 by both readers. This result would suggest that cases of silicosis were unlikely to have been missed by the original coders, but that some opacity codings would not have been so coded according to the ILO scale.

The results of the examinations were traditionally recorded in a card file. In 1979, current results for workers in surface industries began to be entered into a computer data base, followed in 1983 by the results for miners. In 1992, this data base contained information on 68 701 silica-exposed persons who were first exposed to dust in 1950 or later and were still employed in 1979 or later. There were 211 workers diagnosed with silicosis.

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Table 1. Codings of the International Labour Organisation for a sample of study films.

Reader 2	Reader 1		
	≤ 0/1	1/0	≥ 1/1
Subjects not coded as silicotic by original readers (N = 1584)[a]			
≤ 0/1	1560	10	1
1/0	5	3	1
≥ 1/1	1	2	1
Subjects coded as silicotic by original readers[a] (N = 46)[b]			
≤ 0/1	7	0	2
1/0	1	2	8
≥ 1/1	1	1	24

[a] 1560 of the 1584 (98%) coded ≤ 0/1 by both readers.
[b] 36 of the 46 (78%) coded 1/1 or more by both readers; 7 of the 46 (15%) coded 0/1 or less by both readers.

Table 2. Distribution of the subjects and cases by industrial classification (latency ≥ 14 years)

Industrial classification[a]	Subjects under surveillance (N)	Number with silicosis diagnosis	Crude rate (per 1000)
Mines and quarries			
Placer gold (051)	304	—	0.0
Gold quartz (052)	3 493	22	6.3
Copper-gold-silver (053)	208	3	14.4
Nickel-copper (054)	1 665	3	1.8
Silver-cobalt (055)	115	—	0.0
Uranium (057)	2 296	40	17.4
Iron (058)	480	1	2.1
Other metal (059)	469	2	4.3
Stone quarries (083)	165	1	6.1
Sand pits or quarries (087)	413	3	7.3
Contract drilling (098)	541	3	5.5
Miscellaneous (099)	416	1	2.4
Total	10 565	79	7.5
Food and beverage (101—147)	96	—	0.0
Rubber industries (161—169)	246	1	4.1
Primary metal industries			
Iron and steel mills (291)	3 581	19	5.3
Iron foundries (294)	1 692	17	10.0
Smelting and refining (295)	11	—	0.0
Aluminum rolling, casting, extruding (296)	949	1	1.1
Copper and alloy rolling, casting (297)	429	2	4.7
Metal rolling NES (298)	325	1	3.1
Total	6 987	40	5.7
Metal fabricating industries (301—309)	489	4	8.2
Machinery industries (311—318)	742	2	2.7
Transportation equipment (321—329)	1 319	1	0.8
Electrical products (331—339)	239	—	0.0
Nonmetallic mineral products			
Cement manufacture (341)	678	1	1.5
Lime manufacture (343)	86	—	0.0
Gypsum products (345)	239	1	4.2
Concrete products (347)	378	3	7.9
Ready-mix concrete (348)	25	—	0.0
Clay products (351)	922	6	6.5
Refractories manufacture (352)	246	1	4.1
Stone products (353)	226	1	4.4
Mineral wool (354)	15	—	0.0
Glass and products (356)	418	—	0.0
Abrasives (357)	365	1	2.7
Other nonmetallic minerals (359)	34	—	0.0
Total	3 632	14	3.9
Refineries and chemicals (365—379)	798	1	1.3
All industries	25 113	142	5.6

[a] Code of the Standard Industrial Classification in parentheses.

The diagnosis rate varied strongly with the length of time since first exposure; only three workers were diagnosed with < 14 years from the start of exposure. The subjects for this analysis included 26 403 workers with ≥ 14 years from first exposure while still under surveillance.

For each subject, the date of birth, the year of first dust exposure, the date of first diagnosis of silicosis (or the date of last examination if silicosis was not diagnosed), industrial sector, and smoking habits (ever or never cigarette smoker) were abstracted. Life-table methods (4) were used to calculate silicosis detection rates during each year from first exposure. Each person entered the calculation in 1979 (surface sector), in 1983 (mining sector), or in his year of first exposure, whichever came later. We did not determine whether each subject had an examination in any given year. Rather, it was assumed that an examination in any year prior to the one in which silicosis was found would not have been diagnosed as silicosis and included the subject in the denominator of that year. Subjects were withdrawn from the denominator in the year after they were diagnosed with silicosis or the year after their last examination. The cut-off date for follow-up was July 1992.

Poisson regression analysis was used to model silicosis rates while adjusting simultaneously for latency, industrial sector, and smoking (4).

Results

Silicosis rate by sector. Table 2 shows the distribution of the study population and the number with silicosis for the major industrial sectors. The crude rate (unadjusted for latency or smoking) is also listed in table 2.

Silicosis rate by time from first dust exposure. The detection rate of new cases of silicosis was strongly dependent upon the time from first exposure. The detection rate was less than two new cases per 10 000 examinations during the first two decades from first exposure, reached 20 new cases per 10 000 examinations at 27 years from first exposure, and averaged between 20 and 40 new cases per 10 000 examinations thereafter. Figure 1 shows how the cumulative probability of silicosis varied in the mining and primary metal industries according to time from first dust exposure.

Poisson regression analysis of silicosis rates. Poisson regression analysis was used to compare the silicosis rates of the major sectors (mining, primary metal industries, and nonmetallic mineral products) controlling for latency and smoking. The results are shown in table 3. The analysis confirmed that rates were strongly dependent upon the interval from first exposure. The silicosis rate in the interval after 30 years from first exposure was more than 16 times higher than the rate in the period prior to 20 years from first exposure. The silicosis rates were similar in the mining and primary metal sectors. The rate of silicosis was higher among the smokers than among the never smokers (rate ratio 1.54), but the difference was not statistically significant.

Discussion

Some 69 000 silica-exposed Ontario workers have had at least one screening examination since 1979, and between 11 and 26 new cases of silicosis have been diagnosed annually. As would be expected, the detection rate varied strongly with latency. The detection rate was less than two new cases per 10 000 examinations during the first two decades from first exposure, reached about 20

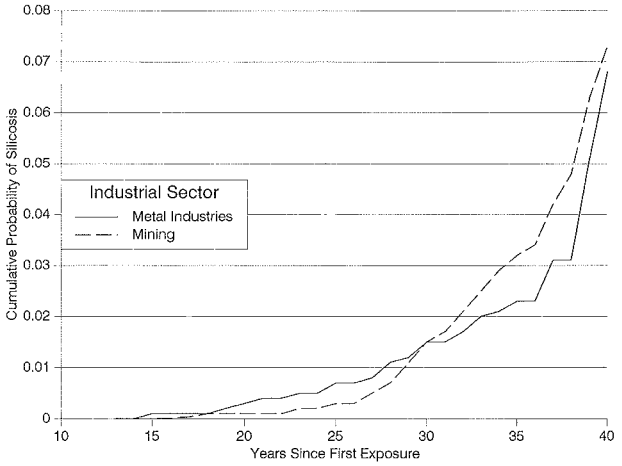

Figure 1. Cumulative probability of silicosis diagnosis versus time from first dust exposure among workers in the mining and primary metal industries under surveillance in Ontario.

new cases per 10 000 examinations at 27 years from first exposure, and thereafter averaged between 20 and 40 new cases per 10 000 examinations.

There were no substantial differences between the major industrial sectors. Figure 1 shows the cumulative probability, among miners and primary metal industry workers, of developing silicosis up to 40 years from first exposure. The cumulative probability was 1.5% for miners and 1.6% for workers in primary metal industries at 30 years from first exposure and was 3.2% for miners and 2.7% for workers in the metal sector at 35 years from first exposure.

It has been shown that asbestos workers who smoke are more likely to develop radiographic asbestosis (5). Since smoking information was available for 98% of the subjects in the study, it was possible to examine whether smokers were more likely to develop silicosis than nonsmokers. The rate of silicosis was 54% higher among the smokers, and the difference was almost statistically significant. It is plausible that a true difference exists but that, because of the small number of nonsmoking silicotics, this study may not have had the power to detect a difference. If smoking is a risk factor for the diagnosis of silicosis, it would explain, in part, the increased risk of lung cancer observed among workers in silicosis registers.

Table 3. Poisson regression analysis of the silicosis rates.

Variable[a]	Rate ratio	95% confidence interval
Time from first exposure		
14—19 years	1.0	
20—24 years	2.7	1.4—5.5
25—29 years	8.5	4.5—15.9
30—34 years	16.2	8.7—30.3
35—39 years	28.7	14.2—57.9
Industrial sector		
Mining	1.0	
Primary metal industries	1.2	0.8—1.8
Nonmetallic mineral industries	0.7	0.4—1.2
Smoking		
Ever smokers versus never smokers	1.54	0.9—2.6

[a] All variables included in the model simultaneously.

Acknowledgments

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Incidence of silicosis among ceramic workers in central Italy

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The incidence of radiological silicosis was studied among 2480 male workers employed in the ceramics industry. The subjects entered the surveillance program during 1974—1987 and were followed through 1991 with annual chest radiographs. The cumulative risk of silicosis (1/1 or greater; p,q,r) reached 48% (95% confidence interval 41.5—54.9) after 30 years of employment. In a multivariate Cox's proportional hazards model, the effect of duration of exposure increased linearly up to the category of 25—29 years; an extremely high hazard risk of 14.6 was found among those with 30 years or more of exposure in comparison with those employed 10 years or less. Smoking habit also significantly contributed to the model, although its role in the biological process is unclear. In conclusion, exposure to silica dust has been associated with a high incidence of silicosis among ceramics workers. The risk estimates are consistent with the recent findings of silicosis incidence among South African gold miners.

Key terms epidemiology, longitudinal study, pneumoconiosis, silica dust, smoking.

Several epidemiologic and pathogenetic aspects of silicosis are well known (1, 2). However, new issues in the field of silicosis have motivated novel scientific controversies. A relationship between silica exposure, silicosis, and lung cancer has been debated (3—5). It has been suggested that the true risk of silicosis is currently underestimated by routine statistics (6). Concerns about the adequacy of current silica standards for preventing silicosis have been raised (7). A considerable number of cases of both silicosis and lung cancer has been predicted to occur in the working population, even at the exposure levels currently permitted in developed countries (8).

Table 1. Industrial hygiene data of respirable silica exposure in ceramic factories of Civitacastellana. (GM = geometric mean, GSD = geometric standard deviation)

Occupation title or location	Samples (N)	Respirable silica (mg · m^{-3})		
		GM[a]	GSD[b]	Range
Sanitary ware				
Molder	40	0.18	2.54	0.02—0.67
Inspection	22	0.26	1.84	0.13—0.60
Mixer	19	0.12	1.95	0.05—0.24
Sprinkler	23	0.24	2.83	0.06—0.89
Warehouseman	13	0.01	1.56	0.01—0.02
Furnace operator	15	0.44	1.68	0.26—0.73
Crockery and pottery				
Molder	28	0.02	2.06	0.01—0.06
Mixer	21	0.04	2.80	0.01—1.14
Painter	37	0.01	2.19	0.01—0.06
Warehouseman	17	0.02	2.95	0.01—0.04
Furnace operator	16	0.02	2.80	0.01—0.04

We present the results of routine medical examinations offered to ceramics workers in an area of central Italy. Surveillance was conducted to describe the rate of radiological changes typical of silicosis. This paper elucidates the role of various factors — duration of exposure, age at first exposure, period of exposure, and cigarette smoking — in the development of radiographic abnormalities.

Subjects and methods

Setting and data collection. The ceramics industry located in Civitacastellana (about 16 000 inhabitants) has been one of the leading production sites in central Italy during recent decades. It employs about 3000 workers in more than 100 factories. In a case-referent study conducted in this town, an increased risk of lung cancer was found among ceramics workers, especially among those receiving disability compensation for silicosis (9).

Exposure to high levels of silica dust still occur in the production of sanitary ware and crockery in Civitacastellana. An industrial hygiene survey (personal samples of respirable dusts) was conducted from 1989 to 1992 in the 10 largest ceramics factories of the area. Gravimetric samples of total dust were collected and silica dust concentrations were measured using X-ray diffraction. The results of the survey are shown in table 1, separately for the sanitary-ware industry and for crockery manufacturers. The average quartz content in the raw material (dry weight) utilized in sanitary ware is about 33 (SD 4)%, and the average respirable dust concentration was about 2 mg · m^{-3}. In 80% of the samples, the concentration level of respirable silicon dioxide exceeded the

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0.1 mg · m^{-3} threshold limit value recommended by the American Conference of Governmental Industrial Hygienists. In crockery manufacturing, the raw material contains 22 (SD 3)% free silica, and the work process involves wet phases. The average level of respirable dust was 0.8 mg · m^{-3}, and only in a few samples did the respirable silica concentration exceed the recommended level. Industrial hygiene data for the past are scant (10) though it can be assumed that silica dust exposure 20 to 30 years ago was three- to fivefold higher than nowadays.

A program of health surveillance was set up in 1974 by the Local Health Unit of Civitacastellana. The follow-up has been continued up to December 1991. The program included an annual medical examination and a standard posteroanterior chest radiograph for all of the exposed workers. The films were classified throughout the years by a reader at the radiology department according to the method recommended by the International Labour Office (ILO) at the time the radiographs were taken (11, 12). For each worker information was available regarding employment history and health status. The following data were collected: gender, year of first employment in the ceramics industry, age at first exposure, year first radiograph was taken and age at that time, initial smoking habits, and readings of all the radiographs made over the years (profusion level, size and type of small opacities). In addition, the subjects were classified according to the type of ceramics industry (crockery and artistic ware, sanitary ware) in which they had spent their career. Those persons who could not be classified because of a change from one sector to another, or because of a lack of relevant data, were allocated into a "mixed and unknown" category.

Data analysis. All male subjects whose chest radiographs were classified with a profusion level equal to 0/0 in the first examination during the period 1 January 1974—31 December 1987 were enrolled in the cohort. The incidence of radiological signs of silicosis up to 31 December 1991 was evaluated. A subject was considered a case when the criterion of a profusion of 1/1 or greater was observed and the radiological appearances were small, rounded opacities (p,q,r). The initial date at which the category 1/1 was identified was considered the time of diagnosis. Since small irregular opacities (s,t,u) could be interpreted as radiological shadows of pulmonary fibrosis caused by cigarette smoking (13, 14), a subject who reached the critical profusion level (1/1), but with only irregular opacities, was not considered a case.

The cumulative incidence of radiological changes was estimated using EGRET software (15), which produces Kaplan-Meier product-limit estimates of the survival curve. The cumulative risk was estimated according to the complement of survival probability; it was evaluated in respect to age and duration of exposure (in this study, equivalent to time since first exposure).

To evaluate the factors associated with the incidence of silicosis, the Cox's proportional hazards model was used to estimate relative risks in a multivariate analysis (16, 17). Each individual contributed from the start of follow-up to the time when a diagnosis of silicosis was made, or to the end of the follow-up period.

In order to evaluate the effect of duration of exposure on the incidence of chest abnormalities, we created a time-dependent variable for exposure duration. This time-dependent variable was factored to obtain a reference category (less than 10 years) and five five-year strata of increasing duration of exposure. The potential for violating the proportional-hazards assumption was assessed by (i) comparing the survival curve of each level of a variable with the survival curve of the reference group for that variable and (ii) fitting models containing an interaction term between the variable of interest and a log-time variable.

Results

Altogether 2980 male subjects were examined in the period 1974—1991; 161 had equivocal signs of pneumoconiosis (0/1 or 1/0), whereas 15 had a profusion level of 1/1 or more. From a total of 2804 candidate cohort members, 2480 workers (88.1%) had at least one more chest radiograph and were included in the analysis; those lost to follow-up were likely to have left the industry. Table 2 shows the descriptive characteristics of the subjects who participated in the study. The cohort members were 29.0 years old on the average and had an average duration of exposure of 4.6 years at the start of follow-up. There were 73.8% ever smokers. The workers were followed for an average of 8.3 years with an average of 7.8 chest radiographs. A total of 231 new cases of silicosis developed during the study period; the mean duration of follow-up among the cases was 7.3 years. The mean age at silicosis onset was 40.8 (SD 7.1) years; 64.1% of the cases were detected among subjects manufacturing sanitary ware. There were also 82 subjects who developed 1/1 small irregular opacities and were censored at the time of such a diagnosis.

The unadjusted cumulative risk of silicosis according to age and duration of exposure are shown in figures 1 and 2. The cumulative risk was 1.3% [95% confidence interval (95%CI) 0.8—2.4] for subjects aged 30 years, 14.4% (95% CI 12.1—17.1) at 40 years, and 37.0% (95% CI 33.3—42.0) at 55 years of age. The cumulative risk increased from 3.4% (95% CI 2.5—4.5) after 10 years of exposure to 20.4% (95% CI 17.2—24.1) after 20 years, and it reached 48% (95% CI 41.5—54.9) after 30 years of exposure.

Table 2. Descriptive characteristics of ceramic workers with a base line profusion level of 0/0 in the first X ray.

Characteristic	Number[a]	Percentage
Year of first exposure		
Before 1970	452	18.2
1970—1987	2028	81.8
Type of industry		
Crockery	502	20.2
Sanitary ware	1042	42.0
Mixed and unknown	936	37.7
Age at first exposure (years)		
≤ 19	826	33.3
20—24	710	28.6
≥ 25	944	38.1
Duration of exposure in first X ray (years)		
<1	347	14.0
1—4	1332	53.7
5—9	443	17.9
10—14	173	7.0
15—19	90	3.6
≥ 20	95	3.8
Smoking habit		
Nonsmokers	649	26.2
Ex-smokers	160	6.5
Smokers	1671	67.4

[a] Total number = 2480.

Figure 1. Cumulative risk of silicosis among ceramics workers in relation to age, as estimated by the Kaplan-Meier method.

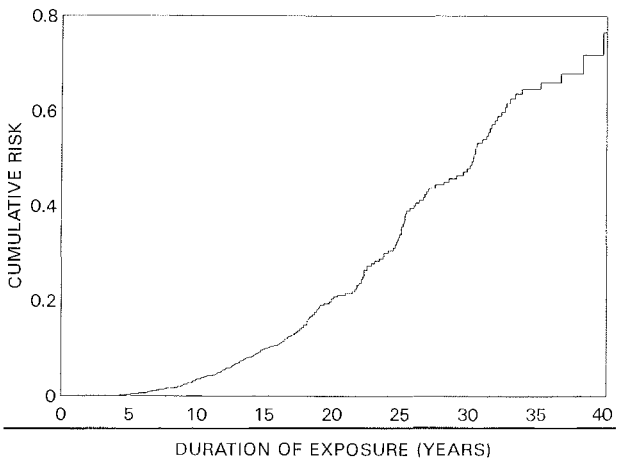

Figure 2. Cumulative risk of silicosis among ceramics workers in relation to duration of exposure, as estimated by the Kaplan-Meier method.

Several Cox's models were fitted to the data set. The results for models of increasing complexity are shown in table 3. Both age at first exposure and duration of exposure were strongly related to the risk of silicosis. Those employed while aged 20—24 years and those older than 24 years when first employed showed a lower risk of silicosis in comparison with subjects employed at a younger age (model 1). The effect of duration of exposure seemed to increase more or less linearly up to the category of 25—29 years, whereas an extremely high hazard ratio (HR) was found for those with 30 years or more (HR 14.6) (model 2). The evaluation of the joint contribution of age at first exposure and duration of exposure on the risk of silicosis was hampered by the strong inverse correlation between the two variables. The simultaneous inclusion of both variables resulted in higher coefficients for duration of exposure, whereas the contribution of age at the start of exposure was not statistically significant. Therefore, in all the subsequent models only duration of exposure was used.

Besides exposure duration, the type of industry and smoking habit also made a significant contribution to the model. The risk was more than doubled among those manufacturing sanitary ware, as well as among those with mixed or unknown exposure (model 3, table 3). There was a statistically significant increased risk among active smokers (HR 1.8), whereas the increased risk for former smokers was not significant (model 4). Interaction terms for smoking and duration of exposure were then added to the model. The interaction term for active smoking and exposure duration was statistically significant (P = 0.037), but it indicated that the combination of the two factors was less than multiplicative. The coefficients for duration of exposure among the nonsmokers and smokers were very similar, with the exception of the last

Table 3. Results of the Cox's proportional analysis. Hazard ratios (HR) and 95% confidence intervals (95% CI) from different models including various factors.

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age at first exposure (years)										
≤ 19	1.0	.	.	.	.	.	.	.	.	.
20—24	0.6	0.4—0.8	.	.	.	.	.	.	.	.
≥ 25	0.2	0.2—0.3	.	.	.	.	.	.	.	.
Duration of exposure (years)										
<10	.	.	1.0	.	1.0	.	1.0	.	1.0	.
10—14	.	.	3.3	2.2—4.8	3.3	2.3—4.9	3.3	2.3—4.9	3.0	2.0—4.5
15—19	.	.	3.4	2.2—5.2	3.4	2.2—5.2	3.3	2.1—5.0	2.8	1.7—4.4
20—24	.	.	4.7	2.9—7.7	4.7	2.9—7.6	4.5	2.8—7.3	3.3	1.8—5.9
25—29	.	.	7.4	4.4—12.4	6.7	3.9—11.2	6.6	3.9—11.2	4.7	2.5—8.9
≥ 30	.	.	14.6	8.6—24.9	13.4	7.8—22.9	13.2	7.7—22.7	9.3	4.8—17.9
Type of industry										
Crockery	.	.	.	.	1.0	.	1.0	.	1.0	.
Sanitary ware	.	.	.	.	2.3	1.5—3.5	2.2	1.4—3.3	2.1	1.4—3.3
Mixed and unknown	.	.	.	.	2.5	1.5—4.0	2.3	1.4—3.8	2.3	1.4—3.7
Smoking habit										
Nonsmokers	.	.	.	.	.	.	1.0	.	1.0	.
Ex-smokers	.	.	.	.	.	.	1.6	0.9—2.8	1.5	0.9—2.7
Smokers	.	.	.	.	.	.	1.8	1.2—2.6	1.8	1.2—2.6
Period of first exposure										
Before 1970	.	.	.	.	.	.	.	.	1.0	.
1970—1987	.	.	.	.	.	.	.	.	0.7	0.5—1.0

category (≥ 30 years), for which the estimated HR was 30.4 (95% CI 12.4—74.7) for nonsmokers and 8.2 (95% CI 3.9—17.1) for smokers.

Finally, employment in more recent years (after 1969) was related to a decreased risk of silicosis (HR 0.7, 95% CI 0.5—1.02, P = 0.06) when all the other significant variables were kept in the model (model 5, table 3). This comparison is somehow suboptimal since both duration of exposure and time since first exposure were clearly shorter for those who entered work in the last two decades. This finding is also reflected in the change in the relative risk estimated for duration of exposure.

Discussion

The study indicates that silicosis is still occurring among workers in the ceramics industry, especially among those manufacturing sanitary ware. Duration of exposure, as a surrogate of cumulative dust exposure, strongly influenced the occurrence of the disease. An effect of age at first exposure was not detected when adjustment was made for exposure duration. The risk seems to be decreasing among those first exposed after 1969, even when the relatively shorter duration of exposure is taken into account.

Smoking seemed to be a determinant of a radiological diagnosis of silicosis in this study. Although it could be possible that smoking reduces the pulmonary clearance mechanism and thus enhances the deposition of particles and the risk of silicosis, the evidence to support such a hypothesis is scant (13). Paradoxically, in a necropsy study among gold miners, Hessel et al (17) showed a slightly inverse relationship between smoking and silicotic changes of the lung parenchyma and no association of smoking with silicosis of the hilar lymph nodes. These findings clearly make a true smoking-silicosis association less likely. The possibility remains that smoking causes a condition which is mistaken for silicosis in the diagnostic procedure. Weiss has recently shown that the appearance of small irregular shadows may be an indication of peribronchial fibrosis associated with pathological changes of chronic bronchitis among smokers (12). Among Vermont granite workers (17), the prevalence of abnormal chest films (mainly irregular opacities) was related to both duration of exposure to granite dust and to cigarette smoking. In this study there was a significant interaction between the two factors in that a smaller effect of duration of dust exposure was found among heavy smokers. Cigarette smoking was also found to be a risk factor for the diagnosis of silicosis among workers in Ontario, Canada. (See Finkelstein, this issue.) It could be hypothesized that irregular shadows can be misinterpreted as the small rounded opacities of silicosis during routine radiographic examinations in worker surveillance.

This study has limitations that should be considered. First, the chest radiographs were performed for worker surveillance and not for epidemiologic purposes. As a consequence, only one reading was available for each film, and there was no possibility to evaluate how the changes in readers affected the results. Random variability tends to obscure true relationships; therefore the positive associations that we found are unlikely to be due to poor data quality.

Second, industrial hygiene data were not available for the past, and cumulative respirable silica exposure could not be estimated. It is difficult, therefore, to compare our data with that of the available epidemiologic literature. It may be interesting to note, however, that, in data on the Vermont granite workers (18), a 30% probability of developing silicosis after 46 years of exposure to respirable silica concentrations of 0.05 mg · m^{-3} has been estimated (19). Although lower estimates have been available from Ontario hardrock miners (19), in a recent study (7) a 25% cumulative risk of silicosis was estimated for South African gold miners after 28 years of mining at respirable silica concentrations of approximately 0.1 mg · m^{-3}. For higher exposure levels, and allowing for a 35-year latency period, the cumulative risk increased steeply, reaching 77%. In our study the risk accelerated in the highest exposure category and reached 48% after 30 years of exposure. If one considers that the past exposure levels in Civitacastellana were probably three- to fivefold the current standard of 0.1 mg · m^{-3} for respirable silica, the results can be considered consistent with the findings among South African gold miners.

Third, the follow-up was limited to active workers under the surveillance program. Thus the risk among those who were retired was not considered. This occurrence probably resulted in an underestimation of the risk, especially considering that, among gold miners, 57% of the silicosis cases were detected after they ceased mining (7). It seems that follow-up studies are lacking for those who leave work when their chest radiographs are normal.

In conclusion, exposure to silica dust has been associated with a high incidence of radiological signs of silicosis among ceramics workers, although the risk of silicosis seems to be decreasing for those entering work in more recent years. Smoking seems to be a determinant of a radiological diagnosis of silicosis, but its role in the biological process remains unclear.

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Preliminary analysis of proportional mortality in a cohort of British pottery workers exposed to crystalline silica

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McDonald JC, Cherry N, McNamee R, Burgess G, Turner S. Preliminary analysis of proportional mortality in a cohort of British pottery workers exposed to crystalline silica. *Scand J Work Environ Health* 1995;21 suppl 2:63—5.

A cohort of 7020 male pottery workers born in 1916—1945 was identified from all employees in dust-exposed trades, subject to medical surveillance by the Benefits Agency Medical Service of the Department of Social Security in Stoke-on-Trent in the United Kingdom. All but 256 (3.6%) were traced, 1016 (15.0%) had died by 30 June 1992, and death certificates were obtained for 940 (92.5%) of the fatalities — 122 from respiratory cancer. After the exclusion of any recorded asbestos exposure, the proportional mortality ratio (PMR) for lung cancer was 1.22 when calculated against national rates ($P < 0.02$), but the PMR against local rates was 1.04. Logistic regression analyses based on 75 nested case-referent pairs for which the required information was available showed that lung cancer mortality was dominated by smoking and significantly affected by past asbestos exposure. However, for 47 pairs in which both the case and referent had a history of smoking, there was also significant evidence that the risk was related to duration of silica dust exposure in pottery work but not to radiological score.

Key terms lung cancer, pottery, British workers.

The British pottery and ceramics industry has, for centuries, been centered in the "five towns" of Staffordshire, of which Stoke-on-Trent is the largest. Products include a wide range of sanitary and domestic ware and materials for industrial use, all entailing potential exposure for the worker to airborne respirable dust with high crystalline silica content. Most of the manufacturing processes include heat treatment at some stage in ovens at temperatures sometimes in excess of 1500°C, with probable conversion of a proportion of the quartz component to tridymite and cristobalite. Although there is little exposure to potential respiratory carcinogens other than silica in the industry, some employees are known to have worked previously in foundries, coal mines, and asbestos-related trades. Dust control in the industry was limited before 1945, but since then has been considerably more effective. During World War II production was greatly reduced.

Preliminary findings on lung cancer mortality from a follow-up of a stratified sample of the current work force of the British pottery industry, included in a survey in 1970—1971, were published by Winter et al (1). The latter investigators had some difficulty in ensuring a complete follow-up and confined their report to the mortality experience of 3669 men under 60 years of age. In this cohort 60 deaths from lung cancer were observed against 42.8 expected from national rates [standardized mortality ratio (SMR) 1.40, $P = 0.007$] and 45.6 from locally adjusted rates (SMR 1.32, $P = 0.023$).

The study on which the present preliminary report was based was initiated after discussion with those responsible for the earlier investigation. Our general approach differed in that it followed the more usual procedure of defining the cohort as subjects at the time of first exposure and in terms of date of birth. Whereas the earlier study covered pottery workers in all parts of the United Kingdom, the present cohort was recruited entirely from refractory, sandstone, and pottery workers subject to health surveillance at Stoke-on-Trent. It is likely that the two cohorts had some members in common.

Subjects and methods

The cohort. From 1931 to 1984, when the legislation was revoked, employers in the United Kingdom were required to notify the silicosis medical boards and their successors of any employee who was to work in specific dust-exposed trades and processes. At the Department of Social Security Boarding Centre, Stoke-on-Trent, those notified are entered into a card register, which is maintained indefinitely. They are then subject to an initial medical examination and further periodic examinations every two years, including full-size chest radiographs (posteroanterior) taken when first seen and every four years thereafter. A standard medical record form, which has changed somewhat over the years, is completed by the physician at each visit and contains the following information: full name, gender, date of birth, national insurance number, job or process for which employed, history with duration of any previous dust-exposed work (eg, coal, asbestos, foundries, quarries, etc), smoking habits, and classification of chest radiograph according to the system of the International Labour Organisation (ILO).

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Table 1. Proportional mortality ratios (PMR) for lung cancer in the cohort and its subcategories, 1961—1992. (90%CI = 90% confidence interval)

	Lung cancer		PMR	90% CI	P-value[a]
	Observed	Expected			
All deaths (N = 940)	122	98.69	1.24	1.06—1.44	0.009
Excluding known asbestos exposure (N = 877)	112	91.61	1.22	1.04—1.43	0.017
Excluding pneumoconiosis on death certificate (N = 899)	115	93.64	1.23	1.05—1.44	0.014
With pneumoconiosis on death certificate (N = 30)	7	4.00	1.75	0.70—3.60	0.111

[a] One-tailed.

Table 2. Distribution of the variables used in the nested case-referent analysis of 75 matched pairs. (ILO = International Labour Organisation)

Variables	Cases (N)	Referents (N)
Smoking		
Nonsmokers	1	17
Current smokers	53	35
Ex-smokers	12	17
Not known	9	6
Exposure (years)		
< 3	23	20
3—4	9	7
5—9	7	15
10—19	12	9
≥ 20	24	24
Small opacities (ILO)		
0/0	69	71
0/1	3	1
1/0—1/2	1	2
≥ 2/1	2	1
Previous asbestos work		
Recorded	11	5
Not recorded	64	70

These records are supposedly destroyed 10 years after last employment under the regulations and not later than at the age of 70 years, but in fact these rules have not been rigorously applied. The records are also destroyed after two years if the center is informed of the subject's death; however, no special steps are taken to learn of these deaths.

Our cohort was defined from the card register as all men born in 1916—1945, with full name, national insurance number, and date of birth for identification and tracing. It numbered 7020.

Ascertainment of deaths and cause of death. Identifying information on the 7020 members of the cohort was given to the Department of Social Security with the request that their vital status be established as of 30 June 1992. Through matching against the Department's central register all but 256 men (3.6%) were traced satisfactorily, in most cases exactly. Of this total, 5748 were reported to be alive, and 1016 (15.0%) were dead.

Information on deaths was then passed to the Office of Population, Censuses and Statistics so that the certified cause of death could be obtained from the National Health Service Central Register. The fact and date of death were confirmed and copies of death certificates were obtained for 940 (92.5%) of the 1016 fatalities. Of these 940 deaths, 122 were ascribed to respiratory cancer (code 162 of the International Classification of Diseases). Pneumoconiosis was recorded on the death certificates as the primary cause in 11 cases and as a contributing cause in 30 cases. This proportion (1.2%) is similar to the 1.0% observed for chrystotile miners and millers (2).

Dust exposure. Extensive records exist for airborne dust concentrations, recorded since the late 1960s in various parts of the industry. These measurements were made gravimetrically on respirable dust with a personal sampler and fell in the range of 0—800 $\mu g \cdot m^{-3}$ (mostly between 100 and 200). Records were increasingly sparse for earlier years, but some related to the 1930s and even earlier. The earlier measurements were mainly dust particle counts made with impinger methods and static samplers. Work is proceeding on these data for use in later exposure-response analyses of mortality and radiographic findings.

Results

Proportional mortality. A series of analyses was made in which the numbers of cases of lung cancer in the cohort were compared with the numbers expected from the proportion of deaths from this cause in England and Wales, 1961—1992, standardized for the quinquennium of birth and age at death. In these and other analyses 90% confidence intervals (90% CI) were calculated, as were probabilities based on a one-tailed distribution of the chi-square. The results are tabulated in table 1.

Overall, even after any recorded asbestos exposure was excluded, the proportional mortality ratio (PMR) for lung cancer (1.22) was significantly raised ($P < 0.02$). The lung cancer PMR for deaths with mention of pneumoconiosis was 1.75, and the risk was higher than for that without (1.23), but with overlapping confidence intervals. However, 70% of the deaths in the cohort were from Stoke-on-Trent, where there is a high mortality from all causes (standardized mortality ratio 1.20), especially for lung cancer (standardized mortality ratio 1.43). The PMR for lung cancer in Stoke-on-Trent during 1979—1983 was 1.17; when the PMR for our cohort was expressed relative to this figure, we obtained an estimated PMR of 1.04.

Nested case-referent study. To assess the effect of smoking habits, duration of occupational dust exposure, previous work with asbestos, and the ILO score for small opacities in the most recently recorded chest radiograph, we analyzed matched pairs by logistic regression. The study was restricted to 75 lung cancer cases and referents for which the X-ray reading was available. The referents for each pair were selected by a random process from cohort members who survived the case matched for date of birth (± 3 years) and date of first dust exposure (± 3 years). The crude distribution of the relevant variables, set out in table 2, showed a similarity in durations of exposure and previous work with asbestos, a relative rarity of X-ray changes, but a substantial difference in smoking

habits. For the latter reason the regression analysis was made first with all 75 pairs and then with 47 pairs for which both the case and the referent had a history of cigarette smoking. Table 3 shows the results of these analyses (with 90% confidence intervals) and demonstrates a significant effect of past asbestos work [odds ratio (OR) 3.3 and 3.8]. For the smoking pairs the results showed an effect of duration of dust exposure in pottery work (OR 2.8), but gave no suggestion that the risk was associated with radiological score (OR 0.9 and 0.8).

Table 3. Results from the logistic regression analyses of matched case-referent pairs (OR = odds ratio, 90% CI = 90% confidence interval)

	All pairs (N = 75)		Smoking pairs (N = 47)	
	OR	90% CI	OR	90% CI
Asbestos exposure	3.3	1.1—10.2	3.8	1.1—12.8
Silica exposure (≥ 10 years)	1.4	0.7—2.7	2.8	1.1—7.5
Small opacities	0.9	0.2—3.7	0.8	0.2—3.6

Concluding remarks

It must be emphasized again that the findings in this report are preliminary. Work in progress will correct the deficiencies in the tracing and ascertainment of cause of death and will allow exposures to be assessed both in duration and estimated concentrations of crystalline silica. Although most exposures to crystalline silica experienced by the cohort members were seldom more than about 200 $\mu g \cdot m^{-3}$, some 150 of the 7020 men are known to have had small opacity scores of 1/0 and above. It will therefore be possible to examine the validity of our work histories and exposure estimates before eventually making more-detailed analyses of mortality by both person-years and case-referent methods.

From the present results it is evident that lung cancer mortality is dominated in this cohort by smoking, with, at most, only weak evidence of any excess attributable to work exposure. Much will depend on detailed analyses of exposure response (3). The high prevalence level of lung cancer mortality in Stoke-on-Trent makes any comparisons against national or local area statistics difficult to interpret. A person-years analysis restricted to 470 deaths from January 1985 to June 1992 gave a lung cancer SMR of 1.28 when calculated against local rates (68 observed, 53.1 expected, 90% CI 1.04—1.57) (3).

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Preliminary study of lung cancer mortality among Western Australian gold miners exposed to silica

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Gold miners from Western Australia were surveyed in 1961. Data were collected on respiratory symptoms, smoking habits, employment history, and chest X-ray signs. Eighty-four percent of the men had smoked at some time, and 66% were current smokers. The prevalence of chronic bronchitis was over 20% at the time of the survey. A follow-up to the end of 1991 has been started which showed that, from 1969 to 1991, 999 miners died. Because vital status has not been ascertained for the whole cohort, a proportional mortality analysis was undertaken as a case-referent study. A strong effect of smoking on the risk of lung cancer was found, along with a slight, but nonsignificant increase in the lung cancer risk for the subjects employed underground for ≥ 40 years after adjustment for smoking. A complete follow-up and a full cohort analysis will enable these effects to be estimated more precisely.

Key terms Australian gold miners, chronic bronchitis, follow-up study, proportionate mortality, record linkage, smoking, tuberculosis.

The International Agency for Research on Cancer has concluded that silica is carcinogenic to animals and that there is "limited" evidence for similar effects in humans (1). The evidence supporting this classification is however not consistent (2). The evidence to date has been interpreted by some as suggesting an association between the presence of silicosis and the occurrence of lung cancer rather than simply between silica exposure and lung cancer. The justification for postulating that fibrosis is the cause of cancer rather than silica itself is not clear. Tuberculosis may also be a confounding factor in some studies. Much of this evidence comes from studies of lung cancer among subjects with silicosis, and findings are difficult to interpret because factors such as smoking are related to both the occurrence of respiratory symptoms (which may then bring subjects with silicosis to medical attention and therefore enhance the likelihood that they will be found to have silicosis) and also to the occurrence of lung cancer.

A recent extensive review has concluded that the overall evidence is sufficient, using standard criteria, to establish causality between exposure to silica and lung cancer (3), although this conclusion remains controversial. Nurminen et al (4) combined dose-response estimates from epidemiologic studies and concluded that silica-exposed workers in Australia had an average excess lifetime risk of 0.5% for lung cancer at the current estimates of quartz dust exposure.

For Kalgoorlie gold miners it has been shown that silica exposure is significantly related to evidence of airway disease (5) and also impaired gas transfer in the lungs (6). Chest X-ray abnormalities have also been shown to be associated with silica and smoking history in the same population (7). It may be that these associations reflect the presence of a common pathway of fibrosis existing between exposure and cancer. Thus the mechanism for a relationship between silica exposure or silicosis and lung cancer remains speculative.

A cohort study of 1974 Kalgoorlie Western Australia gold miners followed from 1961 to 1975 estimated a significantly raised standardized mortality ratio (SMR) of 1.4 for lung cancer; the increased risk was however thought to be due to a higher prevalence of smoking among miners than among other men (8). The aim of this study was to extend the follow-up on this original cohort from 1975 to 1991 and establish whether there was an increased risk of lung cancer for Kalgoorlie gold miners in association with duration of underground employment, smoking, and preexisting bronchitis.

Subjects

There were 1971 subjects who participated in surveys of respiratory symptoms and lung function in Kalgoorlie in 1961 and 1962, and they were included in the current study. Three subjects from the previous report (8) were excluded because their identifying information was lost.

Methods

Records from the surveys held on microfiche were abstracted to provide name, gender, date of birth, response to the questionnaire of the British Medical Research Council on respiratory symptoms, height, job description, duration and time spent at work, smoking

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history, and chest X-ray category of pneumoconiosis. Bronchitis was defined as positive answers to questions about cough or phlegm for at least three months in the year. All the subjects were traced via Western Australia death records from 1969 to 1991 using computerized linkage procedures (9). A proportional mortality analysis was carried out whereby the cases were all deaths from lung cancer and the referents were all deaths from other causes excluding deaths from tuberculosis, other respiratory diseases, and cancers of the larynx or unknown primary site. The latter causes of death were discounted because they may include diseases associated with exposure to silica. This approach differs from the usual proportional mortality analysis, in which expected numbers are calculated, but has been shown to be directly equivalent (10). Analysis was by unconditional logistic regression using the computer program EGRET (11), with age at death, smoking habits, duration of underground employment, and presence of bronchitis at the time of the survey as the covariates.

Results

Table 1 lists 157 deaths excluded from the analysis as being possibly related to silica exposure. There were 98 deaths from lung cancer and 744 reference deaths from other causes. The average age of the study subjects at death was 71 years with a range from 46 to 92 years. The total duration of underground employment ranged from 0 to 48 years.

Table 2 shows that 62% of the cases had bronchitis at the time of the survey compared with 50% of the referents. One case (1%) had never smoked, compared with 113 (15%) referents. The cases had also worked longer underground than the referents, though not significantly so, and fewer of them had never worked underground (20% compared with 24%).

As seen in table 3, there was a strong effect of smoking habit on the risk of lung cancer. The effect of duration of underground employment on the risk of lung cancer appeared to be limited to those employed underground for 40 or more years and was not statistically significant. Because only one lung cancer death occurred among the nonsmokers, the reference category for smoking was changed to smoking less than 15 cigarettes per day to avoid instability in the relative risk estimates. For comparison with other studies, however, estimates with the never smoked group as the base line could be made by dividing the relative risks for all other categories by that for the never smoked group (ie, 0.06). Without adjustment for smoking, the effect of duration of employment was slightly stronger, but again only in the 40 years or more employment group [relative risk 2.5, 95% confidence interval 0.9—7.0). The presence of bronchitis at the time of the initial survey and age at death were not associated with the risk of lung cancer after adjustment for smoking habit.

As a further comparison with previous studies, a cross-sectional analysis indicated a highly significant, mutually adjusted effect of both smoking habit and duration of employment on the prevalence of bronchitis at the time of the survey.

Discussion

Although this study must be considered preliminary, analyses carried out in this way are often a good guide to the results expected in more complete studies in which full follow-up has been completed (12). This study has shown a strong effect of smoking on the relative risk of lung cancer and a possible effect of duration of underground employment among subjects employed for 40 years

Table 1. Deaths among Western Australian gold miners in 1969—1991.

	N
Exclusions	
Pneumoconiosis	37
Other respiratory	101
Tuberculosis	5
Laryngeal cancer	6
Cancer (unknown primary)	8
Cases	
Lung cancer	98
Referents	
Ischemic heart disease	340
Other circulatory disease	179
Other cancer	82
Accidents, poisoning and violence	39
Other causes	104
Total	999

Table 2. Characteristics of the cohort.

	Cases[a] (N = 98)		Referents[b] (N = 744)	
	Number	%	Number	%
Bronchitis at initial survey	61	62	370	50
Smoking habit				
Never smoker	1	1	113	15
Ex-smoker	10	10	130	17
Current smoker				
1—14 cigarettes/day	21	21	135	18
15—24 cigarettes/day	44	45	254	34
≥ 25 cigarettes/day	21	21	95	13
Pipe or cigar only	1	1	17	2
Duration of underground employment				
None	20	20	177	24
0—4 years	8	8	67	9
5—9 years	7	7	54	7
10—19 years	19	19	130	17
20—29 years	21	21	181	24
30—39 years	17	17	114	15
≥ 40 years	6	6	21	3

[a] Mean age at death 69 (SD 8) years.
[b] Mean age at death 71 (SD 9) years.

Table 3. Relative risks of lung cancer, all variables included together in one model.

	Relative risk	95% confidence interval
Smoking habit		
Never smoker	0.06	0.01—0.4
Ex-smoker	0.5	0.2—1.2
Current smoker		
1—14 cigarettes/day	1.0	
15—24 cigarettes/day	1.1	0.6—1.9
≥ 25 cigarettes/day	1.4	0.7—2.7
Pipe or cigar only	0.4	0.05—3.1
Duration of underground employment		
None	1.0	
0—4 years	0.9	0.4—2.1
5—9 years	0.9	0.4—2.3
10—19 years	1.1	0.6—2.3
20—29 years	0.9	0.4—1.7
30—39 years	1.1	0.6—2.3
≥ 40 years	2.3	0.8—6.5

or more underground. Since all the subjects employed underground for 40 or more years in 1961 would have worked in mines during periods when little if any industrial hygiene precautions were taken, they were likely to have been exposed to very dusty conditions (13). The fact that 4% of all deaths were due to silicosis is consistent with this assumption.

Further information needs to be obtained before this study can reach more definite conclusions, and complete follow-up will enable a more powerful analysis. Full vital status follow-up requires manual searching of all Australian public and health records and will require at least 12 months. Data on the intensity of exposure have been collected in periodic surveys of respirable dust in the different mines, and this information will permit estimates of average and cumulative dust exposure for all the subjects. Changes assessed from compulsory periodic miners' X rays held in perpetuity at the Perth Chest Clinic will also enable us to provide an estimate of the effect of established silicosis on the risk of cancer in this group without the possible selection bias involved for subjects with compensated silicosis. The effects of dust exposure on the incidence of radiographic silicosis will also be assessed.

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Lung cancer among workers exposed to silica dust in Chinese refractory plants

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Dong D, Xu G, Sun Y, Hu P. Lung cancer among workers exposed to silica dust in Chinese refractory plants. *Scand J Work Environ Health* 1995;21 suppl 2:69—72.

A retrospective cohort mortality study was conducted for lung cancer among silica and clay brick workers at 11 refractory plants in China. The cohort included 6266 male workers employed before 1962 and followed between 1963 and 1985. The standardized rate ratios (SRR) were obtained by comparing the mortality rates of the silica-exposed cohort with those of a population of 11 470 male steel workers. As expected, significant excesses were observed for all deaths, all cancers, lung cancer, cardiorespiratory diseases, pulmonary heart diseases, and pulmonary tuberculosis. The lung cancer SRR was 1.49 ($P < 0.01$) for the total cohort. The increased lung cancer risk was attributed to the silicotics (SRR 2.10; $P < 0.01$) in the cohort. Higher lung cancer risk was found with increasing latency and severity of silicosis; this finding suggests that the excess was possibly related to occupational exposure to silica dust. Among the silicotics, there was a twofold excess of lung cancer risk among both the nonsmokers and the smokers.

Key terms epidemiologic study, fire brick, refractories, silica exposure, time since first exposure, smoking.

Silicosis has been the most important occupational illness in China since 1951 when health examinations for occupational lung diseases were initiated. The number of newly detected cases per year over the last 20 years has declined sharply compared with the corresponding numbers of the 1950s, and the mean years of silica dust exposure at the time of certification of silicosis has increased. However, according to the bulletin announced by the Ministry of Public Health on 28 January 1991, in the metallurgical industry of China 820 949 workers were exposed to silica dust, and 30 574 workers were certified silicotics.

Goldsmith et al reviewed (1, 2) and complied (3) studies related to silica exposure, silicosis and cancer; the results indicated that iron and steel foundry workers, nonuranium miners, and sandblasters had an excess risk of lung cancer. The authors noted that several issues tend to question silica's etiologic role in the observed excesses of lung cancer. First, these workers, besides being exposed to silica, worked in complex environments containing carcinogens such as polycyclic aromatic hydrocarbons, metallic oxides, arsenic, asbestos, and radon. Excess lung cancer among the workers could have been confounded by exposure to these industrial carcinogens (2, 3). Second, smoking was unadjusted in many early studies (3). In addition, some studies reported either no association with silica exposure or a negative association (3, 4). For these reasons, the issue of silica exposure, silicosis, and cancer risk has continued to be controversial in industrial medicine research.

This study evaluated refractory brick plant workers to measure the risk from lung cancer among silica-exposed workers whose exposure to quartz was and remains relatively pure. In April 1988, according to a directive of the Chinese Ministry of Metallurgical Industry, the Institute of Industrial Health of the Anshan Iron and Steel Corporation (AISC) initiated a retrospective study of 11 refractory plants.

Subjects and methods

The study population consisted of 6266 male refractory brick workers who were subjects of periodic health examinations for silicosis between 1 January 1963 and 31 December 1985. Entry to the study was restricted to those employed before 1962 in manufacturing silica or clay brick. Demographic and employment history was obtained through an interview and an examination of the personnel records of each plant. All deaths were determined from funeral allowance records at each plant. Information on the cause of death was obtained from certificates or from medical records. All causes of death were routinely coded according to the Chinese classification of diseases, injuries and causes of death, similar to the seventh revision of the International Classification of Diseases (ICD-7). The identification of silicotics was based on the 1963 diagnostic standard for pneumoconioses of the Chinese Ministry of Public Health.

The standardized rate ratios (SRR) were calculated (5) for selected causes of death by comparing age- and cause-specific observed numbers of death in the study cohort with expected numbers from a population of 11 470 male workers from 10 rough rolling steel mills. As a means of minimizing exposure to known occupational carcinogens, steel workers ever exposed to silica dust or other known occupational carcinogens were excluded. We evaluated the following: smoking, latency since first exposure,

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radiological status, silicosis, and employment in silica brick or clay brick manufacturing.

Results

The distribution of year of first employment and the follow-up results for the vital status of 6266 members of the refractory brick cohort are shown in table 1. From 1963 to 1985, 871 (13.9%) members died, 5132 (81.9%) were alive, and 263 (4.2%) were lost to follow-up. There were 130 730 person-years of follow-up, 93 169 for the nonsilicotics, and 37 561 for the workers with silicosis. Table 2 shows the number and distribution of the study population (excluding those lost to follow-up) by radiographic categories of silicosis according to the 1963 standards of the Chinese Ministry of Public Health. The silicotics, including simple silicosis and silicotuberculosis, numbered 1827 men, and 4176 men were classified as nonsilicotics.

Table 1. Results of the follow-up for vital status of 5132 Chinese silica brick workers from 1963 to 1985.

Year of 1st exposure	Alive	Dead		Lost to follow-up		Total
		N	%	N	%	
—1950	611	310	30.8	6	0.6	1007
1950—1954	1941	372	15.5	88	3.7	2401
1955—1959	2319	173	6.6	113	4.3	2905
1960—1962	181	16	6.9	56	22.1	253
Total	5132	871	13.9	263	4.2	6266

Table 2. Distribution of the study population by radiographic category of silicosis.

Radiographic categories of silicosis	Number	Percentage
0	2882	48.0
0—I	1294	21.6
I	1202	20.0
II	445	7.4
III	180	3.0
Total	6003	100.0

Table 3 shows the observed and expected deaths and the SRR values for selected causes of death by silicosis status. For the nonsilicotics, there were statistically significant excess SRR values for all cancers (SRR 1.23, $P < 0.05$) and diseases of the respiratory and circulatory system (SRR 1.90, $P < 0.01$). For the silicotics, statistically significant excesses were seen for all causes (SRR 2.10, $P < 0.01$), lung cancer (SRR 2.10, $P < 0.01$), diseases of the respiratory and circulatory system (SRR 1.65, $P < 0.01$), including pulmonary heart disease (SRR 3.08, $P < 0.01$), and pulmonary tuberculosis (SRR 31.31, $P < 0.01$). There were 33 deaths listing silicosis as the underlying cause of death, with zero expected. For the total cohort, there were significant excesses for all causes (SRR 1.44, $P < 0.01$), all cancers (SRR 1.16, $P < 0.01$), lung cancer (SRR 1.49, $P < 0.01$), pulmonary heart disease (SRR 1.79, $P < 0.01$), diseases of the respiratory and circulatory system (SRR 1.73, $P < 0.01$) and pulmonary tuberculosis (SRR 13.22, $P < 0.01$). There was a nonsignificant excess of 32—33% for both stomach and liver cancer among the nonsilicotics, while both sites showed a deficit among the men with silicosis. The SRR for lung cancer among all the refractory brick workers was 1.49 ($P < 0.01$). In this silica-exposed population, workers with silicosis appeared to be at the highest pulmonary cancer risk (and for several other conditions), while among the nonsilicotics there was no excess from lung cancer, SRR 1.11 ($P > 0.05$).

Table 4 shows the results of the latency analysis and demonstrates that for all causes, all cancers, and lung cancer the risk rises with greater latency. When analyzed separately, the lung cancer risk rises with increasing latency for the silicotics (data not shown), but not for those without silicosis. As seen in table 4, the lung cancer and all cancer SRR increased with increasing latency, but

Table 3. The standardized rate ratios (SRR) for selected causes of death.

Causes of death	Nonsilicotics		Silicotics		Total	
	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR
All cancers	148	1.23*	73	1.05	221	1.16**
Esophageal cancer	12	1.31	11	1.62	23	1.44
Stomach cancer	28	1.33	8	0.62	36	1.07
Intestine cancer	6	0.68	—	.	6	0.45
Liver cancer	40	1.32	12	0.75	52	1.13
Lung cancer	30	1.11	35	2.10**	65	1.49**
Other cancers	32	0.98	7	0.41	39	0.77
Cardiorespiratory disease	111	0.96	144	1.65**	255	1.25
Pulmonary heart disease	21	0.74	71	3.08**	92	1.79**
Silicosis	—	.	33	∞	33	∞
Cerebrovascular disease	50	0.83	20	0.43	70	0.66
Coronary heart disease	18	1.12	8	0.73	26	0.97
Other cardiorespiratory disease	22	1.90**	12	1.48	34	1.73**
Pulmonary tuberculosis	15	1.38	222	31.31**	237	13.22**
Diseases of the digestive system	26	1.00	12	0.81	38	0.93
Cirrhosis of the liver	25	1.23	10	0.87	35	1.11
Accident or suicide	62	0.94	8	0.29	70	0.75
Other diseases	11	0.57	5	0.44	16	0.52
Unknown	17	1.04	17	1.47	34	1.22
All causes	390	1.04	481	2.10**	871	1.44**

** $P < 0.01$.

Table 4. Analysis by years since first employment (latency) for selected causes of death of the silica-exposed workers. (SRR = standardized rate ratio)

Cause of death	Duration of exposure									
	0—9 years		10—19 years		20—29 years		≥ 30 years		Total	
	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR
All causes	57	1.08	290	1.44**	351	1.44**	173	1.63**	871	1.44**
All cancers	12	0.74	63	0.92	101	1.31**	45	1.60**	221	1.16
Lung cancer	2	0.88	11	0.76	35	1.77**	17	2.39**	65	1.49**
Cardiorespiratory disease	13	1.67	66	1.22	106	1.15	70	1.41**	255	1.25**
Pulmonary heart disease	2	1.18	25	2.04**	39	1.67**	26	1.83**	92	1.79**
Cerebrovascular disease	3	0.81	14	0.51	35	0.73	18	0.69	70	0.66
Pulmonary tuberculosis	12	10.26**	98	18.56**	88	11.18*	39	10.77**	237	13.22**

** $P < 0.01$.

Table 5. Lung cancer risk by smoking and silicosis status. (SRR = standardized rate ratio)

Group	Smokers		Nonsmokers		Unknown		Total	
	Observed (N)	SRR	Observed (N)	SSR	Observed (N)	SRR	Observed (N)	SRR
Nonsilicotics	21	1.20	7	0.85	2	1.49	30	1.10
Silicotics	21	2.34**	12	2.13*	2	1.09	35	2.10**
All deaths	42	1.58**	19	1.37	4	1.26	65	1.49**

* $P < 0.05$, ** $P < 0.01$.

Table 6. Standardized rate ratio (SRR) from selected causes of death by radiological categories of silicosis.

Causes of death	Nonsilicotics		Silicotics by radiological categories							
			I		II		III		Total	
	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR	Observed (N)	SRR
All causes	390	1.04	253	1.75**	144	2.30**	84	3.72**	481	2.10**
All cancers	148	1.23**	47	1.06	17	0.94	9	1.37	73	1.05
Lung cancer	30	1.11	21	1.97**	10	2.34*	4	2.55	35	2.10**
Cardiorespiratory	111	0.96	79	1.50**	42	1.65**	23	2.52**	144	1.65**
Pulmonary heart disease	21	0.74	39	2.85**	21	3.04**	11	4.45**	71	3.08**
Pulmonary tuberculosis	15	1.38	94	20.70**	77	40.96**	51	72.86**	222	31.21**

* $P < 0.05$, ** $P < 0.01$.

only became significantly elevated 20 or more years after exposure. The lung cancer SRR was < 1.00 for latency of less than 20 years, but rose to 1.77 for 20—29 years of exposure to silica and to 2.39 for a latency of ≥ 30 years of dust exposure. Cardiorespiratory diseases and pulmonary tuberculosis did not show positive gradients for latency.

The SRR values for lung cancer are presented in table 5 by smoking status. Among the silicotics, significant excess lung cancer risks appeared for both the smokers (SRR 2.34) and the nonsmokers (SRR 2.13). Although there was a 20% excess risk for the smoking workers who were nonsilicotics, there was an SRR of 0.85 for nonsmoking nonsilicotics.

We examined the risk differences between silica brick workers and clay brick workers (table not included). For both types of brick workers, there were elevated risks from lung cancer, but the risk was significant only for the silicotics. The same was true for diseases of the cardiorespiratory system, pulmonary heart disease, and pulmonary tuberculosis. With the exception of mortality from all cancers, there were no significant disease excesses for the nonsilicotic clay brick workers.

Table 6 shows the SRR value for selected causes by categories of silicosis. There were clear gradients for all causes of death, lung cancer, diseases of the cardiorespiratory system, pulmonary heart disease, and tuberculosis. The SRR values for lung cancer rose from 1.11 for nonsilicotics to 1.97 for category I, to 2.34 for category II, to 2.55 for category III for silicosis in table 6. We evaluated the lung cancer risk among silicotics by time since first employment and showed that there were positive gradients by latency periods within all three categories of silicosis. Employment of < 20 years showed an SRR of 0.87, while ≥ 30 years had an SRR of 3.78 (tables are not included). Furthermore, when silicotuberculosis was evaluated separately, it had an SRR of 2.24 for lung cancer (11 observed, 4.91 expected, $P < 0.05$), a finding similar to the SRR of 2.08 for simple silicosis (24 observed, 11.54 expected, $P < 0.01$).

Discussion

The associations between silica exposures, silicosis, and lung cancer are under dispute. The epidemiologic substance of the controversy mainly focuses on the following points: (i) the possibility of

confounding by other industrial carcinogens and smoking, (ii) the differential lung cancer risk among silica-exposed workers and those with silicosis, and (iii) uncertainty concerning the severity of silicosis and the risk of lung cancer.

The results of this study show that there was a significant excess risk from lung cancer (SRR 1.49) in the population exposed only to silica dust in the refractory brick and clay industry. For the silicotics, there was a significant excess risk from lung cancer (SRR 2.10, $P < 0.01$), but for nonsilicotics there was none (SRR 1.11). The 49% excess of lung cancer of the silica brick worker population was attributed to the excess of lung cancer among silicotics, even though in our study we observed a doubling of lung cancer risk for nonsmoking silicotics (SRR 2.13, $P < 0.05$). This study supports work by others who showed lung cancer risk ratios between 1.4 and 5.0 for silicotics, as summarized by Goldsmith (3). Our results also support the excess lung cancer risks found by other investigators among firebrick workers (6—8) and smelting furnace repairmen (9—10).

As shown by Zhong et al (this issue) silicosis is an occupational disease with high mortality in China. As seen in table 3, pulmonary tuberculosis plus pulmonary heart diseases (cor pulmonale) accounted for 69.9% of all causes of death. Because silicotics prematurely died of these diseases, the excess of lung cancer may have been underestimated. We observed that 46% of the patients with pulmonary silicotuberculosis died before 20 years of latency or exposure, but 88% of the lung cancer cases died after 20 years of latency; therefore, in this cohort, pulmonary tuberculosis and cor pulmonale may, as causes of death, be competing with lung cancer. Patients with silicosis have damaged pulmonary tissues, and impaired lung clearance. Thus, as duration of exposure increases, neoplasia arises in fibrotic pulmonary tissue. However, nonsilicotics do not have such damage, and risk is less.

Concluding remarks

This study of silica brick and clay workers confirmed significantly high mortality risks for all causes of death, all cancers, lung cancer, cardiopulmonary diseases (cor pulmonale, silicosis, and other respiratory diseases), and tuberculosis. The lung cancer risk in this population was a modest SRR of 1.49. Statistically significant excesses were confined to silicotics only, and this finding held true for both silica brick and silica clay workers. When analyzed by years since first exposure, excess risk paralleled latency, a trend found for the silicotics and the whole cohort only. Among the silicotics, excess lung cancer risk was observed for the nonsmokers and smokers, and the excess increased with latency. For the nonsilicotics, regardless of smoking status, no significant pulmonary cancer risk was shown. We observed striking excesses from cor pulmonale and tuberculosis that increased with the severity of silicosis.

Additional surveillance of these workers will enable us to determine whether excess mortality risks remain in this industry. Furthermore, more research would determine if these workers have elevated risks for other cancers such as lymphatic and gastric malignancies and for other diseases, including autoimmune conditions and renal diseases.

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Mortality among persons with silicosis reported to disease surveillance systems in Michigan and New Jersey in the United States

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Rosenman KD, Stanbury MJ, Reilly MJ. Mortality among persons with silicosis reported to disease surveillance systems in Michigan and New Jersey in the United States. *Scand J Work Environ Health* 1995;21 suppl 2:73—6.

Michigan and New Jersey in the United States maintain silicosis disease registers. In 1988—1992, 372 cases of silicosis were confirmed in Michigan, and, in 1979—1992, 288 were confirmed in New Jersey. A proportionate mortality ratio (PMR) analysis was performed on data from 292 deceased silicotics. Increases in PMR values were found for nonmalignant respiratory disease (NMRD) and lung cancer. The PMR values for NMRD were statistically elevated in all the analyses. The overall proportionate cancer mortality ratio (PCMR) for lung cancer was 1.78 [95% confidence interval (95% CI) 1.22—2.61]. For patients having ever smoked cigarettes, the PCMR for lung cancer was 1.82 (95% CI 1.18—2.81). Never smoking silicotics had a lung cancer PCMR of 1.48 (95% CI 0.43—2.86). For those who had never applied for workers' compensation the corresponding PCMR was higher, 2.10 (95% CI 1.21—3.69), than for those who had applied, 1.45 (95% CI 0.70—2.99).

Key terms cigarettes, lung cancer, obstructive lung disease, silica, workers' compensation.

Repeated epidemiologic studies among patients with silicosis have found an increased risk of death from lung cancer (1). The hypotheses for this association are (i) silica is a carcinogen; (ii) there is an effect from concomitant exposures to other carcinogens (eg, polycyclic aromatic hydrocarbons in foundries); (iii) there is an increased prevalence of cigarette smoking among workers with silicosis; (iv) there is selection bias from studying workers who applied for workers' compensation; (v) there is an effect secondary to fibrosis not specific to silica. The data used in this analysis are from two state-wide silicosis registries. Diagnoses were confirmed and sufficient information was collected on the reported cases to examine the effect of cigarette smoking and concomitant occupational exposures. Because reports are mainly received from hospitals and private practitioners, we have also been able to examine whether patients who apply for workers' compensation have the same risk of lung cancer as workers who do not apply.

Subjects and methods

Michigan and New Jersey maintain silicosis disease registers. Michigan's silicosis register requires hospitals, clinics, employers, and physicians to report all known or suspected occupational diseases. New Jersey's silicosis register became mandatory for hospitals in 1985, and for physicians in 1990.

In both states patients were interviewed and their medical records were reviewed. "B readers" certified by the National Institute for Occupational Safety and Health (NIOSH) evaluated all the chest films to confirm the diagnoses. Confirmed patients were those with a history of silica exposure and either a positive lung biopsy or 1/0 or greater nodular opacities in radiographs and absence of medical conditions which can produce similar X-ray findings. The patients were interviewed by telephone using a standardized questionnaire including a complete work history, smoking history, and whether patients ever applied for workers' compensation. If subjects were deceased, then the next-of-kin was interviewed. From 1988 to 1992, 372 cases of silicosis were confirmed in Michigan, and, from 1979 to 1992, 288 cases of silicosis were confirmed in New Jersey.

The data from both states were combined. Silica exposure industries were coded according to the Standardized Industrial Classification System (2). Vital status was determined through a review of hospital and physician records, including death certificates. Furthermore, to confirm the vital status of all cases in Michigan, all confirmed silicosis cases were matched against the National Death Index data base. In New Jersey, all confirmed cases were matched against listings of all New Jersey deaths.

Proportionate mortality and proportionate cancer mortality ratios (PMR and PCMR, respectively) were calculated with the O/E program of the National Cancer Institute, a modified version of a published program (3). The analysis was limited to white and black men, and age- and time-adjusted mortality ratios with 95% confidence intervals (95% CI) were calculated. Expected ratios of cause of death were derived from male population rates of the United States (3). In addition, smoking-specific expected ratios of cause of death for lung cancer and obstructive lung disease were derived from the CPSII survey of the American Cancer Society (Thun, personal communication).

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Because some patients had missing data, the number of deaths varied in each analysis.

Results

Of the 660 confirmed silicosis patients 292 had died and the PMR was statistically increased for all nonmalignant respiratory disease (NMRD) and statistically decreased for all cancer and all circulatory disease (table 1). Not surprisingly, silicosis was the most common cause of respiratory mortality with 55 deaths. There were 42 deaths from emphysema. Table 1 shows that the PCMR for lung cancer was significantly increased, 1.78 (95% CI 1.22—2.61), while digestive cancer was significantly decreased, 0.25 (95% CI 0.09—0.74).

Tables 2—4 show the PCMR values for lung cancer and PMR values for all respiratory disease by duration of employment, smoking status, and profusion category from chest X rays.

The PMR values for all respiratory disease and lung cancer were greater for ≥ 30 years than for < 10 years of exposure. However, there was no trend of increasing duration of exposure for either lung cancer or respiratory disease (table 2).

As seen in table 3 there was no monotonic trend of increasing PMR or PCMR values for lung cancer with increasing profusion of small rounded opacities or for the presence of large opacities. Although there was no trend by profusion category, the PMR values for respiratory disease were statistically elevated for all the profusion categories.

With the American Cancer Society's expected risks for never and current smokers as the comparison, the PCMR was 3.94 (95% CI 1.53—10.12) for never smoking silicotics and 1.50 (95% CI 0.82—2.76) for current smokers. The PMR values for chronic lung disease showed similar risk levels (table 4).

The PCMR was 1.45 (95% CI 0.70—2.99) for those who had applied for workers' compensation when compared with 2.11 (95% CI 1.21—3.9) for those who had not sought compensation. The risks for respiratory disease were statistically increased whether or not the patients had applied for workers' compensation. The risks for lung cancer were statistically elevated for foundry work-

Table 1. Race adjusted proportionate mortality ratios (PMR) and proportionate cancer mortality ratios (PCMR) for male silicotics — Michigan 1988—1992 and New Jersey 1979—1992. (95% CI = 95% confidence interval)

Cause of death	Number of deaths	Ratio[b]	95% CI
All causes	292	..	..
Infectious disease	6	1.54	0.71—3.37
Tuberculosis	1	2.28	0.40—12.93
All cancer	46	0.67*	0.50—0.89
Cancer of digestive organs[c]	3	0.25*	0.09—0.74
Cancer of lung[c]	26	1.78	1.22—2.61
Cancer of prostate[c]	7	0.99	0.48—2.04
All circulatory disease	80	0.54*	0.44—0.68
All respiratory disease	134	4.87*	4.12—5.76
Pneumonia	14	1.24	0.74—2.08
Emphysema	6	2.23*	1.02—4.86
All external causes	5	0.51	0.22—1.19

[b] Expected based on mortality ratios for the general male population of the United States.
[c] PCMR.
* $P < 0.05$.

Table 2. Proportionate mortality ratios (PMR) and proportionate cancer mortality ratios (PCMR) for male silicotics by duration of years worked — Michigan 1988—1992 and New Jersey 1979—1992. (95% CI = 95% confidence interval)

Cause of death	< 10 years			10—19 years			20—29 years			≥ 30 years		
	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI
Cancer of lung (PCMR)	2	1.54	0.42—5.61	4	1.63	0.63—4.20	7	1.48	0.71—3.05	10	1.73	0.94—3.19
All respiratory disease (PMR)	8	6.03*	3.05—11.91	20	5.99*	2.89—8.88	35	4.86*	3.50—6.77	56	4.43*	3.41—5.75

[a] Expected based on ratios for the general male population of the United States.
* $P < 0.05$.

Table 3. Proportionate mortality ratios (PMR) and proportionate cancer mortality ratios (PCMR) for male silicotics by profusion category for pneumoniocosis — Michigan 1988—1992 and New Jersey 1979—1992. (95% CI = 95% confidence interval, PMF = progressive massive fibrosis)

Cause of death	Category 1[b]			Category 2[c]			Category 3[d]			PMF		
	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI
Cancer of lung (PCMR)	8	1.70	0.86—3.34	5	1.42	0.60—3.32	2	2.16	0.59—7.88	7	1.85	0.90—3.82
All respiratory disease (PMR)	23	4.43*	2.46—5.54	25	3.92*	2.65—5.78	12	6.23*	3.56—10.89	54	5.76*	4.41—7.51

[a] Expected based on mortality ratios for the general male population of the United States.
[b] Category 1 = 1/0, 1/1, 1/2 International Labour Office 1980.
[c] Category 2 = 2/1, 2/2, 2/3 International Labour Office 1980.
[d] Category 3 = 3/2, 3/3, 3/+ International Labour Office 1980.
* $P < 0.05$.

Table 4. Proportionate mortality ratios (PMR) and proportionate cancer mortality ratios (PCMR) for male silicotics by smoking status — Michigan 1988—1992 and New Jersey 1979—1992. (95% CI = 95% confidence interval)

Cause of death	Smoking status					
	Never			Current		
	Number of deaths	Ratio[a]	95% CI	Number of deaths	Ratio[a]	95% CI
Cancer of lung (PCMR)	4	3.94*	1.53—10.12	10	1.50	0.82—2.76
Obstructive lung disease, white males only (PMR)	3	5.97*	1.20—17.45	7	3.58*	1.44—7.39

[a] Expected based on the CPS-II of the American Cancer Society.
* $P < 0.05$.

ers (PCMR 1.65) and for workers in all other industries (PCMR 2.15). The PMR values for respiratory disease were statistically increased regardless of type of industry (tables not presented).

Discussion

Similar to other epidemiologic studies of patients from silicosis registers [reviewed by Goldsmith (1)], this analysis showed increased mortality risk from lung cancer and respiratory disease. The PCMR for lung cancer was 1.78 (95% CI 1.22—2.61) and the PMR for respiratory disease was 4.87 (95% CI 4.12—5.76) (table 1). These respiratory deaths were predominantly due to silicosis and chronic obstructive lung disease.

In contrast to the subjects of other studies based on silicosis registers (4—10), most of the patients in this analysis had been reported to the registers by health care providers and not because they had applied for workers' compensation. Only 24% of this cohort was known to have applied for workers' compensation. In addition, information on cigarette smoking habits, years worked, and severity of disease (as determined by X-ray findings) was available for a large percentage of the cohort. Although the number of individuals who never smoked was small, the lung cancer PCMR for persons who never smoked was 3.94 (table 4). Four never smoking silicotics died of lung cancer. Using smoking-specific reference data of the American Cancer Society to generate expected numbers of deaths produced a PCMR of 1.50 for ever smokers and a PCMR of 3.94 (95% CI 1.53—10.12) for never smokers. Our data do not support the argument that an increased prevalence of smokers among workers with silicosis explains the increased risk of lung cancer.

The respiratory disease PMR values were statistically increased for all the smoking categories. These results are consistent with those of studies that show an association between obstructive lung disease and silicosis (11, 12).

Comparison of the PCMR values of persons who did not apply for workers' compensation with those who did showed an increased PCMR for those who did not apply. Thus our study does not support the position that bias towards lung cancer exists among compensation applicants.

We found no trend of increasing lung cancer risk among persons with greater scarring on their X ray (table 3). Our data therefore do not support the hypothesis that the mechanism of increased lung cancer arises from pulmonary scar tissue.

We found no monotonic trend of increasing risk for lung cancer and all respiratory disease by duration silica exposure (table 2). The lack of an association with duration of exposure is inconsistent with the hypothesis that silica is a direct carcinogen. The statistical increase among men who began work before 1949 suggested that high historical exposures and sufficient latency from first exposure are associated with lung cancer among silicotics. This finding would support an effect of silica or some other workplace exposure.

The lung cancer risks for foundry work and "other" industries were statistically increased. Foundry exposures to potential carcinogens such as polycyclic aromatic hydrocarbons may account for this finding (13). There was a wide variety of industries in the "other" category, including surface and underground mining, sandblasting and sandpaper manufacture. Our data do not include actual dust exposure information that would help to determine whether silica dust was the specific factor causing the lung cancer excess.

There are numerous limitations in our study, for example, the small number of deaths and a lack of complete data on each patient.

Information on smoking, workers' compensation, and duration and decade of exposure was obtained from the patient or next-of-kin. To verify smoking status, we reviewed the medical records of the 11 individuals classified as never smokers who died of lung cancer or chronic obstructive lung disease. Five of the medical records confirmed that the patient was a nonsmoker, five did not mention the patient's smoking status, and one had no available clinical record. Three subjects who died of NMRD had smoked one to two cigars a day, and one who chewed tobacco died of lung cancer. Smoking information was collected after the patient left work, and neither the patient's nor the next-of-kin's response was likely to be influenced by a pending workers' compensation proceeding. We are unaware of any reason why there should be any systematic bias in any of the data collected.

Limitations of proportionate mortality analyses are well known. Unlike typical worker cohorts, this group probably had an increased standardized mortality ratio. Most patients' silicosis was diagnosed in the hospital. Thus increased lung cancer findings suggest that the PMR values are underestimates of risk. Most of the patients in this cohort had advanced silicosis, including 39.5% with progressive massive fibrosis. Our results may not be generalizable to the total population of patients with silicosis because some patients hospitalized for lung cancer or NMRD were then diagnosed as having silicosis. Among the 26 patients who died from lung cancer, medical records indicated that 17 had silicosis at least one year. For four patients, the diagnosis was made at the same time, and for the remaining five there was insufficient information to determine when the silicosis diagnosis was made. Another study limitation is that there is a marked deficit in heart disease and all cancer; this finding is reflected in the PMR analysis by the increases in other causes of death. However, the two causes of increased mortality, lung cancer and respiratory disease, are the conditions of interest.

In summary, this study supports the association between lung cancer and silicosis. Our data suggest this finding cannot be explained by smoking, by profusion scores, or by bias from studying patients who had sought workers' compensation. We cannot rule out the importance of concomitant carcinogens in workplaces that use silica. Five other states in the United States now have silicosis registers similar to those in Michigan and New Jersey. In the future, we hope to readdress this issue using silicosis patients from these states.

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Mortality among silicotics in Genoa, Italy, from 1961 to 1987

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A historical cohort mortality study conducted among 515 silicotic subjects revealed higher than expected risks for all causes [standardized mortality ratio (SMR) 1.89], respiratory tract diseases (SMR 8.89), silicotuberculosis (SMR 27.00), respiratory tract cancers (SMR 3.14), and lung cancer (SMR 3.50). Mortality from cardiovascular diseases was lower than that expected (SMR 0.51). Lung cancer risk increased with duration of occupational exposure (SMR 2.80, 2.99, and 5.02 for 14, 15—29, and 30 years of employment, respectively). Lung cancer risk was higher for the silicotics without tuberculosis (SMR 3.72) than for those with tuberculosis (SMR 2.83). Indirect adjustment for smoking habits, including number of cigarettes smoked per day, showed that smoking would have been responsible for a maximum risk of 1.77. Thus smoking may have explained 50% of the observed excess mortality from lung cancer.

Key terms epidemiology, Italian silicotics, pulmonary tuberculosis, respiratory tract cancer, smoking.

In 1986, the International Agency for Research on Cancer (IARC) critically examined all published studies investigating the link between exposure to silica dusts and lung cancer. It concluded that there was sufficient evidence for the carcinogenicity of crystalline silica in experimental animals and limited evidence for its carcinogenicity in humans (1).

Despite the fact that most human studies have reported an increased lung cancer risk, their interpretation has been hampered by serious study design problems, such as the choice of appropriate reference populations, the lack of knowledge concerning smoking habits, and concomitant exposure to other occupational carcinogens (2). Studies of silicotic subjects suffer from all these limitations and from potential selection and disease misclassification biases. Selection bias may increase the probability of workers (exposed to silica) seeking and receiving compensation for silicosis when other exposures (eg, smoking) are actually responsible for symptomatic lung function impairment (3), while the disease misclassification may result in the inclusion of other pneumoconioses (eg, asbestosis) in the group of true silicotics (4). Both biases have been suspected to increase the estimated epidemiologic measures of association between silicosis and lung cancer. However, recently published data from humans (5—9) showed that smoking habits and disease misclassification bias had a marginal role, if any, in the lung cancer risk estimated for silicotics. Moreover, mechanistic studies of carcinogenicity showed direct damage by crystalline silica through binding to the phosphate backbone of the DNA (deoxyribonucleic acid) strand (Daniel et al and Williams & Saffiotti this issue).

Subjects and methods

Our unit previously reported findings of a historical mortality study of 520 silicotic subjects diagnosed at the Department of Occupational Health of the San Martino Hospital, Genoa, Italy, between 1961 and 1980 and followed through 1981. This research showed increased mortality from respiratory tract diseases [standardized mortality ratio (SMR) 13.36] and respiratory cancers (SMR 6.85) (10). We used the same methods (10) to evaluate the 515 silicosis patients whose follow-up was extended from 1981 through 1987 in this study. SMR values and their 95% confidence intervals (95% CI) were computed for overall mortality and specific causes of death by using EPILOG (11).

Results

The vital status of the 515 silicotic subjects and of a subcohort of 450 individuals for which information on year of first employment, duration of employment, and type of exposure was available is reported in table 1. For the latter subcohort, mean age at entry into follow-up was 55.3 (SD 11.1) years and age at the beginning of employment was 23.4 (SD 8.55) years. The mean length between first employment and the diagnosis of silicosis was 31.9 (SD 13.5) years and the mean length of follow-up was 11.56 (SD 9.6) years. Pulmonary tuberculosis was diagnosed for 117 (26%) silicotics, who contributed 1215 person-years of observation (24% of the total number of person-years).

Table 2 shows the overall and cause-specific SMR values for the entire cohort of silicotics. The overall mortality (SMR 1.66,

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Table 1. Vital status of the cohort of silicotics followed from 1961 through 1987 and the person-years of observation at the date of termination of the study.

Vital status	All silicotics		Silicotics with complete data	
	Number	%	Number	%
Alive	172	33.4	160	35.6
Deceased	301	58.4	290	64.4
All cancer deaths	58	19.3	56	19.3
Lung cancer	37	63.8[a]	35	62.5[a]
Respiratory tract diseases	127	42.2	122	42.1
Other diseases	45	14.9	45	15.5
Silicotuberculosis	35	11.6	34	11.7
Lost to follow-up	42	8.2	—	0
Total	515	100	450	100
Person-years	6214		5141	

[a] Percentage of all cancer deaths.

Table 2. Mortality from selected causes among all the silicotics from 1961 through 1987. [O = observed deaths, E = expected deaths based on age and calendar-year-specific death rates of the male population of Italy (1961—1987), SMR = standardized mortality ratio, 95% CI = 95% confidence interval]

Cause of death[a]	O	E	SMR	95% CI
Malignant neoplasms (140—208)	58	44.0	1.32	1.0—1.70
Respiratory tract (161—165)	39	13.8	2.82	2.01—3.86
Lung (162)	37	11.7	3.15	2.22—4.35
Respiratory tract diseases (460–519)	127	16.8	7.57	6.29—8.97
All deaths (0—999)	301	181.3	1.66	1.48—1.86

[a] Code from the ninth revision of the International Classification of Diseases in parentheses.

Table 3. Mortality from selected causes among the silicotics with complete data (N = 450). [O = observed deaths, E = expected deaths based on age and calendar-year-specific death rates of the male population of Italy (1961—1987), SMR = standardized mortality ratio, 95% CI = 95% confidence interval]

Cause of death[a]	O	E	SMR	95% CI
Malignant neoplasms (140—208)	56	34.9	1.61	1.26—2.15
Buccal cavity, pharynx (140—149)	2	1.18	1.69	0.20—6.11
Stomach (151)	5	5.8	0.87	0.28—2.02
Respiratory tract (161—165)	37	11.8	3.14	2.21—4.33
Larynx (161)	2	1.36	1.47	0.18—5.31
Lung (162)	35	9.99	3.50	2.44—4.87
Prostate (185)	3	2.46	1.22	0.25—3.57
Bladder (188)	1	1.76	0.57	0.01—3.16
Kidney (189)	1	0.56	1.78	0.05—9.92
Lymphatic, hemopoietic (200—208)	1	2.07	0.48	0.01—2.68
Cardiovascular diseases (390—459)	35	68.2	0.51	0.36—0.71
Respiratory tract diseases[b] (460—519)	122	13.7	8.89	7.38—10.6
Digestive tract diseases (520—579)	23	10.9	2.10	1.33—3.16
Ill-defined conditions (780—799)	6	3.51	1.71	0.63—3.72
Violent causes (800—999)	3	5.55	0.54	0.11—1.5
Other diseases[c]	45	29.2	1.54	1.12—2.06
Silicotuberculosis (11.4)	34	1.25	27.0	18.8—38.0
All deaths (0—999)	290	152.9	1.89	1.69—2.12

[a] Code from the ninth revision of the International Classification of Diseases in parentheses.
[b] 96 deaths from silicosis.
[c] Includes two deaths from chronic renal failure (ICD code 585.0).

95% CI 1.48—1.86) was significantly higher than the expected. Mortality from all malignant neoplasms was also higher than the expected (SMR 1.32, 95% CI 1.0—1.70). Particularly elevated mortality risks were observed for respiratory tract diseases (SMR 7.57, 95% CI 6.29—8.97), for respiratory tract cancers (SMR 2.82, 95% CI 2.01—3.86), and for lung cancer (SMR 3.15, 95% CI 2.22—4.35). The exclusion of four lung cancer deaths that occurred within the first year of the diagnosis of silicosis did not significantly alter the lung cancer risk (SMR 2.82, 95% CI 1.94—3.96).

Table 3 shows the overall and cause-specific SMR value for the subcohort of silicotics with complete data. Excess mortality was observed for all causes (SMR 1.89, 95% CI 1.69—2.12), pulmonary tuberculosis (SMR 27.00, 95% CI 18.80—38.00), respiratory tract diseases (SMR 8.89, 95% CI 7.38—10.6), all cancers (SMR 1.61, 95% CI 1.26—2.15), lung cancer (SMR 3.50, 95% CI 2.44—4.87), and respiratory tract cancers (SMR 3.14, 95% CI 2.21—4.33). The analyses for site-specific, smoking-related malignancies did not reveal a significant excess mortality for oropharyngeal (SMR 1.69, 95% CI 0.20—6.11), laryngeal (SMR 1.47, 95% CI 0.18—5.31), or bladder (SMR 0.57, 95% CI 0.01—3.16) cancer. No deaths from esophageal-pancreatic cancer were observed. Mortality from prostate cancer (SMR 1.22, 95% CI 0.25—3.57), kidney cancer (SMR 1.78, 95% CI 0.05—9.92), and lymphatic and hemopoietic neoplasms (SMR 0.48, 95% CI 0.01—2.68) was not found to differ significantly from the expected level. The observed excess mortality from nonmalignant respiratory diseases was largely attributable to silicosis: 96 (80.7%) of the 119 respiratory deaths. Mortality from cardiovascular diseases was significantly lower than the expected value (SMR 0.51, 95% CI 0.36—0.71). The increased mortality from digestive tract diseases (SMR 2.10, 95% CI 1.33—3.16) was mainly due to cirrhosis of the liver (18 deaths). Mortality from other diseases was higher than the expected value (SMR 1.54, 95% CI 1.12—2.06) due to the excess mortality from silicotuberculosis (SMR 27.00, 95% CI 18.80 — 38.00). No deaths from autoimmune diseases and two deaths from chronic renal failure were observed.

Table 4 shows the SMR values for selected causes of death by the pulmonary tuberculosis status as ascertained at the time of the medical examination. Silicotics diagnosed as having pulmonary tuberculosis had a strikingly higher mortality from silicotuberculosis (SMR 72.70, 95% CI 47.90—105.70) than the remaining subjects (SMR 7.99, 95% CI 3.21—16.46). Mortality from lung

Table 4. Mortality from selected causes among the silicotics according to the pulmonary tuberculosis status. (O = observed deaths, SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death	Pulmonary tuberculosis					
	Yes[a]			No[b]		
	O	SMR	95% CI	O	SMR	95% CI
All deaths	93	1.83	1.48—2.24	197	1.93	1.66—2.22
All cancers	9	0.93	0.43—1.77	47	1.86	1.37—2.48
Lung cancer	7	2.83	1.14—5.83	28	3.72	2.47—5.38
Silicotuberculosis	27	72.7	47.9—105.7	7	7.99	3.21—16.46
Respiratory tract diseases	34	6.84	4.74—9.56	88	10.1	8.07—12.39

[a] N = 117, person-years = 1214.
[b] N = 333, person-years = 3927.

cancer and from respiratory diseases was lower among the silicotics with tuberculosis than among those with tuberculosis. For the former group the observed number of cancer deaths did not differ from those expected from the Italian population cancer death rate.

An analysis by type of occupation (data not shown) revealed higher mortality from all cancers (SMR 2.58, 95% CI 1.53—4.08) and from lung cancer (SMR 4.83, 95% CI 2.32—8.89) among the foundry and coke oven workers. These subjects were likely to have had greater occupational exposure to polynuclear aromatic hydrocarbons (12) than refractory, ceramic, and excavation workers (SMR 1.86, 95% CI 0.96—1.87, and SMR 2.78, 95% CI 1.81—4.07, for all cancers and lung cancer, respectively).

The SMR values for all cancers and lung cancer by length of employment and years since first employment are reported in table 5. Increased risks for lung cancer were detected for silicotics with 15—29 years of employment for the latency period 15—29 years (SMR 8.12, 95% CI 2.64—18.94) and with ≥ 30 years of employment for the latency period 30 years (SMR 5.06, 95% CI 2.77—8.49). No cancer deaths were observed for the latency period ≤ 14 years (not reported in table 5). The lung cancer risk increased with increasing length of employment (SMR 2.80, 2.99, and 5.02 for ≤ 14, 15—29, and ≥ 30 years of employment, respectively).

Smoking habits were indirectly adjusted for (13) on the basis of the proportions of smokers, ex-smokers, and nonsmokers of the Italian male population (14), as well as on the basis of the proportions of subjects who smoked ≤ 10, 11—20, 21—40, and > 40 cigarettes per day. These proportions and the associated relative risks (15) that were used to estimate the expected excess mortality from lung cancer due to smoking habits are reported in table 6. Since smoking data were not available for 83 silicotics (16.1%) and the number of cigarettes smoked per day was lacking for 47 smokers (9.1%) in the study group and for 0.6% of the reference population, indirect adjustment was done on the assumption that all the subjects classified as having "unknown" habits in the study group were smokers and that smokers with an "unknown number of cigarettes smoked per day" in the study group were heavy smokers (> 40 cigarettes per day), while in the reference population they were considered light smokers (ie, they smoked ≤ 10

Table 5. All cancer and lung cancer mortality by the length of employment and years since first employment. (O = observed deaths, SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death	Years since first employment								
	15—29			≥ 30			Total		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
All cancers									
Employed ≤ 14 years	3	1.57	0.32—4.61	12	1.59	0.82—2.78	15	1.55	0.87—2.55
Employed 15—29 years	5	2.61	0.85—6.08	13	1.01	0.54—1.73	18	1.21	0.72—1.92
Employed ≥ 30 years	—	.	..	23	2.24	1.42—3.36	23	2.24	1.42—3.36
Total	8	2.06	0.89—4.06	48	1.57	1.15—2.08	56	1.61	1.26—2.15
Lung cancer									
Employed ≤ 14 years	2	3.27	0.40—11.81	6	2.77	1.02—6.02	8	2.80	1.21—5.51
Employed 15—29 years	5	8.12	2.64—18.94	8	2.15	0.93—4.25	13	2.99	1.60—5.12
Employed ≥ 30 years	—	.	..	14	5.06	2.77—8.49	14	5.02	2.74—8.42
Total	7	5.60	2.63—11.54	28	3.24	2.15—4.68	35	3.50	2.44—4.87

Table 6. Crude estimates of the lung cancer rate ratio attributable to differences in smoking habits in the study group and in the Italian male population.

	Risk	Study group			Reference population		
		Smoking habits[a]	Assumption		Smoking habits[d]	Assumption	
			First[b]	Second[c]		First[e]	Second[f]
Smokers	15	48.9			45.6		
1—10 cigarettes/day	4.6	20.6	30.2	20.6	14.6	14.8	15.2
11—20 cigarettes/day	7.5	15.0	22.0	15.0	23.1	23.4	23.1
21—40 cigarettes/day	13.1	3.6	5.26	3.6	6.8	6.9	6.8
> 40 cigarettes/day	16.6	0.6	0.78	25.2	0.5	0.5	0.5
Unknown		9.1	.	.	0.6	.	.
Ex-smokers	4	20.6	.	.	13.5	.	.
Nonsmokers	1	14.4	.	.	40.9	.	.
Unknown	.	16.1	.	.	.		
Rate ratio	.	1.066[1]	1.146[2]	1.767[3]	1	1	1

[a] Smoking habits of the silicotics.
[b] Assuming that those with unknown smoking habits in the study group (16.1%) were all smokers equally distributed within each cigaretters/day group.
[c] Assuming that both "unknown" in the study group (16.1% + 9.1%) smoked > 40 cigarettes/day.
[d] Smoking habits of the referents (14).
[e] Assuming that smokers with unknown cigarette consumption in the reference population (0.6%) were equally distributed with each cigarettes/day group.
[f] Assuming that smokers with unknown cigarette consumption in the reference population (0.6%) smoked ≤ 10 cigarettes/day.
[1] a vs d, [2] b vs e, [3] c vs f.

cigarettes per day). According to these assumptions, the mortality risk from lung cancer attributable solely to smoking ranged between 1.066 and 1.767. Thus the maximum lung cancer risk explainable by smoking was (3.5-1.767)/3.5 or 50%.

Discussion

The findings of our study show that clinically diagnosed silicotics experience a higher than expected mortality from all cancers, lung cancer, silicotuberculosis, silicosis, and digestive tract diseases. Excess mortality from lung cancer and silicotuberculosis is consistent with the results of other studies on silicotic subjects, particularly that by Infante-Rivard et al (16). An analysis by length of employment suggested that exposure to silica dusts may increase the risk of lung cancer among workers who develop silicosis. The observed dose-response relationship between lung cancer risk and length of employment is suggestive of a causal role played by exposure to silica dusts and lung cancer development, although the role of other occupational carcinogens may be important as well. Indirect adjustment for smoking explained about 50% of the excess mortality from lung cancer. The marginal role of smoking in causing the observed excess of lung cancer was confirmed also by the significantly lower mortality from cardiovascular diseases and by the lack of excess risk for smoking-related neoplasms other than lung cancer.

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Silicosis and lung cancer among workers in North Carolina dusty trades

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In 1940—1983, 760 cases of silicosis were identified among male North Carolina (NC) workers in dusty trades. Vital status was ascertained through 1983 for 714 silicotics, and death certificates were obtained for 546 of the 550 decedents. The standardized mortality ratio (SMR) for lung cancer based on United States rates was 2.6 [95% confidence interval (95% CI) 1.8—3.6] for whites, 2.3 (95% CI 1.5—3.4) for whites unexposed to other known occupational carcinogens, and 2.4 (95% CI 1.5—3.6) for whites with no other exposure and diagnosed with silicosis while still employed in dusty trades. In addition, the age- and smoking-adjusted rate for silicotics was 3.9 times higher (95% CI 2.4—6.4) than that of nonsilicotic metal miners. This analysis effectively controlled for confounding by age, cigarette smoking, exposure to other occupational carcinogens, and detection bias. The results congrue with the hypothesis of an association between silicosis and lung cancer.

Key terms dusty trades, lung cancer, silicosis.

In 1987, the International Agency for Research on Cancer (1) concluded that there was sufficient evidence from animals and limited evidence from humans for the carcinogenicity of silica. Subsequently, McDonald (2) suggested that bias, confounding, and chance may explain the findings in humans.

By 1987, there existed a body of published evidence for increased lung cancer mortality among silicotics. However, this evidence was somewhat weakened by study shortcomings. Few studies of silica-exposed workers had employed reference groups of nonsilica-exposed workers, and few studies of silicotics had employed a nonsilicotic reference group defined within the same silica-exposed population. In most studies of silicotics, a definition of "compensable" silicosis was employed which differed between countries. A definition of silicosis based on a standardized radiographic classification was employed in only a few studies.

Detection bias was speculated to be the primary explanation of increased rate ratios for lung cancer mortality among silicotic cohorts, and it was not addressed in any studies before 1987. Detection bias was speculated to arise if the probability of detecting silicosis among lung cancer cases was greater than that among nonlung cancer cases.

In addition to these issues, confounding from cigarette smoking and occupational exposure to potential and known carcinogens such as radon, arsenic, and polycyclic aromatic hydrocarbons was generally not ruled out in most studies prior to 1987. In studies of underground metal and nonmetal miners, the association between silica, or silicosis, and lung cancer mortality was possibly confounded by exposure to radon and arsenic. Similarly, in studies of foundry workers, the association was likely confounded with a variety of potential carcinogens.

During 1983 to 1987, a collaborative study between the United States (US) National Institute for Occupational Safety and Health, the US National Cancer Institute, and the University of North Carolina at Chapel Hill was conducted to address some of the shortcomings of previous studies. In this collaborative study, we evaluated the mortality of 760 North Carolina (NC) workers who were employed in NC dusty trades and who were diagnosed with silicosis during 1940—1983. The results of this study were published during 1991 and 1992 (3, 4).

Data from our study have several advantages over investigations published prior to 1987. First, they represent silicotics in the NC dusty trades with occupational silica exposure. Second, the misclassification of silicosis was minimized because silicosis was defined radiographically. Third, individual data were available on cigarette smoking and employment history in order to adjust for potential confounding from cigarette smoking and exposure to other known occupational carcinogens. Fourth, workers who were examined as part of a voluntary examination conducted at their worksite could be distinguished from those examined as part of a self-initiated examination, often for compensation purposes. Thus detection bias among compensated workers could be minimized by excluding workers who were examined after leaving employment in NC dusty trades. Finally, data were available on a reference group of nonsilicotics with comparable risk factor information.

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The purpose of this paper is to summarize our methods and findings.

Methods

Since 1935, the state of North Carolina has conducted a voluntary program in which medical examinations are offered every one to two years to each worker in the NC dusty trades. The program defines dusty trades to include mining, foundries, quarrying, stone crushing, asbestos and silica manufacturing products, and construction.

Medical examinations are administered by the NC Industrial Commission at the worksite and consist of a posteroanterior chest radiograph and questionnaires on work history, medical symptoms, and, since 1964, cigarette smoking habits. Radiographs are classified for silicosis according to the 1930 Johannesburg Conference Report system.

Work history and cigarette-smoking habit data were abstracted from the NC Industrial Commission medical examination files for 760 silicotics. Vital status from 1940 through 1983 was verified for 714 (94%) of the 760 workers, and death certificates were obtained for 546 (99%) of the 550 deceased. The underlying cause of death was abstracted from the death certificates and coded according to the International Classification of Diseases, Adapted (5). Details of the program and the vital status follow-up have been documented elsewhere (3, 6).

Radiographs were available for 370 of the 760 silicotics. These films were reclassified for pneumoconiosis by three physicians who employed the classification of the International Labour Organisation (ILO) (7). The analysis focused primarily on whites, as there was only one lung cancer death among nonwhite subjects. Details of this reevaluation have also been published elsewhere (4).

The age-adjusted mortality rates of the silicotic cohort were compared to that of the US white male population and to that of a sample of white nonsilicotic metal miners (3). During 1959—1961, the US Public Health Service examined 12 258 metal miners as part of a cross-sectional study of silicosis. The vital status of this sample was ascertained as of 1975 (8). Each worker had been administered a chest radiograph and a questionnaire on work history, cigarette smoking habits, and respiratory symptoms. The chest radiographs were interpreted for pneumoconiosis according to the 1959 ILO classification. Data on 9543 nonsilicotic white males who were employed in nondiesel, nonuranium metal mines were used as a reference group for the NC cohort.

Results

The standardized mortality ratios (SMR) based on US white rates were significantly increased for white male silicotics due to tuberculosis (SMR 30.7), cancer of the intestine (SMR 2.3), pneumonia (SMR 2.4), bronchitis (SMR 7.9), emphysema (SMR 3.6), pneumoconiosis and other respiratory diseases (SMR 32.9), and infectious kidney disease (SMR 6.5). Several SMR values were greater than 1.5, but they did not reach statistical significance, including cancers of the liver (SMR 2.3), prostate (SMR 1.9), and lymphatic and hematopoietic tissue (SMR 1.7), influenza (SMR 2.6), and asthma (SMR 3.1). The lung cancer SMR was also significantly increased for the white male silicotics, 2.6 [95% confidence interval (95% CI) 1.8— 3.6], based on rates for US white males, and 3.0 (95% CI 2.0—4.2), based on rates for NC white males. The SMR values for tuberculosis (SMR 20.5), ischemic heart disease (SMR 2.1), and pneumoconiosis and other respiratory diseases (SMR 56.4) were significantly increased for nonwhites. Because only one case of lung cancer occurred among the nonwhites (SMR 0.7), the remainder of the results presented are for whites only.

The lung cancer SMR values were 2.3 (95% CI 1.5—3.4) for silicotics who had no exposures to other known occupational carcinogens and 4.5 (95% CI 1.8—9.2) for those with other exposures (ie, previous employment in asbestos product manufacturing, olivine mining, talc mining, insulation work, or foundries). The lung cancer SMR was 3.4 (95% CI 2.0—5.3) for workers with a history of cigarette smoking and 1.7 (95% CI 0.5—3.9) for nonsmokers.

In order to minimize the effect of detection bias on the rate ratio for lung cancer mortality, lung cancer SMR values were estimated separately for silicotics who were diagnosed with silicosis while employed in the dusty trades. In addition, lung cancer SMR values were estimated with control for years after silicosis diagnosis. The lung cancer SMR was 2.5 (95% CI 1.7—3.7) for silicotics who were diagnosed while employed and 2.9 (95% CI 0.9—6.8) for those diagnosed after leaving employment. Among those diagnosed while employed, the lung cancer SMR values were 3.8 (95% CI 1.5—7.8) for < 5 years after the silicosis diagnosis, 1.3 (95% CI 0.3—3.9) for 5—9 years, 2.4 (95% CI 1.2—4.5) for 10—19 years, and 2.8 (95% CI 1.2—5.6) for ≥ 20 years. The comparable figures for the silicotics diagnosed after leaving employment were 2.2 (95% CI 0.1—12.2) for < 5 years, 7.0 (95% CI 1.5—20.6) for 5—9 years, and 1.6 (95% CI 0.0—9.2) for 10—19 years (there were no lung cancer deaths for ≥ 20 years).

With the use of the metal miner reference group, the age-adjusted Mantel-Hansel incidence density rate ratios were 3.2 (95% CI 1.8—5.8) for cigarette smokers and 8.6 (95% CI 3.6—20.5) for those who had never smoked. The age and smoking-adjusted rate ratio was 3.9 (95% CI 2.4—6.4).

Among the 370 workers whose radiographs were available and were reclassified, 104 were reclassified as category 0, 160 as simple silicosis (category 1—3), 83 as progressive massive fibrosis, and 23 were unreadable (4).

The lung cancer SMR values for the silicotics whose radiographs were reclassified and who were never employed in a job with exposure to other known carcinogens were 1.2 (95% CI 0.2—4.4) for those whose radiographs were reclassified as category 0 and 2.4 (95% CI 1.0—5.0) for those reclassified as simple silicosis (4). The age-adjusted Mantel-Haenszel rate ratio for simple silicosis compared with category 0 was 1.5 (95% CI 0.4—5.8).

Discussion

The association between silicosis and lung cancer mortality did not appear to be explained by chance, misclassification of silicosis, confounding from cigarette smoking, confounding from exposure to other occupational carcinogens, or detection bias. Lung cancer mortality was significantly higher for white silicotics than for US white males, NC white males, and white male metal miners. The increased lung cancer mortality was not likely a chance finding for the silicotics.

After the silicotics were partitioned by the severity of the radiographic evidence of silicosis, lung cancer mortality was also higher for those reclassified with simple silicosis compared with

those reclassified with category 0. This procedure effectively controlled for the misclassification of silicosis.

Lung cancer mortality was significantly higher among the NC silicotics who had no other occupational exposure than among nonsilicotic metal miners after adjustment for cigarette smoking habits. This procedure effectively controlled for confounding from exposure to other known occupational carcinogens and cigarette smoking.

Finally, lung cancer mortality was increased among the silicotics who had been diagnosed as having silicosis at least 10 years prior to death or at the end of follow-up. In addition the lung cancer SMR was increased and the SMR for all cancers excluding the lung was not increased (0.9) among the silicotics diagnosed while employed in NC dusty trades. This finding suggests that detection bias is an unlikely explanation for the increased lung cancer mortality among NC silicotics.

Our results are consistent with the hypothesis of an association between silicosis and cancer. This evidence is relatively free of the major shortcomings common in previous studies, such as chance, misclassification of silicosis, confounding, and detection bias.

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Silica, silicosis and cancer in Finland

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Approximately 100 000 Finnish workers are currently employed in jobs and tasks that may involve exposure to airborne silica dust. The major industries involved are mining and quarrying; production of glass, ceramics, bricks and other building materials; metal industry, particularly iron and steel founding; and construction. Over 1500 cases of silicosis have occurred in Finland since 1935. Tuberculosis has been a frequent complication of silicosis. Results of studies from several countries strongly suggest that silica dust also causes lung cancer. The results of the relevant Finnish epidemiologic and industrial hygiene studies addressing cancer risk and exposure to quartz dust are summarized.

Key terms ceramics, construction, dust, excavation, glass, iron founding, lung cancer, mining, steel casting, stone industry.

In Finland, heavy occupational exposures to quartz dust trace back to mining operations in the 16th century. From 1910 to the late 1980s a large copper mine represented a prominent source of extensive silica exposure. Iron foundries, steel casting, stone quarries, ceramic factories, and the construction industry constitute trades associated with health hazards from quartz dust. The earliest workplace measurements of dust concentrations were made in 1944, continuing on a sporadic basis. Legislation concerning the work environment, the medical follow-up of Finnish workers in dusty trades, and compensation of silicosis have been operative for decades (1).

Öhman (2) and Noro & Pätiälä (3) conducted pioneering Finnish studies of silicosis in 1927 and 1954. Since the 1970s, epidemiologic and industrial hygiene studies have been conducted on silica dust exposures (4—6), silicosis (1, 7), silicosis and cancer (8, 9), mortality in various silica-related occupations (10, 11), granite workers (12—15), foundry workers (16), copper miners (17), and the work environment and health status of granite workers (18). This communication reviews the results of these studies, with special emphasis on cancer risk.

Occupational exposure to silica dust

About 100 000 Finnish workers are currently employed in jobs and tasks that may involve hazardous exposure to airborne silica dust. In 1980—1989 the Finnish Institute of Occupational Health conducted dust measurements at 146 worksites. The hygienic limit, 0.2 mg · m^{-3}, for respirable quartz was exceeded in 45% of the 802 samples taken from various industries (table 1). The estimated number of exposed workers was about 1000 in the stone industry; about 5000 in mining and quarrying; about 10 000 in the production of glass, ceramics, bricks, and other building materials; about 3000 in iron and steel founding; and about 50 000 in construction and excavating occupations. High silica exposures were also common during sandblasting and grinding in numerous metal industries (6).

Silicosis

The first diagnosis of silicosis in Finland was made in 1914. As a result of a comprehensive search, Ahlman (1) identified 878 cases diagnosed from 1935 to 1964. A total of 667 additional cases was reported from 1964 to 1992 to the Finnish national register of occupational diseases. Thus approximately 1500 cases have occurred since 1935 in a total Finnish labor force that varied between one and two million. In the past, tuberculosis was a frequent complication of silicosis. On the average, the workers with early cases of silicosis had been exposed to mineral dusts with higher silica contents than the workers with more recent cases, particularly in the mining and stone industry. Recently diagnosed cases represent a higher proportion of mixed dust fibrosis. The distribution of cases from 1964 to 1992 is shown in table 1 by industry.

Epidemiology of silica, silicosis and cancer

The results of the Finnish epidemiologic studies of lung cancer risk among workers exposed to silica dust and among silicotics are summarized in table 1.

A follow-up study (14) from 1940 to 1985 of 1026 granite workers exposed to "pure" silica revealed a significant excess mortality [standardized mortality ratio (SMR) 1.6, 95% confidence interval (95% CI) 1.1—2.2] from lung cancer. Confounding by tobacco smoking or concomitant occupational exposures did not explain the risk increment. There were 15 deaths from gastrointestinal cancer (7.4 expected, SMR 2.0, 95% CI 1.1—3.8) for workers employed for at least three months and followed until 1975 (15). From 1970 to 1972 the mean concentration of respira-

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Table 1. Summary of quartz dust levels, numbers of silicotics, and lung cancer risk by industry. (N = number of worksites, n = number of measurements, SMR = standardized mortality ratio, SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Branch of industry	Respirable quartz dust in 1980—1989[a]					Number of notified cases of silicosis 1964—1992	Lung cancer risk							
	% exceeding 0.2 mg · m^{-3}	Mean (mg · m^{-3})	Maximum (mg · m^{-3})	N	n		Census linkage[b] 1971—1980		Cohort studies[c]		Silicotics, mortality[d] 1935—1982		Silicotics, incidence[e] 1953—1991	
							SMR	95% CI	SMR	95% CI	SMR	95% CI	SIR	95% CI
Mining and quarrying	11	0.10	0.7	6	19	92	4.3	2.8—6.5	2.3	1.1—4.3	4.4	2.6—6.7	3.7	2.6—5.0
Stone industry	88	1.29	6.8	12	33	80	1.8	1.0—2.9	1.6	1.1—2.2	2.7	1.1—5.5	2.9	1.6—5.0
Casting and founding						182	1.6	1.3—1.9					1.7	1.1—2.6
Steel	37	0.27	2.6	4	128						1.8	0.5—4.5	1.7	0.8—3.3
Iron	30	0.23	4.9	15	169				1.4[f]	1.1—1.9[f]	2.3	0.9—4.7	1.6	0.9—2.9
Glass, ceramics and building materials production	49	0.90	26.7	43	177	103	1.3	0.8—1.9					3.3	1.6—6.1
Construction	58	1.64	28.9	21	72	25	·	·	·	·	·	·	10.4	1.3—37
Excavation	94	1.58	15.4	10	36	71	2.0	1.3—2.8	·	·	·	·	5.8	2.7—11
Other	41	0.68	8.6	47	145	114								
All	45	0.69	28.9	146	802	667	·	·	·	·	3.1	2.3—4.1	2.9	2.4—3.5

[a] From reference 7.
[b] From references 10 and 11.
[c] From references 15, 16, and 17.
[d] From reference 4.
[e] From reference 12.
[f] Proportional mortality ratio.

ble silica dust was about 1 mg · m^{-3}. The workplace standard was exceeded on the average by a factor of ten in drilling and stone cutting operations (14, 15).

An excess proportional mortality ratio (PMR) from lung cancer (PMR 1.4, 95% CI 1.1—1.9) was reported for iron foundry workers (16). Tossavainen (19) estimated that in iron foundries the probabilities for polyaromatic compounds, silica, and metal fumes as causes of lung cancer would be 0.20, 0.15, and 0.05, respectively.

Lynge and her colleagues (10, 11) followed Nordic cohorts exposed to silica dust for cancer mortality and incidence. The Finnish component was defined as of 1970 and followed-up for lung cancer mortality from 1971 to 1980. Significant excesses were observed for miners (SMR 4.3, 95% CI 2.8—6.5) and workers in the stone industry (SMR 1.8, 95% CI 1.0—2.9), foundries (SMR 1.6, 95% CI 1.3—1.9), and excavation and related industries (SMR 2.0, 95% CI 1.3—2.8). A follow-up study from 1954 to 1986 of 597 copper miners (17) found 10 deaths from lung cancer against 4.3 expected (SMR 2.3, 95% CI 1.1—4.3).

In a mortality follow-up study (8) extending to 1982, 80 deaths from lung cancer occurred among 961 male silicotics diagnosed from 1935 to 1977, against 25.6 expected (SMR 3.1, 99% CI 2.3— 4.1). The excess persisted over various branches of industry and over time. A sevenfold increase for deaths from all pulmonary diseases, including an "infinite" excess for pneumoconiosis and fibrosis, a 4.5-fold increase for chronic bronchitis, emphysema, and asthma, and a 7.4-fold increase for respiratory tuberculosis were observed. The authors noted that tobacco smoking was unlikely to explain the observed lung cancer excess completely (8).

In a subsequent study by Partanen et al (9) the lung cancer excess was confirmed when 811 silicotics diagnosed from 1953 to 1991 were followed for cancer incidence. Excesses were observed for all cancers [standardized incidence ratio (SIR) 1.7 , 95% CI 1.4—1.9], all lung cancers (SIR 2.9, 95% CI 2.4—3.5), squamous-cell lung cancers (SIR 3.3, 95% CI 2.3—4.5), and skin cancers (melanoma: SIR 3.0, 95% CI 0.8—7.6; nonmelanoma: SIR 2.9, 95% CI 1.2—6.1). Neither confounding by tobacco smoking nor detection bias explained the elevated lung cancer risk. The skin cancer excess, a novel finding, may be explained either by other carcinogens in foundries or a silica-induced lowering of immunocompetence, which could lead to a more pronounced effect of solar ultraviolet radiation (9).

Concluding remarks

Silica dust has posed and still constitutes an occupational health hazard for 100 000 potentially exposed workers in Finland. The severity of the risk is characterized by the resulting health risks, including silicosis, silicotuberculosis, and reduced life span. Results of recent Finnish research strongly support the findings of numerous studies from other countries in suggesting that silica dust also causes lung cancer.

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Assessment of silicosis risk for occupational exposure to crystalline silica

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Rice FL, Stayner LT. Assessment of silicosis risk for occupational exposure to crystalline silica. *Scand J Work Environ Health* 1995;21 suppl 2:87—90.

Epidemiologic studies of workers exposed to silica were reviewed to identify data on airborne concentrations of quartz that are not associated with an increased risk of silicosis, the lowest concentrations associated with silicosis, and studies that used statistical models to quantitate the risk of silicosis as a function of silica exposure. The no observed adverse effect levels varied from 7 to 100 $\mu g \cdot m^{-3}$, and the lowest observed adverse effect levels ranged from 8 to 252 $\mu g \cdot m^{-3}$ in five different cohorts. Studies using quantitative exposure-response models revealed a wide difference in the cumulative risk estimates for silicosis. The differences in the risk estimates and the no observed and lowest observed effect levels may have been the result of errors in exposure estimates, physicochemical characteristics of silica and quartz content of the dust, cohort differences, and reader variability. Further research is needed to define the dose-response relationship between silica exposure and silicosis.

Key terms epidemiology, LOAEL, lowest observed adverse effect level, NOAEL, no observed adverse effect level, quartz, risk assessment.

Silica is the designation given to minerals that contain silicon dioxide (1). It occurs naturally in crystalline and amorphous forms. The most common crystalline forms of silica encountered in industry (quartz, tridymite, and cristobalite) have been associated with the development of silicosis in workers (2, 3). However, quartz is by far the most common natural form of silica (1, 3).

Approximately 1 600 000 workers were exposed in the United States to respirable crystalline silica dust in mining and nonmining industries in 1986 (4, 5).

Based on information from death certificates, the reported number of deaths involving silicosis in the United States has decreased gradually from more than 1000 in 1970 to fewer than 400 in 1987 (4). The New Jersey Department of Health reported 121 confirmed cases of silicosis for 1979—1987 (6), and there were 562 cases detected in Ohio in 1989—1994 (7), but the true number of new cases is unknown because of underreporting by employers (8) or misdiagnosis by physicians on death certificates.

Many epidemiologic studies have addressed the relationship between occupational exposure to crystalline silica and silicosis, but few have provided information for quantifying this relationship. Such studies are needed to estimate risks from occupational exposures to crystalline silica and to evaluate the adequacy of current occupational health standards.

The current permissible exposure limit (PEL) set by the Occupational Safety and Health Administration in the United States for respirable crystalline silica (quartz) is 10 $mg \cdot m^{-3}/(\%SiO_2+2)$ for general industry [29 CFR 1910.1000 (CFR = Code of Federal Regulations; see reference 9)]. The current recommended exposure limit for respirable crystalline silica (all types) set by the National Institute for Occupational Safety and Health (NIOSH) is 0.05 $mg \cdot m^{-3}$ (2, 10).

Identifying an exposure limit that will prevent silicosis may also reduce the risk of lung cancer among silica-exposed workers. In 1987, the International Agency for Research on Cancer (IARC) (1) concluded that there is "sufficient evidence" for the carcinogenicity of crystalline silica in experimental animals but only "limited evidence" for the carcinogenicity of crystalline silica in humans. Subsequently, Simonato & Saracci (11) and Pairon et al (12) have reviewed the epidemiologic studies on the relationship of lung cancer to silica dust and concluded that the risk of lung cancer appears to be limited primarily to workers who develop silicosis. One study that controlled for environmental exposure concentrations reported a direct relationship between silica exposure and lung cancer independent of silicosis (13). The hypothesis that the risk of lung cancer is limited to individuals with silicosis is still debatable (14).

Methods

Study objectives. Our review was restricted to epidemiologic studies that have provided quantitative information about the relationship between silica exposure and the risk of silicosis. Two objectives of this review were to identify airborne concentrations of quartz that have not been associated with an increased risk of silicosis [ie, the no observed adverse effect level (NOAEL)] and to identify the lowest concentrations associated with silicosis [ie, the lowest observed adverse effect level (LOAEL)]. The LOAEL and NOAEL values were not determined on the basis of statistical significance, but rather on the basis of biologically meaningful evi-

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Table 1. Summary of six epidemiologic studies of silicosis with environmental data. (ILO = International Labour Office)

Reference	Study design*	Study population	Adverse health effect	Silica (quartz) content of dust (%)
Davis et al (20)	Proportionate mortality study	Vermont (US) granite workers who died between 1952 and 1978 and were employed ≥ 1 years (N = 969)	Silicosis mortality (28 deaths)	9—14 (years 1965—1966)
Hnizdo & Sluis-Cremer (15)	Retrospective cohort study	South African underground gold miners who started working after 1938, worked ≥ 10 years, and were followed until 1991 (N = 2235)	Silicosis (ILO ≥ 1/1, 313 cases)	30
McDonald & Oakes (19)	Retrospective cohort mortality study	South Dakota (US) underground gold miners employed ≥ 21 years (N = 1321)	Pneumoconiosis mortality	39 (settled dust samples)
McDonald & Oakes (19)	Cross-sectional study	Underground gypsum miners employed ≥ 20 years in the United Kingdom (N = 64)	Silicosis (ILO ≥ 1/0, number of cases for ≥ 20 years was not reported, total silicosis cases = 16)	Not reported
Muir et al (16, 17, 21, 22)	Retrospective cohort study	Ontario (Canada) gold and uranium miners who started between 1940 and 1959 and were followed to 1982 or to the end of their dust exposure, whichever came first (N = 2109)	Silicosis (ILO ≥ 1/1, 32 cases)	6.0 for gold mines and 8.4 for uranium mines
Rice et al (18)	Case-referent study	North Carolina (US) dusty trades workers diagnosed with silicosis between 1935 and 1980	Silicosis; radiographic classification not reported for 216 silicosis cases; 672 referents consisted of disease-free dusty trades workers	1—50

dence that the risk for silicosis was above that posed by some background concentrations of silica. The studies that provided information about effect levels (NOAEL and LOAEL) analyzed various categories of silica exposure. When the authors defined these categories as a range of exposures, the midpoint of the range was used for estimating the effect levels. A third objective of this paper was to review studies that present statistical models of the quantitative relationship between silica exposure and the risk of silicosis.

Descriptions of reviewed studies. Table 1 describes the populations and designs of six epidemiologic studies that reported evidence of an exposure-response relationship for silicosis. The study outcomes varied greatly. In four studies concerning South African gold miners, Ontario hardrock miners, North Carolina dusty trades workers, and British gypsum miners, silicosis was defined on the basis of chest X-ray classification (15—19). These studies used different classification systems for diagnosing silicosis from X rays. The other two studies of Vermont granite workers and South Dakota gold miners were based on the diagnosis of silicosis or pneumoconiosis on death certificates (19, 20).

The six studies also differed in the quality of available exposure information. Several studies presented results in millions of particles per cubic foot (mppcf) or as total dust exposure. Exposure estimates were converted by the authors to micrograms of respirable silica per cubic meter ($\mu g \cdot m^{-3}$). These conversions were made using the conversion factors and percentages of silica in published studies. When the findings were expressed as cumulative exposures, the results were converted to the NOAEL and LOAEL values corresponding to 45 years of occupational exposure (a maximum worklife assuming employment from ages 20 to 65 years).

Finally, these studies differed in the statistical methods used to examine the relationship between silica exposure and silicosis. Several studies analyzed their results through categories of exposures that could be used to determine the NOAEL or LOAEL values. Some of the studies (15—17, 21, 22) used statistical models to describe the relationship between silica exposure and the risk of silicosis. These models could not be used to determine the NOAEL since they produce risk estimates at any nonzero concentration of silica exposure. An exception was the study by McDonald & Oakes (19), which examined models with and without a "threshold" parameter. These models were used to identify a NOAEL.

Table 2. Summary of the no observed and lowest observed adverse effect levels (NOAEL and LOAEL, respectively) in six studies of silicosis. ($\mu g \cdot m^{-3}$ = micrograms of respirable silica per cubic meter, mppcf = millions of particles per cubic foot)

Reference	NOAEL		LOAEL	
	$\mu g \cdot m^{-3}$	mppcf	$\mu g \cdot m^{-3}$	mppcf
Davis et al (20)	67.5	9	.	.
Hnizdo & Sluis-Cremer (15)	7	.	20	.
McDonald & Oakes (19)				
Gold miners	.	.	8	0.5[a]
Gypsum miners	35[a]	.	49[a]	.
Muir et al (16, 17, 21)	..[b]	..[b]	..[b]	..[b]
Rice et al (18)	80—100	1	200—252	2.5

[a] Derived from a subcohort of workers with > 20 years of employment; does not reflect a 45-year lifetime of work.
[b] Effect levels could not be derived from this study because the results were only presented in terms of a dose-response model that implied risk at any level of exposure.

Results and discussion

Identification of adverse effect levels. Table 2 lists the NOAEL and LOAEL for each of the six studies. The estimated NOAEL values ranged from 7 to 100 $\mu g \cdot m^{-3}$ and the LOAEL values were between 8 and 252 $\mu g \cdot m^{-3}$.

In the cohort of Vermont granite workers (20), only 1 of the 28 silicosis deaths occurred among the men who were hired after dust controls were implemented in the granite industry. However,

this death was discounted because it was believed to have been caused by emphysema — a diagnosis based on an X-ray reading done two months before the worker's death. During that postcontrol period, the highest concentration of granite dust was 9 mppcf (67.5 μg · m^{-3}); hence 67.5 μg · m^{-3} was chosen as the NOAEL.

A lifetable analysis of silicosis cases among South African underground gold miners (15) was used to derive a NOAEL of 7 μg · m^{-3} and a LOAEL of 20 μg · m^{-3} for a 45-year worklife. No cases of silicosis were observed among 2218 gold miners with cumulative dust exposures of 1 mg · m^{-3}-years (the midpoint of the cumulative dust exposure category), which is equal to 7 μg · m^{-3} for 45 years [1 × 0.3 (for 30% silica)/45 years]. Nine cases of silicosis were observed among 2014 miners in the exposure category of 3 mg · m^{-3}-years (the midpoint of the cumulative dust exposure category), which is equal to 20 μg · m^{-3} for 45 years (3 × 0.3/45).

McDonald & Oakes (19) analyzed two cohorts, underground South Dakota (United States) gold miners and British underground gypsum miners. In the mortality study of 1321 gold miners in the United States, 8 μg · m^{-3} was the lowest concentration at which deaths were observed. However, a NOAEL could not be identified from either the stratified analysis or the model. The study of 64 British gypsum miners used radiographic data from a cross-sectional study done in 1976 and 1977. The NOAEL for small radiographic opacities (≥ 1/0) was 35 μg · m^{-3} on the basis of the threshold model and 33 to 35 μg · m^{-3} on the basis of the stratified analyses of the prevalences in different mines. The LOAEL based on the stratified analysis was 49 μg · m^{-3}. A NOAEL or LOAEL for a 45-year worklife could not be calculated because the results were reported only for men who had worked for 20 or more years.

For workers in the North Carolina dusty trades (18), the NOAEL was 90 to 113 μg · m^{-3} and the LOAEL for silicosis was 225 to 283 μg · m^{-3} for a 40-year worklife (based on the silicosis odds ratios calculated by conditional logistic regression). Ranges exist for the NOAEL and LOAEL values because two methods were used to convert count data (mppcf) to mass concentration units (μg · m^{-3}). When mass was estimated for size fractions, the NOAEL was 1 mppcf (113 μg · m^{-3}). The LOAEL for silicosis using this conversion method was 2.5 mppcf (283 μg · m^{-3}). The second approach used a conversion factor translating cyclone data to count estimates. The count value was multiplied by 0.09 to arrive at mass in milligrams per cubic meter. When this method is used, the NOAEL is 1 mppcf (90 μg · m^{-3}) for a 40-year worklife. The LOAEL is 2.5 mppcf (225 μg · m^{-3}) over a 40-year worklife. For a 45-year worklife, the NOAEL is 80 to 100 μg · m^{-3} (90 × 0.889; 113 × 0.889), and the LOAEL is 200 to 252 μg · m^{-3} (225 × 0.889; 283 × 0.889). However, the NOAEL and LOAEL identified from this study may have been affected by errors in the classification of the silicosis cases. A review of the X-rays found that 104 of the 370 cases categorized as silicosis in this study were actually category 0 (23). Concern also existed that the use of cumulative exposure in this and other studies may ignore differences in risk resulting from different dose-rate patterns. In a reanalysis of the dusty trades cohort data, Checkoway & Rice (24) showed that peak exposures may predict silicosis risk better than cumulative exposures.

Exposure-response models. Only two studies (15, 17, 21, 22) used statistical models to assess the relationship between cumulative silica exposure and the risk of silicosis. Figure 1 shows the cumulative risk of silicosis with a five-year lag for the cohort of Ontario hardrock miners by each of the five readers used in the study by Muir et al (17, 22). This study used a Weibull statistical model (23, 17), which assumes some risk for any exposure. With this model, the current NIOSH recommended exposure limit (REL) of 50 μg · m^{-3} for a 45-year worklife would correspond with a cumulative exposure of 2.0 mg · m^{-3}-years [50 μg · m^{-3} × [45 minus the five-year lag)], and the risk at the NIOSH REL would range from 0.0009 for reader 5 to 0.0062 for reader 2. This nearly sevenfold difference in risk estimates reflects the great uncertainty related to different diagnoses made by individual readers.

The study of South African underground gold miners (15) used the category of ≥ 1/1 of the International Labour Office to define silicosis. This study used an accelerated failure time model, which also assumes some risk for any exposure. Fourteen percent of this cohort (313 cases) met the definition for silicosis compared with 1.5% of the Canadian cohort that included gold miners (16, 17, 22). The silica content of the respirable dust in South African gold mines (after heat and acid treatment) is about 30% (15, 25). In the hardrock mines studied by Muir et al (17), the silica content of the respirable dust was 13 to 17% in the early years of the study when the concentrations were highest. Figure 2 shows that 2.25 mg · m^{-3}-years of exposure (which is equivalent to the NIOSH REL of 50 μg · m^{-3} for a 45-year worklife), the cumulative risk was 0.127. The risk estimates for the South African miners were

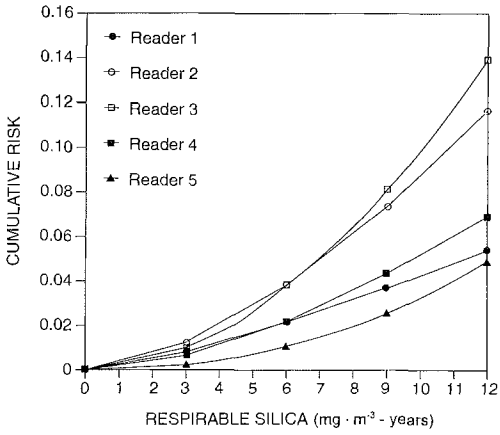

Figure 1. Estimates of silicosis risk based on the Ontario study of hardrock miners (adapted from reference 17).

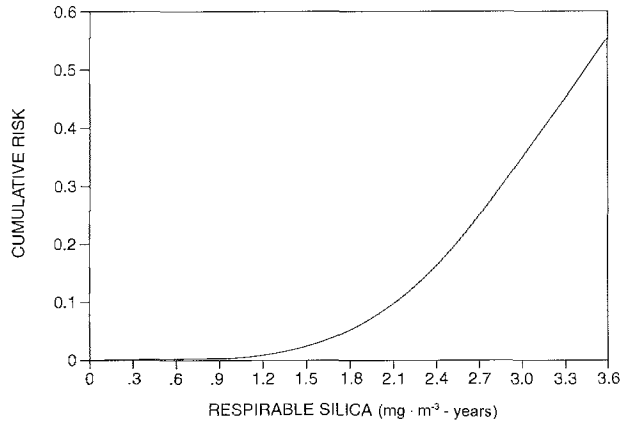

Figure 2. Estimates of silicosis risk based on the South African study of underground gold miners (adapted from reference 15).

clearly higher than those for the Canadian hardrock miners at higher exposure concentrations. Some of the risk differences may have been due to physicochemical differences between the silica particulates (Fubini et al, this volume) and the fact that the Canadian investigators only evaluated currently employed miners while the South African researchers included active and retired miners.

Concluding remarks

The epidemiologic studies of silicosis indicate that the NOAEL varies from 7 to 100 $\mu g \cdot m^{-3}$ and the LOAEL ranges from 8 to 252 $\mu g \cdot m^{-3}$. These wide ranges probably reflect differences in (i) the surface properties and particle sizes of crystalline silica from different mines, (ii) the definition and radiological classification of silicosis cases, (iii) the methods used to estimate exposures and risks, (iv) the background concentrations of airborne crystalline silica, (v) the sample sizes, and (vi) the methods used to convert particle counts to mass concentration units.

The two studies that used quantitative exposure-response models revealed a difference in the cumulative risk estimates for silicosis. For South African gold miners, the cumulative risk estimate for silicosis (0.127) was at least 20 times higher than that for the Ontario hardrock miners (0.0009 to 0.0062). This considerable difference may have resulted from (i) differences in the definition of radiographic silicosis used in the two studies, (ii) possible errors in exposure estimates, (iii) possible underestimation of the quartz content of the dust in the Canadian study (26), (iv) inhalation of aluminum dust as a protective measure by many of the Canadian miners (16), (v) reader variability, or (vi) the use of cumulative exposures to estimate risk. In addition, Muir (27) has hypothesized that exposure to higher concentrations of nonquartz dusts may have reduced the risk of silicosis observed in his study population; this hypothesis may also explain the discrepancy between his results and those of Hnizdo et al (27).

The results from our review raise concerns about the adequacy of current silica standards for preventing silicosis in the United States. However, the large variability between studies reflects a high degree of uncertainty and makes it difficult to draw firm conclusions about safe exposure concentrations. Further research is therefore needed to define the dose-response relationship between silica exposure and silicosis.

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Potential years of life lost and work tenure lost when silicosis is compared with other pneumoconioses

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Zhong Y, Li D. Potential years of life lost and work tenure lost when silicosis is compared with other pneumoconioses. *Scand J Work Environ Health* 1995;21 suppl 2:91—4.

Potential years of life lost (PYLL) and potential years of work lost (PYWL) because of pneumoconiosis were studied using the data from the Nationwide Epidemiological Study on Pneumoconioses in China. The cases were patients diagnosed with pneumoconiosis between 1949 and 1986. The subjects studied for PYLL included 74 741 cases ranging in age from 15 to 75 years, while for PYWL there were 74 224 cases with 1 to 35 years of remaining employment experience. Overall there were 1 489 692 potential years of life lost, and there was an average of 19.9 years for all pneumoconioses. Silicosis had the greatest mean PYLL with an average of 22.1 years. Coal workers' pneumoconiosis was the second leading cause of PYLL with an average of 17.0 years. The mean PYWL for all pneumoconioses was 19.7 years, and the mean PYWL from silicosis was 21.5 years. The conclusion was reached that silicosis is the most serious pneumoconiosis in China with regard to years of life lost, and chronic respiratory diseases such as chronic pulmonary disease and tuberculosis are the main causes of death for patients with pneumoconiosis.

Key terms China, cohort follow-up, potential years of life lost, potential years of work lost, pneumoconioses, silicosis.

Pneumoconiosis is one of the most serious occupational diseases in China. Every year since 1980 there have been about 20 000 workers diagnosed and more than 5000 workers have died annually from pneumoconioses throughout the country. It is a great economic loss, producing a severe toll on workers' health and productive capacity. Many mortality studies of pneumoconiosis have been carried out using different methods, but none have been done using the potential years of life lost (PYLL) and potential years of work tenure lost (PYWL) approach. The objective of this study was to apply PYLL and PYWL and to evaluate the impact of pneumoconioses on the workers who suffer from them.

The concept of PYLL was based on the following hypothesis: the average life-span of a healthy worker is expected to be 75 years. As an example, if a worker dies at 50 years of age, he or she is considered to have lost 25 years of life, or PYLL of 25 years. PYWL is derived from PYLL, with the hypothesis that a healthy worker would be able to work for at least 35 years (1, 2).

Subjects and methods

The information used in the study was drawn from a data base created for the Nationwide Epidemiological Study of 393 797 pneumoconiosis patients in China in 1986 (3). The cases were 79 636 pneumoconiosis patients who died from 1949 to 1986. Of this group, 74 741 cases with various pneumoconioses were selected as the subjects to be studied for PYLL. All of them died between 15 and 75 years of age. There were 74 224 cases with various pneumoconioses who died with a residual work tenure of 1 to 35 years and were subjects for calculating the PYWL.

A reference group of 141 484 cases with pneumoconioses was selected to standardize the constitution of work tenure. We developed a "measurement index" of PYWL (abbreviated IPYWL) based on the principle of proportionate mortality ratio using an indirect method of age standardization.

The formulas for calculating PYLL and PYWL are as follows:

$$\text{PYLL} = \sum_{i=15}^{75} N_{ai} Yai = \sum_{i=15}^{75} N_{ai}(75 - M_{ai}),$$

$$\text{mean PYLL} = \frac{\Sigma \text{PYLL}}{\Sigma N_{ai}},$$

$$\text{PYWL} = \sum_{i=1}^{35} N_{bi} Y_{bi} = \sum_{i=15}^{35} N_{bi}(35 - M_{bi}),$$

$$\text{mean PYWL} = \frac{\Sigma \text{PYWL}}{\Sigma N_{bi}},$$

$$\text{IPYWL} = \frac{\Sigma \text{PYWL}}{\Sigma \text{Ex.}} = \frac{\Sigma \text{PYWL}}{\Sigma (\Sigma N_{bi}) W_i Y_{bi}}.$$

The 95% confidence interval could be estimated as follows:

$$\text{IPYWL} \pm 1.96\text{SE} = \text{IPYWL} \pm 1.96\sqrt{\text{IPYWL}/\Sigma \text{Ex}},$$

where, N_{ai} = number of deaths in age *i* group, Y_{ai} = remaining years to live in age *i* group, N_{bi} = number of deaths in *i* years group of employment, Y_{bi} = remaining years to work in *i* years group of employment, M_{ai} = midvalue of age *i* group of death, M_{bi} = midvalue of employed work tenure group, Ex = expected PYWL, W_i = the standard proportion calculated by numbers of death in *i* year

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group of employment divided by all workers with 1—35 years of employment.

Results

The total PYLL was 1 489 692 years and the mean PYLL was 19.9 years for deaths from all pneumoconioses. Silicosis had a mean PYLL of 22.1 years and coal workers' pneumoconiosis ranked second with a mean PYLL of 17.0 years (table 1). Thus, on the average, the persons with pneumoconioses died at 55 years of age and those with silicosis died at 53 years of age.

Table 2 shows the mean PYLL for various causes of death among persons with silicosis, asbestosis, and coal workers' pneumoconiosis. For those with silicosis, the leading causes of death included pneumothorax (PYLL = 26.6), pulmonary tuberculosis (PYLL = 24.5), and emphysema (PYLL = 24.2). For asbestosis patients the leading causes of death were emphysema (PYLL = 30.0), pulmonary tuberculosis (PYLL = 18.5), and liver cancer (PYLL = 16.5). The leading causes of death for patients with coal workers' pneumoconiosis included emphysema (PYLL = 19.5), cancer of the lung (PYLL = 19.0), and tuberculosis (PYLL = 18.9). Age-specific mortality showed the maximum PYLL for silicosis at 45 years; for CWP and asbestosis the peak was 50 years of age (figures not shown).

Table 3 describes the PYWL, the mean PYWL, and the IPYWL (and the 95% confidence intervals) for different pneumoconioses. The total PYWL for all pneumoconioses was 1 458 436 years, and the mean PYWL was 19.7 years. The mean PYWL was 21.5 for silicosis and 19.8 years for asbestosis; the IPYWL for silicosis and asbestosis was 1.1525 and 1.0649, respectively, both being significantly elevated. Figure 1 illustrates the distribution of PYWL by six types of pneumoconioses. It shows that the highest

Table 1. Potential years of life lost (PYLL) by type of pneumoconiosis in China, 1949 to 1986.

Type of pneumoconiosis	Deaths (N)	PYLL	Mean PYLL
Silicosis	44 108	976 244	22.1
Coal workers' pneumoconiosis	26 356	447 480	17.0
Asbestosis	557	8 542	15.3
Cement worker's pneumoconiosis	408	6 035	14.8
Pottery worker's pneumoconiosis	1 439	21 758	15.1
Foundry worker's pneumoconiosis	1 873	29 633	15.8
Total	74 741	1 489 692	19.9

Table 2. Potential years of life lost (PYLL) by the causes of death for different types of pneumoconiosis.

Cause	Silicosis			Asbestosis			Coal workers' pneumoconiosis		
	N	PYLL	Mean PYLL	N	PYLL	Mean PYLL	N	PYLL	Mean PYLL
All causes	41 738	913 651	21.9	466	6 659	14.3	20 785	347 880	15.1
Pulmonary tuberculosis	15 300	374 455	24.5	78	1 440	18.5	4 832	91 495	18.9
All cancers	3 593	65 443	18.2	129	1 843	14.3	2 948	48 268	16.3
Esophagus	444	7 495	16.9	12	145	12.1	622	9 325	16.4
Stomach	129	2 383	18.5	7	78	11.1	84	1 388	16.0
Liver	726	15 085	20.8	19	313	16.5	586	11 155	15.5
Lung	1 758	30 860	17.6	79	1 158	14.7	1 130	18 000	19.0
Circulatory diseases	7 117	141 022	19.8	148	1 980	13.4	6 335	96 218	15.9
Hypertension	558	8 515	15.3	16	200	12.5	504	6 705	15.2
Hypertensive heart diseases	324	4 915	15.2	11	138	12.5	274	3 875	13.3
Arterial heart disease	303	5 568	18.4	16	245	15.3	275	4 448	14.1
Cor pulmonale	5 932	122 025	20.6	105	1 398	13.3	5 282	81 190	16.2
Respiratory disease	19 321	332 728	17.2	91	1 393	15.3	6 670	111 900	15.4
Pneumonia	844	18 485	21.9	17	243	14.3	412	6 690	16.8
Asthma	366	7 610	20.8	—	—	—	379	6 203	16.2
Pneumoconioses	15 029	232 208	15.5	66	1 010	15.3	5 138	86 300	16.4
Pneumothorax	1 036	27 600	26.6	—	—	—	322	6 280	16.8
Emphysema	1 599	38 648	24.2	2	60	30.0	66	1 115	19.5
Others	447	8 178	18.3	6	80	13.3	353	5 313	16.9

Table 3. Potential years of worklife lost (PYWL) for different types of pneumoconiosis in China. (IPYWL = measurement index for PYWL, 95% CI = 95% confidence interval)

Type of pneumoconiosis	Number	PYWL	Mean PYWL	Expected PYWL	IPYWL	95% CI
All pneumoconioses	74 224	1 458 436	19.7	.	.	.
Silicosis	43 720	938 185	21.5	814 066	1.1525	1.1501—1.1548
Coal workers' pneumoconiosis	25 168	423 088	16.8	468 628	0.9028	0.9001—0.9055
Asbestosis	610	12 095	19.8	11 358	1.0649	1.0459—1.0839
Cement pneumoconiosis	421	6 753	16.0	7 839	0.8614	0.8409—0.8819
Pottery pneumoconiosis	1 277	19 553	15.3	23 778	0.8223	0.8108—0.8338
Foundry pneumoconiosis	1 801	31 323	17.4	33 534	0.9340	0.9237—0.9444

Table 4. Potential years of work lost (PYWL) for the different stages of pneumoconiosis. (IPYWL = measurement index for PYWL, 95% CI = 95% confidence interval)

Stage	Deaths (N)	PYWL	Mean PYWL	Expected PYWL	IPYWL	95% CI
I	29 449	530 218	18.0	54 834	0.9670	0.9696—0.9644
II	27 544	554 036	20.1	51 286	1.0803	1.0831—1.0774
III	17 231	374 183	21.7	320 841	1.1663	1.1700—1.1625
Total	74 224	1 458 436	19.7	1 382 051	·	·

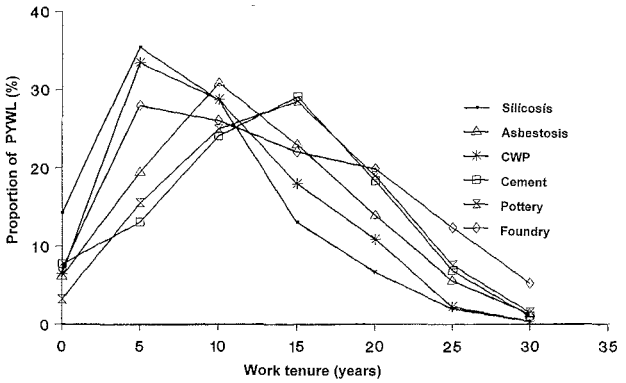

Figure 1. Proportion of potential years of life lost (PYWL) by type of pneumoconiosis. (CWP = coal workers' pneumoconiosis)

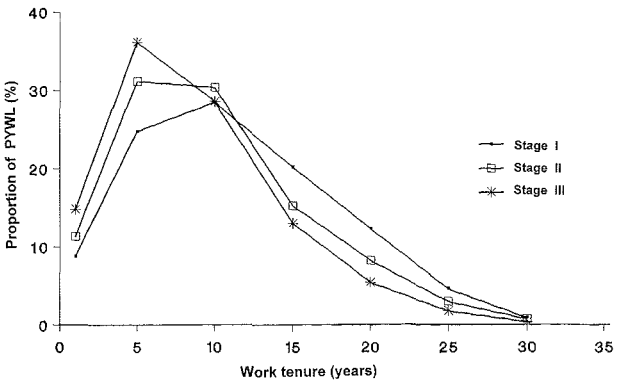

Figure 2. Proportion of potential years of life lost (PYWL) for different stages of pneumoconioses.

proportion of PYWL was found within five years of work tenure for silicosis, coal workers' pneumoconiosis, and foundry workers' pneumoconiosis and was at 10 years of work tenure for asbestosis and at 15 years for pottery and cement workers' pneumoconiosis.

Table 4 indicates the status of work tenure lost in different stages of pneumoconioses. The mean PYWL for stages I, II, and III were 18.0, 20.1, and 21.7 years, respectively. The proportional IPYWL was 0.9670, 1.0803, and 1.1663, respectively, and the latter two indices were statistically significant. Figure 2 shows that the highest proportion of PYWL for stages II and III was at 5 years of work tenure; for stage I it was 10 years.

The mean PYWL values were compared by different causes of death from all pneumoconioses, and the results were similar to that in table 2, but are not shown. Specifically, the greatest risk for the mean PYWL included pneumothorax, pulmonary tuberculosis, and emphysema. Furthermore the proportional IPYWL values for pneumothorax, tuberculosis, and emphysema were significantly elevated.

Discussion

From 1949 to 1986 there were 79 636 deaths among 393 797 patients with pneumoconiosis in China. In this study, there were 74 741 subjects for the PYLL analysis (ie, 93.8%) between the ages of 15 and 75 years and 74 224 cases (ie, 93.2%) with 1—35 years of work tenure for PYWL. Therefore, the studied subjects were clearly representative of the total pneumoconiotic patient population in China.

PYLL is a function of mean age at death (4). It is based on the concept that a healthy person will live for 75 years. Subjects not reaching this age, and who die from causes of interest (cancers and respiratory diseases), would be considered as having years of life lost. The life lost corresponds to the extent of hazard from special causes of death. Therefore, studying special causes would help to define and prevent the main causes of premature death in this cohort.

The mean PYLL of all pneumoconioses was 19.7 years, but the mean PYLL of silicosis was 22.1 years and was more than that for all pneumoconioses. Thus silicosis could be considered the most serious pneumoconiosis, having caused more years of life lost than other occupational lung diseases. The greatest proportion of PYLL for silicosis was at 45 years of age, while it was at 50 years of age for asbestosis and coal workers' pneumoconiosis. Therefore, silicosis during these years was more dangerous to workers at younger ages than the other pneumoconioses were.

The mean PYLL was the greatest for emphysema, pneumothorax (except among those with asbestosis), and pulmonary tuberculosis among the workers with silicosis, asbestosis and coal workers' pneumoconiosis. Those with coal workers' pneumoconiosis had an elevated risk of PYLL for lung cancer as well. Therefore, chronic respiratory diseases such as chronic lung diseases and pulmonary tuberculosis caused more years of life lost and were the main causes of premature death among patients with pneumoconiosis.

The total PYWL was 1 458 436 years, of which 938 185 years (64.3%) were due to silicosis and 423 088 years (29.0%) to coal workers' pneumoconiosis. From these data it is clear that silicosis and coal workers' pneumoconiosis were the leading pneumoconioses in China from 1949 to 1968 and caused the greatest loss of work tenure. In a comparison of the mean PYWL between different pneumoconioses, it was found that the mean PYWL of silicosis and asbestosis was 21.5 and 19.8 years, respectively. There is a legal stipulation in China that a worker should stop working when he or she is diagnosed with pneumoconiosis. Our results suggest that the average length of dust exposure was only 15.3 years for the workers before they were diagnosed with pneumoconiosis and lost 19.7 years of employment. Silicosis and asbestosis were the

leading causes of work tenure lost for all pneumoconioses, and this finding was confirmed by the elevated proportional IPYWL for silicosis and asbestosis as well. The highest proportion of PYWL was in the five-year interval of work tenure for both silicosis and asbestosis.

In a comparison of the different stages of pneumoconiosis, the mean PYWL for stage II or stage III of pneumoconioses was significantly more than that of stage I and that of all pneumoconioses. The result shows that stage II and III caused greater loss of work years than stage I. Since work tenure is defined from the date of first employment to the date of pneumoconiosis diagnosis, regardless of stage the patients having developed stage II or III had a shorter duration and a higher intensity of dust exposure.

It was seen from the mean PYWL that pneumoconiosis complicated by chronic respiratory diseases and pulmonary tuberculosis were the leading causes of death from 1949 to 1986. Although work environments may not have changed much, we believe the risk has declined over the last 30 years, and the rate of pneumoconiosis needs to be examined by decade-specific comparisons. In order to measure that change, field investigations are necessary to monitor silica dust levels and to reduce the risk of pneumoconiosis.

Concluding remarks

Silicosis is the most serious type of pneumoconiosis in China. The leading causes of death among patients with pneumoconioses are emphysema, pneumothorax, and pulmonary tuberculosis. Controlling silica and other workplace dust exposures will prevent pneumoconiosis, including complications such as chronic lung disease and tuberculosis. Pneumoconiosis stages II and III represent significantly higher mortality risks, as measured by the PYWL, than stage I does. The PYLL and PYWL can be used as indices to evaluate the risks of occupational exposures to workers.

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Evaluation of crystalline silica as a threshold carcinogen

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The Office of Scientific Affairs within the California Department of Toxic Substances Control has reviewed the evidence on the carcinogenicity of crystalline silica. The authors consider the current evidence to be convincing to classify crystalline silica as a human carcinogen by the inhalation route. The weight of evidence for both rats and humans indicates that fibrotic and silicotic lesions in the lung result from inhalation exposure to crystalline silica and that lung cancer is secondary to those lesions in the lung. Thus crystalline silica should be considered to have a threshold for causing cancer. The critical exposure criterion is that exposure level which does not produce a fibrogenic or silicotic response; thus it is necessary to determine the no observed adverse effect level (NOAEL) for fibrogenesis. The authors recommend that the United States Environmental Protection Agency review all appropriate studies to develop a reference concentration that can be used for regulatory purposes.

Key terms fibrosis, human carcinogen, inhalation, lung cancer, reference concentration, silicosis, threshold.

Crystalline silica has been found in ash produced when certain biogenic materials are burned to generate electricity. These materials include rice hulls, wood, straw, and sewage sludge. The California Department of Toxic Substances Control has been struggling with the following two questions: (i) should ash containing respirable crystalline silica be classified as hazardous waste, and (ii) what is a safe level of exposure for respirable crystalline silica? In order to answer both questions, regulatory agencies must identify the primary human health hazard that is posed by exposure to silica, delineate the probable mechanism by which silica causes the health effect, and, finally, provide a toxicity criterion value that can be compared with potential ambient exposures to determine the risk from these exposures and to establish safe emission levels. Neither United States or California regulatory agencies have developed accepted ambient criterion values for respirable crystalline silica. The only possible values available are those that are specific for occupational exposure: threshold limit values (TLV) published by the American Conference of Governmental Industrial Hygienists, permissible exposure limits (PEL) from the Occupational Safety and Health Administration, and recommended exposure limits (REL) listed by the United States National Institute for Occupational Safety and Health (1). These values are meant to be used in the workplace and are not casually applied to nonoccupational settings (2). The Office of Scientific Affairs within the California Department of Toxic Substances Control reviewed the literature on the adverse health effects of crystalline silica — silicosis and respiratory cancer — and determined that the weight of evidence suggests the following: (i) silica should be classified as a known human carcinogen and (ii) the safe level of silica should be based on a threshold model in which fibrotic lung disease is a necessary precondition for the appearance of cancer (3—5).

Classification of respirable crystalline silica as a known human carcinogen

In 1987, the International Agency for Research on Cancer (IARC) published its evaluation of the carcinogenic risk of silica. It concluded that the evidence was sufficient to show that crystalline silica causes cancer in experimental animals, but the evidence was limited regarding the carcinogenicity of silica for humans (6). In 1990, IARC published the results of several epidemiologic studies on the relationship between lung cancer and silica (7). In addition, there have been numerous other studies reported in the literature. The workers evaluated by IARC in both volumes and elsewhere can be divided into the following three groups: (i) workers exposed occupationally to silica and a variety of other agents that can cause lung cancer, (ii) workers probably exposed only to silica in their work environment, and (iii) workers with silicosis. In most of the studies described in the 1987 IARC report, little or no data were provided on smoking or relative exposure levels. However, as a group they show an increase in silicosis and lung cancer among silica-exposed workers (6). We focus on studies in groups ii and iii, since they provide information relevant to the question of the carcinogenicity of silica. Eleven of the twelve selected studies of workers (8—19) indicate that exposure to silica dust results in a modestly increased risk of lung cancer, with a statistical significance of < 0.05 in five studies (11, 12, 15, 18, 19). The observed:expected ratios ranged from 1.2 to 2.9 for lung cancer. Simultaneous exposure to other carcinogenic agents cannot be ruled out in any of these studies. However, ceramic, granite, and

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stone workers are exposed primarily to silica, and nine of these studies focused on workers in these industries. Eight of the nine studies showed an increased risk of lung cancer, the single exception being the study by Costello & Graham (8).

Relationship between silicosis and lung cancer

Group iii studies (ie, lung cancer among workers with silicosis) show that the association becomes much stronger in silicotic persons, the observed:expected ratios ranging from 1.7 to 6.9 in 10 studies (3—5, 20—26). In three of the four studies comparing silicotic and nonsilicotic persons (3—5, 20), lung cancer risk was increased twofold for the silicotics, whereas the number of observed lung cancer cases among the nonsilicotics was virtually unchanged from that expected (observed:expected 1.3, 0.9, 1.0) (3—5). In two studies of Italian ceramic workers and German slate workers, there was little or no known exposure to other lung carcinogens in the workplace (4, 5). In one study of Italian silica brick workers, the mortality from respiratory cancer was nearly the same for silicotic and nonsilicotic persons (observed:expected 1.7 and 2.1, respectively) (20).

In addition to the presented studies at least eight other epidemiologic studies have been published recently on the relationship between work in dusty trades, silicosis, and lung cancer. Meijers et al (27) did not find any relationship between work in Dutch dusty trades and lung cancer. Hessel et al (28) and Carta et al (29) did not find any relationship between lung cancer and the presence or severity of silicosis in South African and Sardinian miners. However, four studies found a strong association between silicosis and the incidence of or mortality from lung cancer. Forastiere et al (30) and Chia et al (31) showed an excess risk of lung cancer among silicotic patients which could not be accounted for by smoking. Sherson et al (32) found a positive correlation between silicosis in long-term employees of foundries (more than 20 years) and lung cancer incidence. Infante-Rivard et al (33) reported that the risk of death from lung cancer was more than three times higher than expected for silicotic workers. In a recent extensive review of the epidemiologic data that includes an examination of the relationship between silicosis and lung cancer, Goldsmith (34) concluded that chronic silicosis predisposes to an increased lung cancer risk.

These observations from humans are consistent with results seen when rats, mice, or hamsters are exposed to crystalline silica. Saffiotti et al (35) reported that, in rats, lung tumors are seen only when there is also a fibrotic response. Histologically, epithelial hyperplasia was nearly always associated with areas of fibrosis. Mice develop fibrosis but no persistent epithelial hyperplasia and no tumors. Hamsters exposed to crystalline silica in the respiratory tract do not mount a fibrotic response and do not get lung tumors. Saffiotti and his co-workers (35) postulated that these responses in rodent species may be representative of different susceptibilities in subsets of the human population.

Discussion

There are two conclusions that can be drawn from these data. First, the studies presented and published by IARC and elsewhere provide compelling and sufficient evidence for the carcinogenicity of respirable crystalline silica in humans. Second, increased lung cancer risk is concentrated among the exposed workers who develop silicosis (36). The question is whether it is plausible that the sequence of events culminating in silicosis occurs independently from the direct action of crystalline silica on cellular DNA (deoxyribonucleic acid). This direct action could result in the initiation of the carcinogenic process. Silica has been shown to cause the formation of micronuclei in cells and the transformation of tissue-cultured cells (6). However, crystalline silica does not appear to be mutagenic in bacterial systems and does not induce sister chromatid exchanges, chromosome aberrations, or aneuploidy (6). Daniel et al (this volume) have shown that silica can interact directly with DNA by hydrogen bonding in vitro. Another question that must be addressed when the possibility of silica acting directly on DNA is considered is "Do lung epithelial cells have the capability to phagocytize particles so that silica can gain access to the DNA of the cell type that eventually becomes cancerous?" In an in vitro experiment, Daniel et al (this issue) observed silica particles in the nuclei of cultured lung epithelial cells from rats after the application of crystalline silica. In summary, there is some evidence that crystalline silica has the ability to enter the cell nucleus and interact directly with DNA under in vitro conditions but, as yet, there is no evidence that these events occur in vivo and little evidence that silica is mutagenic.

The epidemiologic evidence examined in this paper and the animal studies summarized by Saffiotti et al (35) and Saffiotti & Stinson (37) suggest that fibrogenic and carcinogenic processes do not occur independently, but that silicosis is a necessary precondition for carcinogenesis. If so, there are several postulated mechanisms (38, 39) as Williams & Saffiotti (this volume) have observed. First, fibrosis causes structural disorganization of the microstructure of the lungs. This disorganization leads to the production of various cytokines causing growth disturbances with subsequent chronic dysplasia, increased proliferation of epithelial cells adjacent to fibrotic areas, and serendipitous survival of mutated cells in that epithelial population. Second, with increased fibrosis, the lung is less able to clear other bioactive agents with consequent increased opportunity for interaction between these agents and susceptible cells (40). Third, pulmonary macrophages, damaged by engulfing inhaled silica particles, produce cytokines and possibly set off autoimmune reactions which could accelerate not only fibrotic changes in the lung but also the proliferation of mutated cells (38).

Concluding remarks

On the basis of this review we believe that there is sufficient evidence to classify crystalline silica as a human carcinogen. Therefore, wastes containing crystalline silica should be considered hazardous and assessed for potential carcinogenic risk. We agree with the recommendation made by the California Environmental Protection Agency, Office of Health Hazard Assessment, that the long-term effects of inhaling crystalline silica should be tested by the US National Toxicology Program. The testing protocol should address the following questions: (i) do lung cancers appear only in rodents with fibrosis, (ii) are pulmonary tumors located in the same area as the silicotic nodules, (iii) does fibrosis occur before neoplasia or at lower doses, (iv) does the severity of fibrosis correlate with the incidence of tumors, (v) does silica cause tumors in tissues other than lung, and (vi) what is the exposure level that does not produce a fibrogenic or silicotic response?

Our opinion is that the linearized multistage model should not be used to estimate carcinogenic risks due to ambient silica exposure or to develop toxicity criterion values. This linearized model was developed from studies of mutagenic radiation effects and

assumes a nonthreshold mechanism for carcinogenicity. Crystalline silica does not appear to be mutagenic (6). Instead, fibrogenesis, the *sine qua non* of the carcinogenic response to silica in humans, seems to exhibit a threshold.

We recommend that the US Environmental Protection Agency establish a reference concentration for crystalline silica based on a no observed adverse effect level (NOAEL) for fibrogenesis. Rice & Stayner (this issue) calculated NOAEL values ranging from 7 to 30 $\mu g \cdot m^{-3}$ from human epidemiologic studies on silica exposure and silicosis. Applying an uncertainty factor of 10 to these values to protect sensitive human subpopulations (40) provides possible toxicity criterion values or safe levels of 0.7 to 3.0 $\mu g \cdot m^{-3}$. These levels assume that the development of silicosis is the critical threshold event. They are higher than those based on cancer slope factors calculated using the linearized multistage model. Using the multistage model to derive safe levels depends on the assumption that the development of lung cancer is independent of the development of silicosis and that any exposure to crystalline silica poses some risk. The safe level of silica in air corresponding to a one-in-a-million risk is 0.02 $\mu g \cdot m^{-3}$ calculated using a cancer slope factor of 4.5×10^{-5} $(\mu g \cdot m^{-3})^{-1}$ and 0.04 $\mu g \cdot m^{-3}$ using a cancer slope factor of 2.3×10^{-5} $(\mu g \cdot m^{-3})^{-1}$ (Collins & Marty, this issue). The evidence supports the NOAEL approach because it best reflects the probable mechanism by which silica causes cancer in humans. Although using this approach may result in slightly higher safe levels, we believe these levels would adequately protect human health.

Disclaimer

The views expressed herein by the authors do not necessarily represent the official policies of the California Department of Toxic Substances Control or of any other state or federal agency.

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Cancer risk assessment for crystalline silica to implement California's Hot Spots Act

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Crystalline silica has been identified as a probable human carcinogen. To assess the potential for adverse health effects due to environmental exposures to respirable crystalline silica, a quantitative estimate of carcinogenicity has been made using incidence data from three studies in which long-term silica inhalation caused lung tumors in rats. The uncertainties in risk assessment in general and in the risk assessment for silica in particular are discussed.

Key terms carcinogen, multistage model, risk assessment, silica, uncertainty.

California's Air Toxics Hot Spots Information and Assessment Act of 1987 requires industrial facilities to quantify routine air emissions of designated chemicals, to perform a risk assessment if the emissions may affect public health, and to notify the public of significant risks. Because the International Agency for Research on Cancer identified crystalline silica as a probable human carcinogen (class 2A) since there was sufficient evidence from laboratory animals and limited human evidence (1), crystalline silica became subject to the Hot Spots Act. Its inclusion led to need for a quantitative estimate of its carcinogenicity. This paper reviews the methods and results of a quantitative risk estimate and discusses the uncertainties and needs for future research.

Methods

Because of difficulties in quantitating workplace exposures, human data on the carcinogenicity of crystalline silica were not readily amenable to quantitative risk assessment. (However see Goldsmith et al, this issue.) Therefore, three inhalation studies on rats were used (table 1). In addition, data from intratracheal instillation were considered for comparison.

Dagle et al (2) exposed three-month-old Fischer-344 rats to 51.6 mg · m^{-3} Min-U-Sil 5 quartz 6 h a day, 5 d a week for up to 24 months. Subgroups of five animals per sex were withdrawn at 4, 8, 12, and 16 months and observed until death or killed at 24 months. The average length of exposure to quartz was assumed to be 12 months. Ten of 53 exposed females had epidermoid (squamous-cell) lung carcinomas. Three animals with tumors were in the five animals withdrawn after only four months of exposure. One of 47 exposed males had an epidermoid carcinoma of the lung.

Holland and his co-workers (3, 4) exposed 60 female Fischer-344 rats, nose only, for 6 h a day, 4 d a week, for 83 weeks, to 12 mg · m^{-3} Min-U-Sil quartz dust aerosol with a mean geometric particle size of 2.0 ± 0.2 μm (70% respirable). Twenty total tumors (6 adenomas, 11 adenocarcinomas, and 3 squamous-cell carcinomas) were observed in 18 animals, of which six (the adenomas) were not malignant. Thus between 12 (if two animals had two different malignant tumors) and 14 (if all malignant tumors were in different animals) rats had malignant tumors. For risk assessment the value of 13 was selected. [Page 271 of the paper states: "In three cases, both adenocarcinomas and epidermoid carcinomas were present in the same lung, in one instance in the same lobe (Fig. 26—6)" (3). If so, then a total of 11 + 6 = 17 animals, not 18 as stated in the paper, would have tumors.]

Muhle et al (5) exposed groups of eight-week-old Fischer-344 rats to DQ12 silica, which contained 87% crystalline alpha-quartz, 6 h a day, 5 d a week, for 24 months (whole-body exposure). The concentration was 1 mg · m^{-3} with 74% respirable. Four of 50 males and 8 of 50 females developed malignant lung tumors. There was one malignant lung tumor in the 100 controls (sex not specified). (See Muhle et al, this issue, for added details.)

Holland et al (6) gave weekly intratracheal instillations of 7 mg of Min-U-Sil quartz for 10 weeks to Sprague-Dawley rats. The animals developed both fibrosis (15 of 36 animals) and carcinomas (5 of 36 animals) of the lung. Groth et al (7) deposited a single dose of 20 mg of Min-U-Sil silica into male Fischer-344 rats. Of the 67 treated rats, 30 developed lung adenocarcinomas. The doses were assumed to be equivalent to a similar inhalation dose spread out over the animals' lifetimes.

The dose of silica delivered in the three inhalation studies (2, 3, 5) was calculated using the exposure data in milligrams per cubic meter of the respirable silica provided and an allometric equation for rat inhalation (8):

$$I_{rat} = 0.8\ W^{0.8206},$$

where I is the inhalation rate in cubic meters per day and W is the body weight in kilograms. No adjustment was made for particle

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Table 1. Determination of silica potency.

Study	Nominal respirable exposure ($mg \cdot m^{-3}$)	Animal lifetime dose ($mg \cdot kg^{-1} \cdot d$)[a]	HED[b] ($mg \cdot kg^{-1} \cdot d$)	Tumor incidence	Inhalation unit risk	
					– Surface area correction	+ Surface area correction
Dagle et al, female rats (2)	51.6 0	4.90	0.703	10/53 0/47	2.0×10^{-5}	1.4×10^{-4}
Dagle et al, male rats (2)	51.6 0	4.47	0.759	1/47 0/42	5.0×10^{-6}	2.9×10^{-5}
Holland et al, female rats (3)	12 0	1.08	0.16	13/60 0/54	9.8×10^{-5}	6.8×10^{-4}
Muhle et al, male and female rats (5)	1 0	0.133[c]	0.021	12/100 1/100	4.1×10^{-4}	2.6×10^{-3}
Muhle et al, female rats (5)	1 0	0.14	0.020	8/50 0/50	6.1×10^{-4}	4.2×10^{-3}

[a] For the purpose of the calculations the body weight of all the female rats was taken to be 0.207 kg, the average body weight of quartz-exposed females in the Dagle et al study (3). The daily air intake of a rat was calculated from the formula $I(m^3) = 0.8bw^{08206}$ (8). The body weight used for the males was 0.342 kg, the average body weight of quartz-exposed males in the Dagle et al study (3).

[b] HED = human equivalent dose, calculated by dividing the animal dose by $(bw_{human}/bw_{rat})^{1/3}$.

[c] The group was evenly divided between males and females. The authors did not group the results by sex, but stated that there were four malignant lung tumors in the males and eight in the females.

retention in the lung. For example, if a female rat weighs 0.207 kg, then:

$$I_{rat} = 0.22\ m^3 \cdot d^{-1},$$

$$\text{Animal dose} = \frac{12 \times 0.70 \times 0.22 \times 6/24 \times 4/7 \times 581/683}{0.207}$$

$$= 1.085\ mg \cdot kg^{-1} \cdot d.$$

A human equivalent dose was also calculated using a body surface area scaling factor (9, 10):

$$\text{Human equivalent dose} = \frac{1.085}{(70/.207)^{1/3}} = 0.156\ mg/kg - d.$$

The computer program GLOBAL 86, which fits the linearized multistage model to the experimental data (10, 11), was used. Its mathematical expression is:

$$P(d) = 1 - e - (q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k),$$

where P(d) is the lifetime probability of developing a tumor at dose d, q_0 is a constant that accounts for the background incidence of cancer, and q_1, q_2, ... q_k are coefficients that allow the data to be expressed to various powers of the dose to obtain the best fit (10). The program computes maximum likelihood estimates (MLE) and upper 95% confidence limits (UCL) of risk associated with a particular dose. The model is based on several assumptions about carcinogenesis. Cancer is assumed to be an irreversible process which originates in single cells and involves numerous biological stages. The rate of occurrence at each stage varies linearly with dose. The output of the GLOBAL 86 program in units of $(mg \cdot kg^{-1} - d)^{-1}$ was converted to units of $(\mu g \cdot m^{-3})^{-1}$ by assuming that a 70-kg person inhales 20 m^3 of air per day.

Results and discussion

Inhalation unit risks. Carcinogenic potency is expressed as the inhalation unit risk, the theoretical upper bound probability of contracting cancer by breathing 1 $\mu g \cdot m^{-3}$ of the material for a lifetime. Table 1 shows the unit risks for silica exposure; they were calculated both with and without a surface area scaling factor. The lowest inhalation unit risk was obtained from male rats in the Dagle study, while the highest was seen in the Muhle study, which used the lowest silica concentration. The inhalation unit risks varied from 5.0×10^{-6} $(\mu g \cdot m^{-3})^{-1}$ to 2.6×10^{-3} $(\mu g \cdot m^{-3})^{-1}$. To incorporate as much of the data as possible into the risk number used for the hot spots program, a geometric mean was taken of the four values for risk: Holland, females; Dagle, females; Dagle, males; Muhle, both sexes. This procedure resulted in mean cancer risk values of 4.5×10^{-5} $(\mu g \cdot m^{-3})^{-1}$ without the surface area scaling factor and 2.9×10^{-4} $(\mu g \cdot m^{-3})^{-1}$ with the surface area scaling factor. For comparison, unit risks determined in California's toxic air contaminant program have ranged from 1×10^{-6} $(\mu g \cdot m^{-3})^{-1}$ for methylene chloride to 38 $(\mu g \cdot m^{-3})^{-1}$ for dioxin.

Theoretical cancer risk for people. The value of 2.9×10^{-4} $(\mu g \cdot m^{-3})^{-1}$ predicts that a person would theoretically incur a 10^{-5} lifetime cancer risk by continuously breathing air containing 0.03 $\mu g \cdot m^{-3}$ silica, while the value of 4.5×10^{-5} $(\mu g \cdot m^{-3})^{-1}$ estimates a 10^{-5} risk from a silica concentration of 0.2 $\mu g \cdot m^{-3}$. A worker exposed to the threshold limit value of 100 $\mu g \cdot m^{-3}$ for a worklife (45 years, 8 h a day, 5 d a week, 48 weeks a year) would incur a theoretical lifetime cancer risk of $100 \times 8/24 \times 5/7 \times 48/52 \times 45/70 \times 2.9 \times 10^{-4} = 4.1 \times 10^{-3}$, a risk that would be difficult to identify in epidemiologic studies of lung cancer in silica-exposed workers.

In California, the most sensitive sex, site, and species is used for cancer risk assessment (12). Since this procedure required a calculation for females only in the Muhle study (5), the potency was calculated using a tumor incidence of either 0/50 or 1/50 for controls. The unit risks were very similar [6.1×10^{-4} and 5.7×10^{-4} $(\mu g \cdot m^{3-})^{-1}$, respectively, without surface area scaling and 4.2×10^{-3} and 3.8×10^{-3} with surface area scaling]. The higher value of each pair was used for calculating a geometric mean with the results from females in the Dagle et al (2) and Holland et al (3) studies. The risks estimated using only females (and without surface area scaling) had a geometric mean of 1.1×10^{-4} $(\mu g \cdot m^{-3})^{-1}$. The corresponding values with surface area scaling had a geometric mean of 7.4×10^{-4} $(\mu g \cdot m^{-3})^{-1}$, values two to three times greater than the preceding ones.

Intratracheal studies with rats. Unit risks were calculated from the intratracheal studies for comparative purposes. From the Groth et al study (7), unit risks of 2.5×10^{-3} $(\mu g \cdot m^{-3})^{-1}$ and 1.5×10^{-2} $(\mu g \cdot m^{-3})^{-1}$ were estimated without and with a surface area

scaling factor. From the Holland et al (6) study, unit risks of 1.8×10^{-4} $(\mu g \cdot m^{-3})^{-1}$ and 1.2×10^{-3} $(\mu g \cdot m^{-3})^{-1}$ were calculated without and with surface area scaling. These risks may be higher than those from inhalation studies because the nasal passage is bypassed during intratracheal instillation and the dose is given early in the life span.

Inhalation study with mice. Wilson et al (13) exposed female Balb/cBYJ mice by inhalation to up to 1950 $\mu g \cdot m^{-3}$ Min-u-Sil 8 h a day, 5 d a week for 570 d. Tumor incidence was not increased by silica; at the highest concentration, 4 of 16 animals had lung tumors versus 4 of 13 of the controls. Based on the unit risk from the three studies of female rats and a surface area scaling factor between mice and rats of approximately 2, an approximate unit risk for mice would be 5.5×10^{-5} $(\mu g \cdot m^{-3})^{-1}$. The number of excess tumors predicted in the highest dose group would be 5.5×10^{-5} $(\mu g \cdot m^{-3})^{-1} \times 1950$ $\mu g \cdot m^{-3} \times 8/24 \times 5/7 \times 16$ mice = 0.4 tumors. The observed result is consistent both with no effect of silica and with the 0.4 additional tumors predicted.

Uncertainties in risk assessment. There are many uncertainties in risk assessment (14): (i) selection of test species, (ii) different susceptibility between the sexes, (iii) measure of dose, (iv) tumor response in test species (eg, variability in tumor diagnosis), (v) statistical variability in tumor response data in test species, (vi) selection of a specific dose-response model (linearized multistage versus other), (vii) calculation of uncertainty in dose-response (use of 95% upper confidence limit versus maximum likelihood estimate), (viii) interspecies extrapolation method, (ix) expression of human dose (concentration at contact site versus dose to target tissue) and (x) description of target humans (variation in sensitivity in human population due to age, sex, genetics, etc). In addition there are uncertainties specific to a risk assessment for silica. Silica is carcinogenic in rats by inhalation (table 1) and in rats and other animals by injection into lung and pleura (1). It is also able to cause mammalian cell transformation, an in vitro analog of cancer induction (1).

Dose-response. When this risk assessment was carried out, a dose-response study in the rat had not been done in a single laboratory. The three positive inhalation studies with rats do not exhibit a dose-response relationship among themselves (figure 1). The tumor responses at three different levels of silica were similar (16, 19, and 22% malignant tumors). In the Dagle study (2), there were varying lengths of exposure to quartz, and therefore the difficulty in comparing the studies is increased. However, the fact that quartz is not metabolized and may provide a persistent "foreign body" stimulus once it is deposited in the lungs may make the application of traditional dose-response concepts to silica-based carcinogenesis more problematic.

In a recent study, female Wistar rats were exposed to two levels of silica (6 and 30 mg $\cdot m^{-3}$) for only 29 d at 6 h a day early in life (15). After 24 months the lung tumor responses to the two levels of silica were not very different (6 mg $\cdot m^{-3}$ silica, 37 of 85 rats; 30 mg $\cdot m^{-3}$ silica, 43 of 85 rats; controls, 0 of 85 rats). Attempts to apply the linearized multistage model to the data did not yield an acceptable fit.

Surface area scaling. Since most toxicants must cross a surface to exert a toxic effect or act at a cell surface receptor, a surface area scaling factor is routinely used in animal-to-human extrapolation (10). Thus the estimation of higher cancer risks for humans than would be predicted without scaling is consistent with the concept that humans are more sensitive to toxicants than animals. However, use of surface area scaling may not be appropriate for silica because it is a particle and causes cancer only in the tissue it first contacts, the lung. It is worth noting that Goldsmith et al (this issue) have predicted a lower cancer risk based on epidemiologic data than we predicted using rodents.

Greater tumor incidence among females. Another uncertainty is the observation that silica-induced lung tumors are more likely (5) or much more likely (2) to be induced in female rats. Women are considered to be more susceptible to silicosis than men (16). Whether women are at greater risk than men for lung tumors after silica exposure is not clear (17, 18).

Malignant and benign tumors. Only malignant tumors were used in the calculations. A more health protective approach would be to combine benign and malignant tumors if histological evidence indicates that the benign tumor may become malignant. Holland et al (3) reported six adenomas. Muhle et al (5) reported six benign lung tumors. Omitting benign tumors results in an underestimation of cancer risk.

Single species data. More confidence in an animal-based risk assessment would derive from the presence of positive tumor incidence data for more than one species. However, hamsters test negative by inhalation (6) and by intratracheal instillation (6, 19, 20). The mouse has not been adequately tested (13, 21).

Silicosis as a necessary precursor to cancer. Perhaps the greatest uncertainty results from the possibility that cancer, as a sequel to silica exposure, may only occur after the nonmalignant disease silicosis is induced. In workers, lung cancer due to silica exposure usually occurs after silicosis (18, 22). In lung pathology (23), scar cancer is a recognized entity, occurring in conjunction with fibrosis, possibly because the hyperplasia involved in fibrosis may lead to an increased probability of a mutation leading to neoplasia. However, Holland et al (6) have stated that "While most of the evidence points to a preexisting scar that may later give rise to a neoplasm, there is some evidence that suggests that certain pulmonary tumors, particularly adenocarcinomas, create a localized fibrotic response during active growth of the tumor [p 493]."

A few occupational studies indicate that cancer may occur in the absence of silicosis (18, 24, 25). But the induction of lung

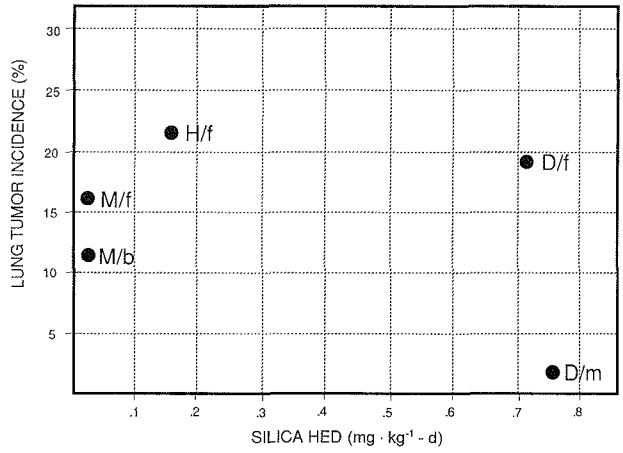

Figure 1. Lung tumor incidence versus silica dose. Human equivalent doses (HED) of silica were calculated as shown in table 1 and plotted against tumor incidences from the animal studies (see the text). [M = Muhle et al study (5), H = Holland et al study (3), D = Dagle et al study (2), f = females, m = males, b = both sexes]

cancer without silicosis is controversial (22, 26, 27). Epidemiologic studies of silica are often complicated by confounding exposures to asbestos, radionuclides, polycyclic aromatic hydrocarbons (PAH) if diesel equipment is used, arsenic, and cigarette smoke. Occurrences of silicosis due to chronic environmental exposures are rare and not fully validated (28, 29).

In the three rat studies, many more animals had fibrosis than cancer. It was not mentioned if there were any rats that had cancer without fibrosis. Holland et al (3) stated that "Most animals surviving beyond 400 days of exposure exhibited pronounced pulmonary fibrosis . . . [p 276]." Muhle et al (30) reported that 92% of their silica-exposed rats had a moderate degree of fibrosis by the end of the study. Silica-induced tumors occur later in life. No lung tumors were observed in studies involving 2300 female Wistar and Sprague-Dawley rats exposed to up to 50 mg of silica when the exposure lasted 12 months or less (A Brammertz, University of Aachen, unpublished results). Holland et al (3) indicated that the first lung tumor was observed after 651 d of exposure, although the paper states that the first tumor in any exposed group appeared at approximately 17 months.

Intratracheal instillation studies of silica indicate that rodents vary in their susceptibility to silica-induced fibrosis. The mouse is less susceptible than the rat (31) and the hamster is much less susceptible than the rat (4, 19, 20). If fibrosis is a mandatory step in the pathway to silica-induced cancer, it might explain why hamsters exposed to silica have tested negative for cancer induction.

If silicosis, a nonmalignant disease, must occur before cancer occurs, there would be a threshold for silicosis and consequently for subsequent lung cancer (as suggested by Klein & Christopher, this issue). Thus low environmental levels, below the threshold concentration, would pose no cancer risk. The standard application of the linearized multistage model may, therefore, be inappropriate. Silica would not be an initiator of carcinogenesis, but rather a promoter or cytotoxic agent (32).

Differential retention of silica. The potential difference in the retention of silica between rat and human lungs (27) has not been addressed in this report. Our risk assessment was a preliminary one carried out to implement the California Hot Spots Act and, although it was done according to standard procedures, it did not receive extensive peer review. If particle retention in humans and rats is similar, a correction would not be needed.

Silica as a toxic air contaminant. The inhalation unit risks for silica were put on a list of screening cancer potency values for the hot spots program (33). These values were not as highly peer reviewed as the unit risks developed by the Environmental Protection Agency and by California regulatory programs such as the toxic air contaminant program (34) and Proposition 65 (35). With the use of screening cancer potency values (33), some dusty facilities had high theoretical cancer risks due solely to their silica emissions. Some of the public interpreted the risk assessment results as certain cancer cases. Because of the preliminary nature of the unit risk factors, it was recommended that the use of the silica risk assessments be deferred until more extensive peer review could be obtained; that review is now underway.

Research needs

Respirable crystalline silica meets the criteria for a carcinogen (1, 18). Numerical estimates of its carcinogenicity based on inhalation studies with rats involve considerable uncertainty. Most naturally occurring silica particles are too large to be respirable. Human activities like mining and sand blasting often make them respirable. The potential for cancer risk must be dealt with rationally, even when the scientific data currently available are limited. Some specific areas for research to clarify some uncertainties in the risk assessment for silica include proper inhalation concentration-response studies with both rats and mice; mechanistic studies of silica's toxicity at the cellular and molecular level to determine if it is an initiator, a promoter, a cytotoxic agent, or has multiple roles; and analysis of epidemiologic studies to derive an inhalation unit risk number and to correlate it with the risk numbers derived from animals, as done by Goldsmith et al (this issue). The National Institute of Environmental Health Sciences in the United States has been asked to address some of the research questions that can be answered using laboratory animals.

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Comparative cancer potency for silica from extrapolations of human and animal findings

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The International Agency for Research on Cancer has judged that the evidence for the carcinogenicity of silica in animals is sufficient, and for humans it is limited. With the use of the Global 86 computer model, animal and human cancer potency data were extrapolated and the findings compared. The animal findings were based on inhalation rat studies. The cancer slope factors ranged from 2.3×10^{-5} to 6.0×10^{-3} for $(1\ \mu g \cdot m^{-3})^{-1}$ among three experimental studies. The epidemiologic findings were from gold workers exposed to quartz and diatomaceous earth workers exposed to cristobalite. The cancer slope factors ranged from 6.8×10^{-7} to 1.85×10^{-5} for lifetime exposure to $1\ (\mu g \cdot m^{-3})^{-1}$ of silica dust. Because of the many uncertainties involved in extrapolating to humans from animal data, more rational risk assessments are achieved when data from silica-exposed workers are used than when laboratory findings are relied on.

Key terms cancer risk assessment, comparing rat and human extrapolations, cristobalite, dose-response findings.

Silica exposure is widespread, it has occupational cancer and non-cancer health effects, and it has animal and human data supporting its classification as a toxic substance. Silica dust levels are regulated in workplaces in the United States by the Occupational Safety and Health Administration (OSHA), the time-weighted average (TWA) being 0.1 mg · m^{-3} of crystalline silica over an 8-h day. For two crystalline polymorphs (cristobalite and tridymite), the TWA standard is more strict, 0.05 mg · m^{-3} (1). For both of these standards, the permissible exposure limits are designed to prevent silicosis. The International Agency for Research on Cancer (IARC) evaluated crystalline silica and judged it to be a probable human carcinogen according to findings of sufficient evidence for carcinogenicity in laboratory animals and limited evidence for humans (2). Based in part on IARC's evaluation, California's Proposition 65 Science Advisory Panel judged airborne, respirable crystalline silica to be a carcinogen in 1988 (3). In 1991, silica was listed as a carcinogenic air toxin in the California Toxic Hot Spots legislation, AB 2588 (4). In the language of the Toxic Hot Spots bill, California's air pollution control districts (and other agencies) are required to conduct risk assessments to guide the formulation of policies regarding hazardous ambient air emissions.

As with other airborne respiratory hazards such as arsenic, asbestos, coke oven emissions, and radon, cancer risks have been assessed for ambient environmental exposures (5). This process requires extrapolation of the risks using the cancer potency slope or the geometric means of several slope lines according to established methods (6). This paper contrasts the cancer risk assessments developed for humans and for animals.

Background

The first findings demonstrating that quartz produced tumors were reported by Wagner et al. (Summarized in references 2 and 7.) Wagner and her colleagues showed that intrapleurally injected silica dusts produced histiocytic lymphomas in several strains of rats. Since 1983, silica (as Min-U-Sil and DQ12 quartz) has been shown to be a pulmonary carcinogen in four lifetime rat studies using both intratracheal injection and inhalation methods (8—11). Because the studies by Holland et al (8), Dagle et al (10), and Muhle et al (11) applied inhalation methods to expose the animals to silica (similar to the route of exposure in humans), their findings were used in the extant risk assessment extrapolations (12, 13). (See also Collins & Marty, this issue.) There have also been two epidemiologic studies of white South African gold miners and California diatomaceous earth workers exposed to inhaled silica dust showing dose-response gradients for lung cancer (14, 15). The cancer risk assessment for the human and animal data are presented below.

Assumptions for extrapolating from animals to humans

For all three risk assessment extrapolations from data on rodents, several standard assumptions were used. First, the lifetime silica dust exposure in the experimental studies was converted from micrograms per cubic meter to micrograms per kilogram per day. Thus one assumes that the body weight (BW) of adult female rats is 0.207 kg and that of male rats is 0.342 kg. The daily air intake of a rat (Ira) is assumed to be $0.8 \cdot BW^{(0.8206)}$ (17). The fraction of

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silica aerosol deposited (DF) in the lung is 23% (18). Thus the animal dose (AD) is obtained by multiplying the Ira times the silica dust concentration (Sdc) times the hours exposed per day (Hexp) times days exposed per week (Dexp) times days exposed per exposure period (Mexp) times the respirable fraction (Rspf) times the deposition fraction (DF). This numerator is then divided by the rodent body weight to obtain the animal dose (AD):

$$AD = (Ira \times Scd \times Hexp \times Dexp \times Mexp \times Rspf \times DF)/BW.$$

Thus, to obtain the AD (in milligrams per kilogram per day) for female F344 rats in Dagle et al's study (10), the calculation is as follows:

$$[(0.8)\ (0.207\ kg^{(0.8206)})\ (51.6\ mg \cdot m^{-3})\ (6\ h/24\ h)\ (5\ d/7\ d/week)\ (494/730)\ (100\%)\ (0.23)]/0.207\ kg = 1.52\ mg \cdot kg^{-1} \cdot d^{-1}.$$

To obtain the human equivalent dose (HED) from the animal dose, we assumed that an average human weighs (avg BW) 70 kg and applied a surface area correction factor (SACf) which equals $(avgBW/BW)^{(1/3)}$. Thus the human equivalent dose = AD/SACf, and, continuing the Dagle et al example, SACf = $(70\ kg/0.207\ kg)^{(1/3)}$ = 6.97 and HED = $(1.52\ mg \cdot kg^{-1} \cdot d^{-1})/6.97 = 0.22\ mg^{-1} \cdot kg^{-1} \cdot d^{-1}$.

Last we assumed a standardized human inhalation rate of 20 m^3 of air per day and a 70-year lifetime exposure (16) for those living where ambient silica levels are the greatest. Table 1 summarizes the cancer risk from the extrapolation of experimental findings to 1 $\mu g \cdot m^{-3}$ of ambient silica.

Extrapolation methods

To conduct a cancer risk assessment, the linearized multistage model, developed by Crump and his colleagues in the form of the GLOBAL 86 program (18), was used to estimate the cancer potency slope for silica. This model has been used by the California Environmental Protection Agency and the Department of Health Services and the United States (US) Environmental Protection Agency for previous cancer health risk assessments. The program uses the animal tumor incidence data to compute maximum likelihood estimates (MLE) and upper 95% confidence limits (UCL). The upper 95% confidence limit is regarded as the upper limit of the estimated risk and, because of the nonthreshold assumption regarding carcinogens, the MLE and upper 95% confidence limits are linear at low doses (18). When the upper 95% confidence limit is estimated at an exposure value of 1 $mg \cdot kg^{-1} \cdot d^{-1}$ (the "unit" cancer risk level in public health extrapolations), it is defined as the q1* or cancer potency slope (CPS). The q1* results are converted from milligrams per kilogram per day to micrograms per cubic meter (used for inhalation risk assessments) by first multiplying the CPS value by 20 m^3 of air per day, multiplying that product by 10^{-3} $mg \cdot \mu g^{-1}$, and dividing the whole product by 70 kg, the average weight of an adult.

The following equation gives the cancer potency slope (q1*) from the Dagle et al female rat tumor study (10) in micrograms per cubic meter per day for an adult who is a lifetime resident in a location where there is mean exposure to 1 $\mu g \cdot m^{-3}$ ambient silica dust, as

$$\text{unit cancer risk} = (q1^*)\ (20\ m^3 \cdot d^{-1})(10^{-3}\ mg \cdot \mu g)/(70\ kg)$$

or

$$(0.36)\ (20)\ (0.001)/(70) = 1.0 \times 10^{-4}\ (\mu g \cdot m^{-3})^{-1}.$$

Table 1. Summary of risk assessment calculations for rat inhalation studies. HED = human equivalent dose, CPS = cancer potency slope or q1*, ICPS = inhalation cancer potency slope or q1* converted to airborne exposure.

Research	Sex	HED ($mg \cdot kg \cdot d^{-1}$)	CPS $(mg \cdot kg \cdot d^{-1})^{-1}$	ICPS $(\mu g \cdot m^{-3})^{-1}$
Dagle et al (10), Min-U-Sil quartz	Male	0.240	0.08	2.9×10^{-5}
	Female	0.220	0.36	1.0×10^{-4}
Holland et al (8), Min-U-Sil quartz	Female	0.050	3.83	1.1×10^{-3}
Muhle et al (11), DQ12 quartz	Male	0.046	10.73	3.1×10^{-3}
	Female	0.043	20.89	6.0×10^{-3}

Another way of describing this information is that the adult lifetime excess of cancer risk from inhalation of 1 $\mu g \cdot m^{-3}$ of silica based on the Dagle et al study (10) of female rats is 1 in 10 000.

Risk assessments from animal and human dose-response gradients

To find the individual cancer risk from lifetime exposure to silica levels, one multiplies the unit cancer risk factor by the measured silica concentration:

individual lifetime cancer risk = silica exposure × unit cancer risk [q1*].

The cancer potency or unit risk factor estimated by Goldsmith et al (13) ranged from 2.3×10^{-5} (based on data from male rats in Dagle et al's study) to 6.0×10^{-3} (based on data from female rats in Muhle et al's study) for a $(1\ \mu g \cdot m^{-3})^{-1}$ for lifetime air exposure to respirable silica dust. These findings are similar to those estimated by the California Environmental Protection Agency's Office of Health Evaluation and Assessment, which range from 2.9×10^{-4} $(\mu g \cdot m^{-3})^{-1}$ (without correction for surface area differences between rodents and humans) to 4.4×10^{-5} $(\mu g \cdot m^{-3})^{-1}$(with surface area correction). (See Collins & Marty, this issue.) Brantner & Klein (12) also conducted a cancer risk assessment for silica exposure based on the same three animal studies. They derived a single CPS of 3.55×10^{-5} $(\mu g \cdot m^{-3})^{-1}$ for quartz. Another interpretation of these findings is that, if lifetime exposure to quartz is 1 $\mu g \cdot m^{-3}$, then the cancer risk will be greater than 1 in 100 000, and a Proposition 65 warning about cancer risk is required to be posted by the source of the emissions (3).

The experimental findings from Muhle et al (11) have the greatest cancer potency slope and the lowest dose, while the results from Dagle et al (10) show the shallowest slope with the greatest dose. The latter result may be a function of the high dose levels, 51.6 $mg \cdot m^{-3}$, used in the Dagle et al study. (This level of exposure likely exceeds the maximum tolerated dose for rats.) Goldsmith et al (13) excluded these high dose levels, and a clear dose-related gradient emerged for the remaining animal data. The finding suggests that, although these separate studies show that silica is a carcinogen in rodents, overall, there appears to be some dose-related gradient except at high doses.

Epidemiologic studies of silica-exposed workers

The epidemiologic findings among white South African gold miners (14) and among California diatomaceous earth workers (15) demonstrated dose-response lung cancer findings for quartz exposure. Applying methods designed by Nurminen et al (19),

Table 2. Cancer potency slopes and inhalation unit risk factors calculated from epidemiology studies of silica-exposed workers.

Researcher	Mineralogical species	CPS[a, b] $(mg \cdot kg \cdot d^{-1})^{-1}$	ICPS[c] $(\mu g \cdot m^{-3})^{-1}$
Hnizdo & Sluis-Cremer (15)[d]	Silica	3.09×10^{-4}	6.75×10^{-5}
Checkoway et al (16), total cohort	Cristobalite	8.43×10^{-3}	1.83×10^{-7}
Checkoway et al (16), smokers	Cristobalite	1.16×10^{-2}	2.53×10^{-7}

[a] The cancer potency slopes (CPS) are for an assumed work lifetime of 40 years.
[b] The lifetime adjusted CPS corrects for the partial exposure in occupational settings: lifetime CPS = crude CPS × (8 h/24 h) (5 d/7 d) (50 weeks/52 weeks) (40 years/70 years).
[c] Inhalation cancer potency slope.
[d] Adjusted for smoking.

Ruble & Goldsmith (20) developed estimations of cancer potency slope from epidemiologic dose-response findings. They applied historical dust exposure levels from Hnizdo & Sluis-Cremer (15) and estimated from the work of Checkoway et al (15) with a 15-year lag time for the total cohort and for smokers. The number of person-years at risk for each dust exposure concentration was used as a denominator to fit the requirements for the Global 86 model (20). Adjustments were also made to reflect the less than lifetime exposure consistent with workplace (ie, 40 years' employment, 8-h workshifts, 50 h workweeks, and 50 weeks per year). As shown in table 2, the cancer slope factors ranged from 6.8×10^{-7} to 1.85×10^{-5} for lifetime exposure to 1 $(\mu g \cdot m^{-3})^{-1}$ of silica dust.

Discussion

Because of the many uncertainties in extrapolating to humans from animal data (21, 22), more rational risk assessments are achieved when data from silica-exposed workers are used than when laboratory findings are relied on. Cancer potency estimation from silica-exposed workers produces shallower slope extrapolations than from rats and thus enables risk managers to develop recommendations having less uncertainty in the quantification of risk.

There is no disputing the ability of silica to cause silicosis (23, 24). Noncancer risk extrapolation focuses on the likelihood of silicosis among workers exposed to quartz dust over a work life (19). The US Environmental Protection Agency (25) and Gift & Faust (26) reviewed the silicosis epidemiology literature to determine the acceptability of studies for calculating an ambient silica regulation. The no observed adverse effect levels (NOAEL) were very close, between 0.05 $mg \cdot m^{-3}$ to 0.3 $mg \cdot m^{-3}$, and the reference concentrations (RfC) ranged from 0.03 $\mu g \cdot m^{-3}$ to 2.06 $\mu g \cdot m^{-3}$ (26). Taking the lowest RfC and applying it to the aforementioned cancer risk values means that lifetime ambient exposure of 0.03 $\mu g \cdot m^{-3}$ would not result in an excess risk beyond acceptable levels based on human extrapolation, but may result in excess cancer when animal methods are used.

Concluding remarks

The extrapolation procedures for assessing risk for crystalline silica seems very straight-forward and compelling as a means to protect public health. However, there have been objections raised to extrapolation from animal studies (27) because all the positive studies were not done using the same protocol and because these studies were not initiated to evaluate the cancer hazards from silica. There is the possibility that costly emissions controls may be required that do little to reduce public lung cancer risk. Goldsmith (22) and Hertz-Picciotto (21) raised the issue of whether using animal data is appropriate when there are high-quality epidemiologic data demonstrating dose-response gradients. Despite the fact that extrapolations from experimental studies may provide greater cancer potency for equivalent exposure, extrapolations from human findings should be seriously considered for risk assessment purposes. This approach should be adopted because these data reflect the species (humans) for which the risk assessment is directed and because the measured lung cancer risks resulted from actual workplace exposures. In addition these findings represent risks in the realm of human exposure and the biological process, while there have been no demonstrated respiratory cancer risks from environmental silica exposures. More research is needed on cancer risk assessment methods, an activity which may lead to extrapolations that are more rationally based on epidemiologic findings.

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Section 5. Future research directions and areas of focus

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Biogenic amorphous silica

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Biogenic amorphous silica (BAS) is a natural constituent of living matter (eg, unicellular organisms and crop plants). Diatoms, whose siliceous remains are the geologic precursors to diatomaceous earth, actively process soluble silica into BAS. In some plants, a portion of the BAS exists externally as pointed or irregularly shaped fibers. Although silica-related adverse health effects are usually attributed to crystalline forms, such effects could occur as a result of exposure to BAS at high temperatures (above 800°C), where crystalline silica, a known human toxicant is formed. BAS fibers from food crops can be ingested and lead to adverse health effects due to irritative processes. Airborne BAS fibers from rice can be inhaled during burning or incineration. Fibrous or nonfibrous BAS can adsorb toxic organic compounds and facilitate their entry into the lung. Recommendations for research are suggested to address the issue of potential health effects due to exposure to BAS.

Key terms biogenic amorphous silica, crop plants, diatomaceous earth, environmental exposure, fibers, inhalation, occupational exposure, review.

Amorphous silica exists in more than one form. Some forms are associated with nonvegetative matter, such as volcanic glasses and various manufactured sols, gels, powders, and glass fibers (1—3), while other forms (ie, biogenic amorphous silica) are found in living matter [eg, viruses, bacteria, fungi, diatoms (a group of algae), sponges, and plants] (1, 4). For the current discussion, the focus will be on the biogenic amorphous silica (BAS) associated with fossilized diatoms and crop plants.

Amorphous silica is considered less toxic than crystalline silica, to which are attributed the silica-related adverse health effects, silicosis, and lung cancer (5). Amorphous silica is currently not classifiable as to its carcinogenicity to humans (5). The noncancer toxicity associated with amorphous silica is more ambiguous than for crystalline silica, although in vitro cytotoxicity and in vivo lung lesions have been observed with some industrial amorphous silica in rats (6, 7). The current threshold limit value for amorphous silica is 10 mg · m^{-3} (total dust) for uncalcined diatomaceous earth, precipitated silica and silica gel; 2 mg · m^{-3} (respirable dust) for fumed silica; and 0.1 mg · m^{-3} (respirable dust) for fused silica (8).

Exposure to amorphous silica from diatomaceous earth and crop plants may present unique situations not examined in most studies. The purpose of this paper is to describe the conditions under which human exposure to amorphous silica from diatomaceous earth and crop plants occurs. Where information is available, potential exposure-related health effects are discussed. Recommendations for research are also suggested.

Diatomaceous earth

Diatomaceous earth is the geologic product of decayed unicellular organisms called diatoms (1, 9). As part of the normal life cycle, diatoms take up soluble silica, probably as silicic acid [$Si(OH)_4$] from the surrounding water and transport it across the plasma membrane in saturable, energy-dependent steps (9, 10). The transported $Si(OH)_4$ then undergoes a series of reactions that ends in biomineralization producing biogenic amorphous silica and deposition in the diatom valve (frustule). The BAS levels in diatoms vary with species and range from less than 1 to almost 50% by weight (1). Over geologic time, the siliceous frustules of the diatoms accumulate and become diatomaceous earth.

Exposure to amorphous silica in diatomaceous earth occurs among workers who process the raw material into manufactured products. During a heating (calcining) step at temperatures of 982—1093°C, which includes the addition of a flux agent such as sodium carbonate, some amorphous silica in diatomaceous earth is transformed into a polymorph of crystalline silica, cristobalite (11). The temperature-induced transformation is a known phenomenon and has been studied with industrial silicas, including precipitated and vitreous silicas (12, 13). Hence, at the heating step of the manufacturing cycle, diatomaceous earth workers can experience inhalation exposure to high levels of respirable cristobalite and can therefore be at risk for adverse pulmonary health effects associated with this silica polymorph (14).

Crop plants

Like the silica in diatoms, the accumulation and deposition of silica in certain vascular (higher) plants is a normal biological process. Little is known, however, about the specific steps in uptake, accumulation, and deposition. For the grasses (including rice and sugar cane), silicic acid is taken up from the soil by active transport or passive diffusion (1). In rice, the concentration of

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silicic acid in the vascular tissue may reach 650 ppm as it is transported towards the leaves (4).

The amorphous silica in rice undergoes a temperature-dependent transition to crystalline silica (cristobalite), similar to that observed for diatomaceous earth. When rice hulls are incinerated at temperatures above 800°C, cristobalite is formed, and the conversion to this silica polymorph is prevented when furnace temperatures are lowered (15). If precautions are not taken, cristobalite can be inhaled by facility workers in proximity to the ash as it is removed from the baghouse or where it is stored on site. A potential for environmental exposure also exists if uncovered ash is disturbed by high winds.

Some of the amorphous silica in plants exists as fibers, and the fibrous forms vary by crop. In wheat and millet, silica fibers exist externally as regular hair-like projections with sharp pointed ends (4, 16). In sugar cane and rice the fibers are less regular, sometimes resembling twigs (17, 18). Concern about amorphous silica fibers is based on the adverse health effects associated with exposure to asbestos mineral fibers, particularly those with aspect ratios (length divided by diameter) greater than three. Although extensive epidemiologic data exist on the relationship between exposure to asbestos fibers and human disease (2, 19), little health research has been done on exposure to fibers of biogenic amorphous silica. Sinks et al (20) reported the absence of mesothelioma among Hawaiian sugar cane workers; however, other pulmonary end points were not addressed.

Exposure to fibers of amorphous silica may occur environmentally through the ingestion of silica-containing plants. The suggestion has been made that in the parts of the world where such plants are a staple food item, high esophageal cancer rates may be related to the ingestion of the amorphous silica fibers (16). However, the results of a mouse bioassay were contradictory (21). Skin tumors developed after direct dermal exposure to the amorphous silica from the grain or to the fiber-bearing grain, whereas gastrointestinal tumors did not occur after the latter was ingested. Although the mean aspect ratio of the fibers from the grain was 10 before the grain was added to the diet, the value after the grain was ground was not reported. The evidence thus suggests that tumor formation in relation to amorphous silica exposure is probably at the level of irritative and reparative processes.

Inhalation exposure to amorphous silica fibers occurs during harvesting, crop burning, or incineration. Such exposure can be occupational or environmental. Environmental exposure would occur during crop burning due to the air transport of residual particulate matter. Airborne fibers with aspect ratios greater than three were determined during sugar cane burning (17), rice straw harvesting and burning (18), and rice hull incineration (22). These fibers were not equivalent, however, to the long, thin, pointed structures associated with the external tissue of many grasses.

To date, laboratory studies on the biological effects of amorphous silica fibers have not been carried out in large part due to the unavailability of sufficient material. An epidemiologic study (23) on the respiratory health of California rice farmers has taken place, and the preliminary X-ray evidence is consistent with exposure to respirable silica dust. The nature of the specific exposure giving rise to the X-ray findings could not be determined however.

Interactions

The foregoing discussion has been restricted to exposure to amorphous silica separate from simultaneous exposure to other contaminants, although such exposures are known to occur. For example, polycyclic aromatic hydrocarbons (PAH) are detected in the smoke from rice straw burning in California, and they may be partially responsible for the mutagenesis observed in standard bacterial assay systems (24). Dioxins and dibenzofurans are also found in the smoke from rice straw burning in Japan (25). Particulates, in general, may facilitate the uptake and distribution of toxic substances, such as the carcinogenic PAH to the lung. One result may be enhanced tumor formation, as observed by Saffiotti et al (26) and Kimizuka et al (27). Other changes, such as increased retention time in the lung and altered PAH metabolite profiles (28, 29), may also occur.

Although the mechanisms for the particle-associated enhanced or altered PAH-induced biologic effects are not understood, in vitro studies may provide some insight. The facilitated transport of a PAH across lipid bilayers or isolated cell membranes was demonstrated if the PAH is first adsorbed onto amorphous silica particles that are respirable (30, 31). Hence the presence of PAH (and perhaps other organic compounds) in the environment of a population exposed to amorphous silica could exert interactive influences on the biological outcome. In the case of exposure to amorphous silica, the presence of organic toxins should be taken into consideration when the relationship between amorphous silica exposure and adverse health outcomes is studied.

Research needs

Many gaps exist in the knowledge about the relationship between exposure to amorphous silica and potential health effects. To assess the health risk due to exposure to amorphous silica adequately, studies are needed on the mechanism of disease processes associated with exposure to silica in general and to biogenic amorphous silica in particular. For example, more research is needed on the consequences of the interactions between soluble toxins and respirable silica particles. More information is also needed on exposure levels of amorphous silica. To address this concern, improved methods for preparing large amounts of purified amorphous silica fibers need to be developed. The result from studies such as the ones suggested in this presentation will add to our knowledge of the role of amorphous silica in silica-related disease and enable risk assessors to evaluate risks due to exposure to amorphous silica more rationally.

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Policy development for compensating workers exposed to crystalline silica in Ontario, Canada

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The Ontario Workers' Compensation Board develops policy for diseases by considering scientific information within legal, political, and social contexts. The purpose of this paper is to describe the process used to develop a policy for lung cancer among gold miners and to examine the extent to which this process assists the development of similar guidelines for workers with silica dust exposure. The scientific and policy questions are similar, both requiring consultation with stakeholders. To improve the development process for the gold miner policy, consultation for silica and lung cancer needs to be more inclusive. The resulting procedures would also need to be precise enough to assist adjudicators to make decisions without limiting their ability to decide each claim on the merits of the case. The major challenge is to ensure that the final policy is scientifically and legally supportable and acceptable to both workers and employers.

Key terms gold mining, lung cancer, policy, silica, silicosis, workers' compensation.

Because the Ontario Workers' Compensation Board has received claims from lung cancer patients who had been occupationally exposed to silica, the staff of the Board have begun to develop a policy proposal to help adjudicators decide on these claims. Although all policy development for disease claims begins with an assessment of the scientific evidence, there are issues beyond which need to be resolved before a final policy can be approved and implemented. This paper describes and discusses these issues. For this purpose it uses the current Ontario gold miners' compensation as an example and compares the relevant issues for gold mining and silica exposure.

Policy making of the Ontario Workers' Compensation Board

According to the Ontario Workers' Compensation Act of 1915, compensation for disease was provided if a worker had an industrial illness due to employment. Initially, such compensation was approved only for the following conditions: anthrax from handling wool, hair, bristles, hides and skins; lead poisoning and its sequelae; poisoning from other metals and substances such as arsenic, mercury, and phosphorous; and ankylostomiasis, a hookworm disease commonly found among miners. Currently the Act[2] defines occupational disease as follows (1): (i) a disease resulting from exposure to a substance relating to a particular process, trade, or occupation in an industry, (ii) a disease peculiar to or characteristic of a particular industrial process, trade, or occupation, (iii) a medical condition that, in the opinion of the Board, requires a worker to be removed temporarily or permanently from exposure to a substance because the condition may be a precursor to an industrial disease, or (iv) any of the diseases appearing on the list found in schedule 3 or 4 of the enabling law (1).

It is specified in the Act that for diseases and work processes included in schedule 3 or 4, a presumption of work-relatedness is appropriate. If a claimant has a disease listed in schedule 3 and was employed in the stated work process, the disease is presumed to be due to the nature of employment unless the contrary is shown. If a claimant has a disease listed in schedule 4 and was employed in the appropriate work process, the ailment is conclusively presumed to be due to the nature of the employment. With this definition and the addition of diseases to the two lists of compensable conditions, the Board today compensates many more diseases than earlier.

When the policy for lung cancer and gold mining was developed in 1988, the first question for the Board was whether lung cancer among gold miners was an industrial disease. The next question was how to determine if a person's lung cancer was due to the claimant's employment. As discussed later, similar questions are being asked about lung cancer and workplace silica exposure.

Policy development process

A condition is considered an "occupational disease" under the Act when an association exists between the disease and a work process

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2 On 9 December 1994 the Act to Amend the Workers' Compensation Act received Royal assent. This amendment charged the words "industrial disease" to "occupational disease" and the Industrial Disease Standards Panel to the Occupational Disease Panel. There were no substantive changes to these sections of the amendment.

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or a disease and a work substance as described in the first two definitions given earlier (ie, when the relationship between a disease and a work process is defined as causal). Because it is often difficult to obtain scientific consensus on disease causation, the Act established, in 1985, a body known as the Industrial Disease Standards Panel (now known as the Occupational Disease Panel) to resolve some of these issues.

The Panel is composed of a maximum of nine members and includes representatives of the public and the scientific community and persons with technical and professional expertise. The mandate of the Panel is to investigate possible occupational diseases and report its findings to the Board as to whether a "probable connection" exists between a disease and an industrial process, trade or occupation in Ontario. In particular, the Act states that the Board must solicit a written stakeholder opinion and publicly respond to the Panel's findings. After considering the opinion of stakeholders, the Board may accept, reject, or amend the Panel's findings. The Panel can identify its own issues for review and can also respond to questions raised by the Board. The issues brought to the Panel often lack scientific and stakeholder consensus, are controversial, and often elicit a great deal of public interest.

In 1985, the Act also established the Workers' Compensation Appeals Tribunal to hear appeals from workers or employers disputing Board decisions. The current gold miner policy was developed within the context of the Panel process, the Tribunal decision, additional scientific information, and further consultation with workers and employers.

Table 1. Guidelines from the 1988 gold miner policy for workers' compensation (3).[a]

Necessary conditions	Necessary evidence to meet conditions
Worked in an Ontario gold mine	Substantiated occupational history
Gold miner had primary lung cancer	Medical evidence establishing primary cancer of trachea, bronchus or lung
Biologically plausible latency period	Minimum of 15 years between first employment in "dusty gold mining"[b] occupation and diagnosis of cancer of the trachea, bronchus or lung
Worked during dutiest years of gold mining	Evidence of "dusty gold mining" in Ontario prior to 1945
Sufficient and consistent evidence of occupational exposure	At least one of three based on chest X-ray, weighted dust exposure index, age at which gold mining started and years of "dusty gold mining" experience before 1945. For example: a chest X-ray rating of 4 or more as rated by the chest X-ray classification system of the Ontario Workers' Compensation Board and a weighted dust exposure index of 60 or more, where weighted dust exposure is the sum of (i) years worked in "dusty gold mining" in Ontario pre-1936, multiplied by 4; (ii) years worked in "dusty gold mining" in Ontario from 1936 to 1944, multiplied by 3; (iii) years worked in "dusty gold mining" in Ontario from 1945 to 1954, multiplied by 2; (iv) years worked in "dusty gold mining" in Ontario after 1954, multiplied by 1.

[a] *Policy statement:* "Primary cancer of the trachea, bronchus or lung are accepted as industrial diseases . . . as characteristic of gold mining in Ontario prior to 1945" (2).

[b] "Dusty gold mining" is defined by the coding system of the Ontario Workers' Compensation Board.

Policy on lung cancer among gold miners

Because of a significant number of claims submitted to the Board in the 1980s by Ontario gold miners or their survivors, the Board asked the Panel to investigate the relationship between lung cancer and gold mining. To expedite the policy development process, the Board also commissioned a prominent cancer epidemiologist in Toronto to review the relationship between gold mining in Ontario and lung cancer deaths. Combining the recommendations of the Panel and independent scientific opinion (2), and using additional analyses by the Board staff, the Board of Directors approved a policy in January 1988 to guide the adjudication of claims from gold miners who developed lung cancer (3).

Because an excess of lung cancer deaths was found among gold miners employed before 1945, the policy was designed to compensate all miners with lung cancer who worked in an Ontario gold mine prior to 1945 and belonged to subgroups which had significantly elevated mortality from lung cancer (table 1). Workers not in these subgroups were automatically excluded from compensation because it was believed that further investigation would not detect any additional gold miners whose lung cancer was work-related.

This policy recognized cancer of the trachea, bronchus, or lung as an industrial disease characteristic of gold mining in Ontario prior to 1945. In addition it provided numerous conditions to be met for qualification for compensation: employment in an Ontario gold mine, employment during the dustiest years of gold mining, diagnosis of primary lung cancer, a biologically plausible latency period, and sufficient and consistent evidence of occupational exposure. The policy also listed the evidence needed to meet each condition. Experience in Ontario prior to 1945 would be the necessary evidence to indicate that the miner worked during the dustiest years of gold mining, and an Ontario-classified chest X-ray code of 4 or more (representing an intermediate stage between normality and abnormality and consistent with known exposure history) (see Finkelstein this issue for definition) and a weighted dust exposure index (table 1) of ≥ 60 would be one of three ways of demonstrating sufficient and consistent evidence of occupational exposure (3). If the worker met all of the necessary conditions, neither smoking nor any other factors were considered, and the claim was allowed.

Adjudicators experienced little difficulty in administering the gold miner policy until March 1989, when the Workers' Compensation Appeals Tribunal heard the appeal of the wife of a gold miner who died of lung cancer. The widow was denied survivors' benefits because there was no evidence that her husband had mined gold in Ontario prior to 1945. The Tribunal concluded that compensation cannot be denied because an individual worker does not meet every requirement set out in the policy of the Board (4). The Panel stated that the Act requires that a decision about causation be made on the merits and justice of the individual case in every single claim. In this claim, after investigating the special circumstances of the miner's work environment, the Panel decided that the miner had unusually high dust exposure and that his disease was probably work-related. After seeking legal opinion on the issue, the Board of Directors recognized the need to revise the gold miner policy and also instructed adjudicating staff to reconsider all of the 253 claims that had been denied under the policy (4).

At about the same time, Kusiak et al (5) published a paper on risk factors for lung cancer among gold miners. The paper provid-

ed new information on probable causative agents of lung cancer excess, and its findings were useful in the re-adjudication of the denied claims and for future claims.

A revised gold miner policy was adopted on 29 August 1991 (6). It contained the same five necessary conditions for establishing that the worker's lung cancer was related to gold mining. However, the policy had only two requirements: (i) that there must be a substantiated occupational history of gold mining and (ii) that there must be medical evidence establishing the presence of primary cancer of the trachea, bronchus, or lung.

Instead of "necessary evidence" as stated in the original, the revised policy listed evidence that is "persuasive" in substantiating that each of the necessary conditions has been met. Persuasive evidence for "sufficient and consistent occupational exposure" includes the factors listed in the 1988 policy, as well as additional factors identified by Kusiak et al (5) (eg, work in dusty mines, significant arsenic levels, or significant levels of radon progeny).

Finally, the policy states that "all decisions shall be made in accordance with the real merits and justice of the case, and all available evidence of work and nonwork factors is to be considered to make a determination of work-relatedness in each individual case" (6).

Evaluation of the gold miner policy

The process used to develop the gold miner policy was long and arduous. The scientific assessment had its roots in the release (in 1983) of a study by Muller et al (7). An analysis of the same cohort by a scientific panel appointed by the Industrial Disease Standards Panel and an independent scientific review in 1988 were added to the process (2). Finally Kusiak et al (5) provided more information. After more than eight years, all of the analyses concurred that there was likely a causal association between gold mining and lung cancer.

The consultation process in the development of the original gold miner policy consisted primarily of written submissions to the Ontario Workers' Compensation Board. For the revised policy, there was a 1-h face-to-face meeting between Board staff and workers' representatives and another similar meeting between Board staff and employers' representatives. Since 1991, after consultation on the revised gold miner policy took place, consultation on other Board policies has become more extensive.

Acceptance of the final policy was mixed. Workers and their representatives were satisfied with the recognition of lung cancer among gold miners as an industrial disease. They also approved of the open-ended wording for demonstrating sufficient and consistent occupational exposure. However, they would have preferred that lung cancer and gold mining be entered into schedule 3 of the Regulations of the Act and given a presumption of work relatedness. Some employers' representatives did not however recognize the causal relationship between lung cancer and gold mining and argued that the excess lung cancer mortality in the gold miner cohort was due to smoking. Hence they are particularly concerned about the lack of consideration of smoking in the policy. Furthermore, adjudicators have had difficulty in applying the policy because it requires considerable case-by-case evaluation and provides limited guidance in certain instances.

Under the original gold miner policy, 249 lung cancer claims were allowed, and 253 claims were denied. With the re-adjudication of denied claims under the revised policy, an additional 79 claims were allowed.

Toward a policy on silica exposure and lung cancer

Before proceeding with a general policy on occupational silica exposure, the following scientific questions need to be answered: (i) is there a causal connection between silicosis and lung cancer and, if so, under what circumstances would lung cancer likely occur in workers diagnosed with silicosis, and (ii) does silica exposure cause lung cancer and, if so, under what circumstances is lung cancer likely to occur among workers exposed to silica?

Scientists have hypothesized the following three possible mechanisms for an association between silicosis and lung cancer (8): (i) crystalline silica could be a carcinogen that directly causes lung cancer and the presence of silicosis in a worker is an indication that the worker has been exposed to large amounts of silica, (ii) silica causes silicosis and silicosis may be an intermediate pathological state leading to lung cancer, or (iii) cigarette smoke (which includes many known carcinogens) may attach to crystalline silica dust. Since heavy doses of polyaromatic hydrocarbons are not easily cleared from the lungs, the lungs would be exposed to high doses of a known carcinogen.

Although most, if not all, mortality studies among silicotics show elevated mortality from lung cancer, the interpretation of the findings is still controversial. Worldwide, at least 10 cohort studies on silicotics have been published since 1987 (9). All of these studies reported excess mortality from all causes [standardized mortality ratio (SMR) ranging from 140 to 302] and from lung cancer (SMR ranging from 129 to 685). The Ontario study by Finkelstein et al (10) reported a lung cancer SMR of 230 for silicotic miners and 302 for silicotic surface workers. Some reviewers (11, 12) believe that cohorts of silicotics, especially those who receive workers' compensation, are neither representative of silica-exposed workers nor of silicotics in general. They may be compensated because of poor health or because they have more symptoms due to smoking. Such interpretations are refuted by more recent studies showing that excess lung cancer is found among silicotics identified by a registry and active surveillance programs (13). (See Merlo et al and Rosenman et al, this issue.) In addition, even though smoking has been either directly or indirectly adjusted for in most studies, an excess of twofold or more still persists. Therefore, it is reasonable to conclude that silicosis is a probable cause of lung cancer death, whatever the underlying mechanism.

To assess the causal relationship between silica exposure and lung cancer, additional mortality studies have been conducted among several cohorts of silica-exposed workers worldwide since 1987 (9). The studies investigated workers in different ore mining operations, in ceramic manufacturing, and in granite and stone work. Results of these studies are not consistent. Most do not show a dose-response relationship when duration of employment is used as a measure of dose. In studies showing elevated lung cancer risks, the excess is concentrated mainly among workers who were diagnosed as silicotic (13). In cases when an excess has been shown among nonsilicotics, the excess has usually been less than 50% (a risk measure of 1.5) (13). Although some scientists support occupational silica exposure as carcinogenic (9), there are others who would disagree (11).

Policy issues

Even with a consensus on the preceding scientific issues, the policy direction which follows is not straightforward. One option

available is to revise the listing of silicosis in schedule 3 to read "silicosis and its sequelae." This change would recognize the clear and consistent relationship between silicosis and lung cancer, as well as silicosis and other sequelae, such as tuberculosis and cor pulmonale. Guidelines would be developed to inform stakeholders and adjudicators of the sequelae for silicosis and the circumstances under which these conditions are most likely to occur.

As yet there is no scientific consensus on whether a causal relationship exists between crystalline silica and lung cancer, even though the International Agency for Research on Cancer (IARC) identifies silica as a probable human carcinogen (14). More investigations on the relationship between silica exposure and lung cancer in the absence of silicosis, particularly in Ontario cohorts, may help to clarify the issue. Failing that, what is needed is consultation among stakeholders to arrive at some form of consensus on the issue. Therefore, this appears to be a perfect task for the Occupational Disease Panel.

No matter what the final policy will be, it is clear that the issue of smoking cannot be ignored. Similarly, changes in workplaces where silica is encountered will also need to be considered. As a result of preemployment and annual chest X-rays for all miners between 1928 and 1983 and the enactment of the Designated Substance Regulation for Silica in 1983 to control the level of silica exposure in Ontario workplaces, the numbers of silicosis claims to the Board have decreased. In the 1940s, the Board allowed an average of about 50 silicosis claims a year. Between 1990 and 1994, the number of allowed claims dropped to about 20 per year. Therefore, it is important to ensure that any policy that is developed recognizes that data of past silica exposure is likely to be unreliable and that the nature and amount of silica exposure currently being encountered in Ontario workplaces differ from those in the past.

Concluding remarks

Ontario is the only worker's compensation jurisdiction in the world to recognize lung cancer among gold miners as an industrial disease. The gold miner policy has helped to lay the groundwork for the developments of many other workers' compensation policies in Ontario, including one on silica exposure and lung cancer. However, both the development process and the resulting policy on gold miners have their weaknesses. The process provided limited stakeholder discussion with the Board and between workers' and employers' representatives. The resulting policy, while based on scientific evidence, nevertheless, falls short of providing concrete guidance for adjudicators to use in making decisions on claims. In addition, it lacks advice on how to consider previous smoking in the decision making.

It is clear that future policy development for lung cancer claims among silica-exposed workers should contain wide and extensive consultation with stakeholders. Included in the process must be scientific experts, workers and their representatives, employers, and adjudicators, who must implement any policy that is approved.

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Future research needs in the silica, silicosis and cancer field

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Goldsmith DF, Wagner GR, Saffiotti U, Rabovsky J, Leigh J. Future research needs in the silica, silicosis and cancer field. *Scand J Work Environ Health* 1995;21 suppl 2:115—7.

Key terms biology, cancer, future research, physicochemistry, prevention, silica, silicosis, risk assessment.

Biological evidence of the relationships among silica exposure, silicosis, and the risk of cancer is evolving. When the First International Symposium on Silica, Silicosis and Cancer convened in 1984, suspicions based on studies with laboratory rats were raised that the inhalation of silica dust may produce pulmonary tumors. In addition there was limited information from epidemiologic studies on silica-exposed workers and compensation claimants with silicosis who appeared to have elevated risks for pulmonary and gastric malignancies. The findings were generally supportive of a hypothesis articulated in the mid-1930s by a British pathologist that either silica was carcinogenic or silicosis acted as a cancer precursor (1).

In the last decade the hypothesis was re-examined by the scientific community, including four major agency reviews of the silica and cancer issue by the International Agency for Research on Cancer (2), the Science Advisory Panel of California's Proposition 65 (3), the Australian National Occupational Health and Safety Commission (4), and the Occupational Disease Standards Panel of Ontario, Canada (5). In addition there have been numerous published literature reviews (6—10) on this topic. This supplement of the *Scandinavian Journal of Work, Environment & Health* contributes to the body of knowledge by assembling key papers from the Second International Symposium on Silica, Silicosis, and Cancer convened in October 1993 in San Francisco, California.

Purpose

The purpose of this paper is to summarize the current state of knowledge and to suggest areas needing further research. It is clear by the scope of the papers presented at the Second Symposium that many new insights have been gained during the last 10 years of investigation and some new disciplines have begun to focus on this area of investigation. Specifically, the results by investigators such as Stopford & Stopford and Dosemeci et al in this issue expand our insights into the exposure assessment and industrial hygiene aspects of silica emissions. The work in this field has stimulated the interests of the physicochemistry community represented by Fubini et al, Guthrie & Heaney, and Shoemaker et al. They have raised perceptive questions about differential toxicity for silica particles according to surface area and surface chemistry, the freshness of particulate cleavage, and the roles played by other surface metals. Rabovsky reminds us that the biological activity of amorphous silica, including biogenic silica fibers, remains to be determined. These areas seem ripe for new collaborations between the disciplines of mineralogy, environmental hygiene, and silica toxicology. The importance of the accurate measurement of silica exposure and cumulative lung burdens remains a priority for both epidemiology and for hazard surveillance studies. Although there is extensive literature linking silica dust measurements to the risk of chronic silicosis, only during the past three to five years have adequate industrial hygiene data become available for dose-response studies of occupational silica exposure and cancer (11—13).

In the field of tumor biology, data from two rat studies in the past seven years confirmed the initial findings that inhaled silica can produce pulmonary cancers (14, 15). (See Muhle et al, this issue, for additional findings.) Saffiotti and his colleagues described the histogenesis of rat lung reactions to instilled quartz leading to lung tumors — mostly adenocarcinomas — adjacent to silicotic granulomas, with an emphasis on progressive hyperplasia of alveolar type II epithelial cells (16). There remains the question of why rats are responsive to the fibrotic and oncologic potential of silica, while other rodents appear to be either resistant or nonresponsive (17). The work of Williams et al and Daniel & Saffiotti in this issue have added to the biochemical understanding of the likely role silica plays in carcinogenesis. In particular, the ability of silica to bind with DNA (deoxyribonucleic acid) in vitro and its mechanistic links through transforming growth factor β1 suggest

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new avenues for additional investigation. In addition, while freshly cleaved silica has been known previously to be more toxic and to produce greater levels of reactive oxygen than aged dust, Shoemaker and his colleagues have provided new vital evidence of these phenomena.

New epidemiology studies of populations exposed to silica continue to bring evidence to this field. Although practitioners in occupational medicine have known for decades the role of silica in causing silicosis and methods to prevent this disease, information (this issue) on residual silicosis rates in Ontario, Canada, and China and among ceramic workers in Italy helps define the level of risk for exposed workers. New findings such as those by Rosenman et al, Dong and his co-workers, Merlo and his colleagues in this issue, Finkelstein (31), and Goldsmith and his co-workers (18) add to the mounting literature showing that silicotics have significantly higher risks for lung cancer. These findings must be considered in context. Silicotics are less healthy than the general population, including increased cancer risks, but why are the cancer risks now emerging and what are the pathological and biochemical mechanisms to explain the current findings?

Despite numerous studies of diverse occupational cohorts, the question of association between quartz exposure and lung cancer continues to fuel scientific debate and new research investigations [such as the immunologic role of silica in carcinogenicity (19)]. Studies asking similar questions in different populations and using a variety of methods have arrived at contradictory conclusions. It is difficult to quantify silica exposures accurately, particularly when cohorts are assembled for historical prospective investigation. Furthermore, exposures to other toxic agents such as radon, smoking, and other known carcinogens make this task more difficult. Misclassification of exposure and patterns for selecting study subjects may act to bias the risk measures. Despite these common limitations, some studies (11, 12, 20—24) presented in the Second Symposium or published elsewhere suggest an increased lung cancer risk even in the absence of radiological silicosis. Other research (13) suggests no association. When complete, the preliminary research presented by McDonald et al and de Klerk and his colleagues in this issue will expand data in this evolving field.

Another discipline being applied in this area is quantitative risk assessment (25), which seeks to extrapolate the potential cancer and noncancer risks of silica relative to occupational and ambient environments. Although some authors suggest that there is no need to conduct risk determinations (26), this supplement of the *Scandinavian Journal of Work, Environment & Health* has included five new perspectives on the issue by Collins & Marty, Goldsmith et al, Klein & Christopher, Rice & Stayner, and Zhong & Li. The methodology for occupational risk assessment is in the process of being modified (27), and new documents relative to this question are being planned by agencies in Australia and the United States. Thus there is likely to be more, rather than less, quantitative risk assessment focusing on silica in the future.

What next?

Ultimately, a determination must be made on the best available evidence as to the probable health effects of exposure to quartz at various exposure levels. In this instance, the evidence supporting concern about cancer risk among workers with silicosis is generally consistent, temporally appropriate, consistent with laboratory models, and it also has overall coherence (9). In some investigations, but not all, exposure-response or dose-response relationships have been reported (11, 12).

There is no debate about the need to eliminate exposure conditions which inevitably lead to silicosis (32). The extent to which additional measures are justified to control exposures producing silicosis depends on the interpretation of often contradictory literature. Perhaps current laboratory investigations directed towards improving our understanding of the toxicity of crystalline silica dusts combined with longer follow-up of occupational cohorts will provide the scientific basis for such action. In the meantime, the public health dictum of prudent action in the face of uncertainty should guide preventive efforts. Specifically, preventive efforts should be intensified to control silica emissions in sand blasting, mine drilling, and other types of work in which high silica dust levels occur (28, 29). The need for more precise investigation should not be used to avoid the imperative of health protection. Standard setting and the adoption of health protective measures are an iterative process: the best available information should inform the best course of action. Experience gained in the implementation of new approaches should be evaluated through ongoing hazard and health surveillance, as well as through continued research. As more information emerges, recommendations for and the application of improved dust control practices must evolve. And in no instance should the egregious exposure conditions [described by Weisenfeld et al in 1993 at the Second Symposium (30)] continue unabated, because these conditions will inevitably lead to silicosis and perhaps to lung cancer. Thus the application of current knowledge will go far to eliminate the possibility of future disease.

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