EXHIBIT 26

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Crystalline Silica, Quartz,
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This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

Concise International Chemical Assessment Document 24

CRYSTALLINE SILICA, QUARTZ

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based tolerable intakes and guidance values.

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

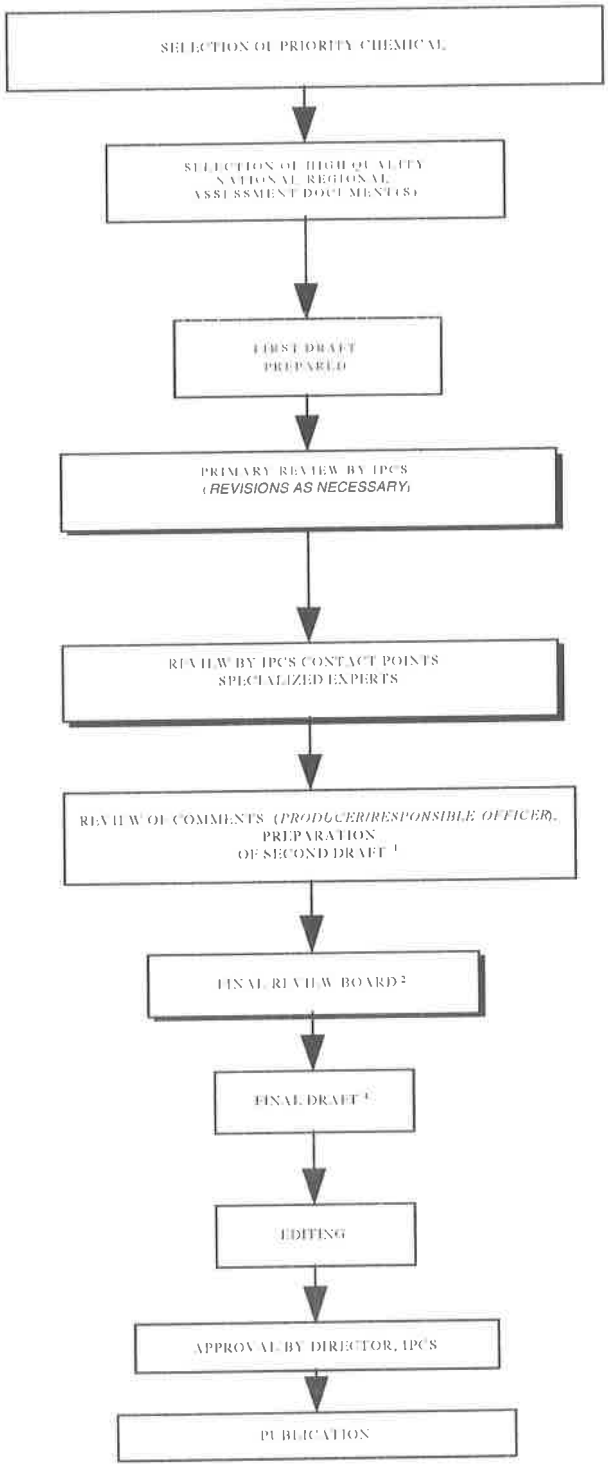
The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board

industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on crystalline silica, quartz was based on the following three extensive peer-reviewed documents on the health effects of crystalline silica, including quartz: (1) a review of published human studies and reports on the adverse health effects of quartz exposure (NIOSH, forthcoming), (2) a review of the carcinogenicity studies conducted by the International Agency for Research on Cancer (IARC, 1997), and (3) a review of the non-cancer health effects of ambient quartz (US EPA, 1996). The source documents had different emphases on different end-points, and the CICAD was developed to assess all the adverse health effects identified in these documents. It is to be noted that despite the different emphases, the final conclusions of all source documents were very similar. A comprehensive literature search of several on-line databases was conducted. Data identified as of March 1999 are included in this review.

This CICAD considers the most common form of crystalline silica (i.e., quartz). It does not consider experimental studies of the effects of other forms of crystalline silica (e.g., cristobalite, tridymite, stishovite, or coesite), coal dust, diatomaceous earth, or amorphous silica, because their *in vitro* toxicities differ from that of quartz. Differences in induction of fibrogenicity of quartz, cristobalite, and tridymite were demonstrated *in vivo* in an early rat study. However, there are virtually no experimental studies that systematically evaluated exactly the same material to which humans are exposed. The IARC Working Group considered the possibility that there may be differences in the carcinogenic potential among polymorphs of crystalline silica. However, some of the epidemiological studies evaluated lung cancer among workers in "mixed environments" where quartz may be heated and varying degrees of conversion to cristobalite or tridymite can occur (e.g., ceramics, pottery, and refractory brick industries), and exposures specifically to quartz or cristobalite were not delineated. Although there were some indications that cancer risks varied by industry and process in a manner suggestive of polymorph-specific risks, the Working Group could reach only a single conclusion for quartz and cristobalite. The CICAD reflects the discussion and conclusion of that source document; therefore, when considering the carcinogenicity of quartz in the occupational setting, it does not distinguish between epidemiological studies of quartz and those of cristobalite.

The peer review process for this CICAD was targeted to include review by an international group of experts selected for their knowledge about the current controversies and issues surrounding quartz. Information on the nature of the peer review and the availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Sydney, Australia, on 21–24 November 1999. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0808) for crystalline silica, quartz has been reproduced in Appendix 4 (IPCS, 1993).

Quartz (CAS No. 14808-60-7) is a frequently occurring solid component of most natural mineral dusts. Human exposures to quartz occur most often during occupational activities that involve movement of earth, disturbance of silica-containing products (e.g., masonry, concrete), or use or manufacture of silica-containing products. Environmental exposure to ambient quartz dust can occur during natural, industrial, and agricultural activities. Respirable quartz dust particles can be inhaled and deposited in the lung; however, no conclusions have been made about the clearance kinetics of quartz particles in humans.

Quartz dust induces cellular inflammation *in vivo*. Short-term experimental studies of rats have found that intratracheal instillation of quartz particles leads to the formation of discrete silicotic nodules in rats, mice, and hamsters. Inhalation of aerosolized quartz particles impairs alveolar macrophage clearance functions and leads to progressive lesions and pneumonitis. Oxidative stress (i.e., increased formation of hydroxyl radicals, reactive oxygen species, or reactive nitrogen species) has been observed in rats after intratracheal instillation or inhalation of quartz. Many experimental *in vitro* studies have found that the surface characteristics of the crystalline silica particle influence its fibrogenic activity and a number of features related to its cytotoxicity. Although many potential contributory mechanisms have been described in the literature, the mechanisms responsible for cellular damage by quartz particles are complex and not completely understood.

Long-term inhalation studies of rats and mice have shown that quartz particles produce cellular proliferation, nodule formation, suppressed immune functions, and alveolar proteinosis. Experimental studies of rats reported the occurrence of adenocarcinomas and squamous cell carcinomas after the inhalation or intratracheal instillation of quartz. Pulmonary tumours were not observed in experiments with hamsters or mice. Adequate dose–response data (e.g., no-adverse-effect or lowest-adverse-effect levels) for rats or other rodents are not available because few multiple-dose carcinogenicity studies have been performed.

Quartz did not test positively in standard bacterial mutagenesis assays. Results of genotoxicity studies of quartz conflict, and a direct genotoxic effect for quartz has not been confirmed or ruled out.

In experimental studies of particles, results may vary depending on the test material, particle size of the material, concentration administered, and species tested. The experiments with quartz particles involved specimens from various sources, using various doses, particle sizes, and species, which could have affected the observations.

Data on the reproductive and developmental effects of quartz in laboratory animals are not available.

The adverse effects of quartz in aquatic organisms and terrestrial mammals have not been studied.

There are many epidemiological studies of occupational cohorts exposed to respirable quartz dust. Silicosis, lung cancer, and pulmonary tuberculosis are associated with occupational exposure to quartz dust. IARC classified inhaled crystalline silica (quartz or cristobalite) from occupational sources as a Group 1 carcinogen based on sufficient evidence of carcinogenicity in humans and experimental animals; "in making the overall evaluation, the Working Group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs" (IARC, 1997).

Statistically significant increases in deaths or cases of bronchitis, emphysema, chronic obstructive pulmonary disease, autoimmune-related diseases (i.e., scleroderma, rheumatoid arthritis, systemic lupus erythematosus), and renal diseases have been reported.

Silicosis is the critical effect for hazard identification and exposure–response assessment. There are sufficient epidemiological data to allow the risk of silicosis to be quantitatively estimated, but not to permit accurate estimations of risks for other health effects mentioned above. (A pooled risk assessment of epidemiological studies of silica and lung cancer is in progress at IARC.)

The risk estimates for silicosis prevalence for a working lifetime of exposure to respirable quartz dust concentrations of about 0.05 or 0.10 mg/m^3 in the occupational environment vary widely (i.e., 2–90%). Regarding exposure to ambient quartz in the general environment, a benchmark dose analysis predicted that the silicosis risk for a continuous 70-year lifetime exposure to 0.008 mg/m^3 (estimated high crystalline silica concentration in US metropolitan areas) is less than 3% for healthy individuals not compromised by other respiratory diseases or conditions and for ambient environment (US EPA, 1996). The silicosis risk for persons with respiratory diseases exposed to ambient quartz in the general environment was not evaluated.

Uncertainties exist in the evaluation of epidemiological studies and the risk assessment of health effects related to quartz dust exposure. The difficulties, many of which are inherent to the study of respiratory diseases in occupational populations, include limitations in the amount and quality of historical exposure data, deficiencies in data on potentially confounding factors, such as cigarette smoking, and difficulties in the interpretation of chest radiographs as evidence of exposure. In addition, occupational exposures to quartz dust are complex because workers are frequently exposed to dust mixtures that contain quartz and other mineral varieties. Properties of the dust (e.g., particle size, surface properties, crystalline form) may differ according to geological source and can also change during industrial processing. Such variations can affect the biological activity of the inhaled dust. The IARC Working Group evaluated the carcinogenicity of crystalline silica (including quartz) and focused on epidemiological studies that were the least likely to have been affected by confounding and selection biases and that evaluated exposure–response relationships (IARC, 1997).

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

"Silica," or silicon dioxide (SiO_2), occurs in either a crystalline or non-crystalline (amorphous) form. Crystalline silica may be found in more than one form (polymorphism), depending on the orientation and position of the tetrahedra (i.e., the three-dimensional basic unit of all forms of crystalline silica). The natural crystalline forms of silica are "-quartz, $-quartz, "-, $$_1$-, and $$_2$-tridymite, "- and $-cristobalite, coesite, stishovite, and moganite (IARC, 1997). This document discusses the most common form of naturally occurring crystalline silica — quartz (CAS No. 14808-60-7). Cristobalite (CAS No. 14464-46-1) and tridymite (CAS No. 15468-32-3) exist in nature, but they can also be created during industrial processes, such as the calcination of diatomaceous earth, ceramics manufacturing, foundry processes, silicon carbide manufacturing, and any other process in which quartz is heated to high temperatures (NIOSH, 1974; Altieri et al., 1984; Virta, 1993; Weill et al., 1994; IARC, 1997).

Quartz is a colourless, odourless, non-combustible solid and a component of many mineral dusts (NIOSH, 1997). It is insoluble in water (NIOSH, 1997). When quartz is cut, ground, or milled, the crystal is fractured, and Si and Si–O radicals may be generated on the cleavage surfaces (Castranova et al., 1996). Trace metal impurities, such as iron and aluminium, can modify the surface reactivity of quartz (Fubini et al., 1995; Fubini, 1997, 1998; IARC, 1997; Donaldson & Borm, 1998).

Most of the experimental studies described in section 8 used Min-U-Sil or DQ 12 quartz. Min-U-Sil is a trade name, and the number that follows (e.g., Min-U-Sil 5) describes the particle size of the sample (e.g., Min-U-Sil 5 is #5 μm in diameter). The purity is 99% quartz (IARC, 1997). However, the geological sources of crystals have varied; consequently, the associated impurities may have varied. The particle size distributions of Min-U-Sil and several other reference standards for the quantification of quartz in coal mine dust have been investigated (Huggins et al., 1985), but a comprehensive report has not been published on the analytical characteristics of a standard sample of Min-U-Sil and the reproducibility of its aliquots (Saffiotti et al., 1993). DQ 12 is a quartz sand that contains 87% crystalline silica; the remaining proportion is amorphous silica, with small contaminations of kaolinite. All DQ 12 samples originate from the same source, but its particle size and composition have not been reported recently (IARC, 1997). Furthermore, many experimental and epidemiological studies do not state the source and properties of the quartz that is used as a test material or collected in the workplace (Mossman & Churg, 1998).

Additional physical and chemical properties of quartz are presented in the International Chemical Safety Card (ICSC 0808) reproduced in this document (Appendix 4).

3. ANALYTICAL METHODS

Mineral dust particles, such as quartz particles, are typically described by diameter size (e.g., geometric mean diameter) and aerodynamic diameter. Both characteristics are important in determining whether the particle is respirable (IARC, 1997). Analysis for airborne quartz is usually by X-ray diffraction or infrared spectrophotometry in combination with filter collection methods (IARC, 1997). Dust levels can be based on counts from an impinger or on mass collected on a filter (IARC, 1997). Currently, the latter method is more commonly used. Most countries (e.g., the USA, the United Kingdom, Germany, Japan, and Australia) require that the sample be restricted to the respirable fraction (IARC, 1997). The estimated detection limit for quartz in respirable dust samples is 0.005 mg using US National Institute for Occupational Safety and Health (NIOSH) method 7500 (i.e., X-ray powder diffraction) (NIOSH, 1994a). The estimated detection limit for quartz in respirable dust samples with NIOSH method 7602 (infrared absorption spectrophotometry) is also 0.005 mg (NIOSH, 1994b).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Quartz is abundant in most rocks, sands, and soils (IARC, 1997). The extensive natural occurrence of quartz and the wide uses of the materials that contain quartz are directly related to potential occupational exposures to quartz for workers in many industries and occupations. Virtually any process that involves movement of earth (e.g., mining, farming, construction), disturbance of silica-containing products such as masonry and concrete, or use of sand and other silica-containing products (e.g., foundry processes) may potentially expose a worker to quartz (IARC, 1997).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Environmental exposures to quartz can occur when ambient quartz is emitted into the air as a component of particulate emissions produced by natural, industrial, and farming activities (US EPA, 1996). These activities include construction and demolition, quarrying and mining, dust from travel on paved and unpaved roads, electrical power generation, agricultural tilling, forest fires, volcanic eruptions, and wind erosion (US EPA, 1996; IARC, 1997).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Ambient quartz is emitted to the environment as a component of particulate emissions. The available data on concentrations of quartz in the non-occupational environment (i.e., ambient air), including data collected by the US Environmental Protection Agency (US EPA),

are limited (US EPA, 1996). The US EPA's Inhalable Particulate Network provides a data set of quartz concentrations that were collected from high-volume or dichotomous samples of ambient aerosols in 25 US cities in 1980 (Davis et al., 1984). Average quartz concentrations were highest (and most variable) in air masses in continental interior sites. Ambient quartz concentrations collected from high-volume filter samples of total suspended particulates in 10 US cities ranged from 0 $\mu g/m^3$ (Portland, Oregon) to 15.8 $\mu g/m^3$ (Akron, Ohio) (Davis et al., 1984). Both of those findings were based on one sample in each city (US EPA, 1996).

Non-occupational inhalation of quartz may occur while using a variety of commercial products, such as cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar (US Department of the Interior, 1992). Data representing quantitative exposure levels of respirable quartz during non-occupational uses of commercial products are not available.

Although quartz particles may be present in water, quantitative data on concentrations of quartz in potable or other forms of drinking-water are not available (IARC, 1997).

Occupational quartz dust exposure is probably one of the most documented workplace exposures. Nearly every mineral deposit contains some quartz (Greskevitch et al., 1992); thus, most quartz exposures are to mixed dust with a variable quartz content that must be measured by dust collection and analysis (Wagner, 1995). Compliance officers for the US Occupational Safety and Health Administration measured respirable quartz in 255 industries that were targeted for inspection, excluding mining and agriculture. In 48% of the industries, average overall exposure exceeded the permissible exposure level (10 mg respirable dust/m^3 divided by % silica + 2) (Freeman & Grossman, 1995).

Respirable quartz levels exceeding 0.1 mg/m^3 have been reported in many industries worldwide and are most frequently found in metal, non-metal, and coal mines and mills; in granite quarrying and processing, crushed stone and related industries; in foundries; in the ceramics industry; and in construction and sandblasting operations (IARC, 1997). IARC summarized data from the main industries for which quantitative quartz exposure levels were available in the published literature or where major occupational health studies were conducted (IARC, 1997). The IARC review is condensed here and presented by industry. Many processes in these industries include potential exposures to other substances with known adverse health effects, including carcinogenicity. Information about the health hazards for a particular industry, the variability of the proportion of quartz found in total dust samples from different industries, and the estimated proportion of workers exposed to defined concentrations is available elsewhere (e.g., IARC, 1984, 1987, 1997; Burgess, 1995; Linch et al., 1998).

The mean respirable quartz level in mining operations (i.e., underground and surface mining, milling operations) inspected in the USA from 1988 to 1992 was usually less than 0.10 mg/m^3, but a significant percentage of samples exceeded the permissible exposure limit (see above) (Watts & Parker, 1995; IARC, 1997). Estimated arithmetic mean respirable crystalline silica levels (form of "crystalline silica" was not specified) for 1950–1959 and 1981–1987 in 20 Chinese mines (10 tungsten, 6 iron–copper, and 4 tin) decreased about 10-fold between those periods. The estimated arithmetic mean level of respirable silica (mg/m^3) for the older period and the more recent period, respectively, were as follows: underground mining, 4.89, 0.39; surface mining, 1.75, 0.27; ore dressing, 3.45, 0.42; tungsten mines, 4.99, 0.46; iron and copper mines, 0.75, 0.20; and tin mines, 3.49, 0.45 (Dosemeci et al., 1995; IARC, 1997). Respirable quartz concentrations in underground dust from South African gold mines ranged from 0.05 to 0.58 mg/m^3 in surveys taken during 1965–1967 (Beadle & Bradley, 1970). In a copper mine in Finland, the mean concentration of respirable quartz in the general mine air was about 0.16 mg/m^3 until 1965, 0.12 mg/m^3 in 1966–1975, and 0.08 mg/m^3 after 1981 (Ahlman et al., 1991).

Exposure to respirable quartz dust can occur in granite quarrying and processing, including crushed stone and related industries. Geometric mean air concentrations and air concentrations of quartz from personal breathing-zone samples collected during various jobs in the granite quarrying and processing industries and crushed stone and related industries in Finland, the USA, and the United Kingdom ranged from 0.03 to 1.5 mg/m^3 and from not detectable to 135 mg/m^3, respectively (Donaldson et al., 1982; Eisen et al., 1984; Koskela et al., 1987; Davies et al., 1994; Kullman et al., 1995; IARC, 1997). In US granite quarries and sheds, control measures implemented in the late 1930s and the 1940s resulted in 10- to 100-fold reductions of formerly high dust levels (Davis et al., 1983; IARC, 1997).

In India, personal respirable dust levels of 0.06–1.12 mg/m^3 (average 0.61 mg/m^3 with a free silica content of 15%; form of silica not specified) were generated during the manufacture of slate pencils from natural rock. Average personal dust concentrations measured in previous surveys in 1977 and 1982 were 10- to 100-fold higher (Fulekar & Alam Kham, 1995; IARC, 1997).

Foundry occupations can involve exposure to quartz-containing sands and parting powders (e.g., silica flour). The quartz content of sands ranges from 5% to nearly 100% (IARC, 1997). Foundry occupations with particularly high potential exposures to quartz (e.g., sand or silica flour) are those jobs that involve sand preparation and reclamation, knocking-out or shaking-out, cleaning of castings (i.e., fettling, grinding, sandblasting), and furnace and ladle refractory relining and repair (IARC, 1997). Mean personal respirable quartz levels in iron, steel, aluminium, brass, and other types of foundries ranged from 0.19 to 5.26 mg/m^3 in Finland (Siltanen et al., 1976; IARC, 1997) and from 0.13 to 0.63 mg/m^3 in Sweden (Gerhardsson, 1976; IARC, 1997); in Canadian iron and steel foundries, the mean personal respirable quartz concentration was 0.086 mg/m^3 (Oudyk, 1995; IARC, 1997).

IARC presented respirable quartz dust levels for jobs in ceramics, brick, cement, or glass industries in China (Dosemeci et al., 1995), Italy (Cavariani et al., 1995), the Netherlands (Buringh et al., 1990), South Africa (Myers et al., 1989; Rees et al., 1992), the United Kingdom (Bloor et al., 1971; Fox et al., 1975; Higgins et al., 1985), and the USA (Anderson et al., 1980; Salisbury & Melius, 1982; Cooper et al., 1993) and noted that jobs involving mixing, moulding, glaze spraying, and finishing were associated with higher exposure levels, often in the range of 0.1–0.3 mg/m^3 (IARC, 1997). In ceramic and pottery manufacturing facilities, exposures are mainly to quartz, but potential exposures to cristobalite may occur where high temperatures are used (e.g., ovens) (IARC, 1997). In refractory brick and diatomaceous earth processing facilities, the raw materials (amorphous or crystalline silica) are processed at temperatures near 1000 °C, with varying degrees of conversion to cristobalite (IARC, 1997).

In the construction industry, drilling, sandblasting, sawing, grinding, cleaning, and many other actions that are applied to concrete, mortar surfaces, brick, rock, and other silica-containing substances and products can result in the generation of a fine airborne dust (Lofgren, 1993; Linch & Cocalis, 1994; NIOSH, 1996; IARC 1997). Concrete finishers and masons in the USA (Lofgren, 1993), caisson workers in Hong Kong (Ng et al., 1987a), and construction site cleaners in Finland (Riala, 1988) have had respirable quartz exposure levels of at least 0.10 mg/m^3, and some exposures were many times higher.

Sandblasters in US steel fabrication yards were exposed to a mean exposure of 4.8 mg/m^3 of respirable free silica (type of silica not specified). Samples were collected from the workers' breathing zones, inside and outside protective hoods. Other yard workers had mean respirable free silica exposures ranging from 0.06 to 0.7 mg/m^3 (Samimi et al., 1974).

In the USA, average personal respirable quartz exposures ranged from 0.02 to 0.07 mg/m^3 during rice farming activities (Lawson et al., 1995), and median airborne quartz levels during fruit harvesting ranged from 0.007 to 0.11 mg/m^3 (Popendorf et al., 1982; Stopford & Stopford, 1995).

Exposures to respirable quartz have been noted in "miscellaneous" operations (IARC, 1997). Studies of US waste incinerator workers (Bresnitz et al., 1992), US wildland firefighters (Kelly, 1992; Materna et al., 1992), and workers in Canadian silicon carbide manufacturing plants (Dufresne et al., 1987) reported respirable quartz levels that were generally below 0.1 mg/m^3. Gemstone workers in Hong Kong (Ng et al., 1987b), US workers involved with refuse burning, transfer, and landfill activities (Mozzon et al., 1987), and US maintenance-of-way railroad workers (i.e., broom operators and ballast regulators) (Tucker et al., 1995) had exposures to respirable quartz above 0.10 mg/m^3.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Quartz enters the body as a particle. Usually the particle is inhaled, and it may be deposited in the lung. Solid particulates such as quartz are often described by size range. For example, "coarse" particles are usually described as particles with a diameter more than 2 μm; "fine" particles are those with diameters in the range of 0.1–2.0 μm; and "ultrafine" particles are described as particles with a diameter less than 0.1 μm. While particle size is often described as geometric mean diameter in inhalation studies, the aerodynamic characteristics of the particle are important, too. In humans, inhalation of "respirable" particles involves exposure to the particles in a mineral dust that are able to penetrate into the alveolar spaces of the lungs. It is generally considered that respirable particles have an aerodynamic diameter of <3–4 μm, while most particles larger than 5 μm may be deposited in the tracheobronchial airways and thus not reach the alveolar region (IARC, 1997). Particles deposited in the respiratory bronchioles and proximal alveoli are cleared more slowly and are more likely to injure the lung.

There are few data on quartz dust burdens in human lungs, and no conclusions have been drawn

about the clearance kinetics of quartz particles in humans (IARC, 1997). It has been observed that the deposition and clearance of quartz and other inhaled particles in other animals vary with species (IARC, 1997; Oberdörster, 1997). Short-term inhalation exposures (i.e., <10 days) in rats have shown that respirable quartz particles can be deposited in the lung and translocated into epithelial cells and to the interstitium and may eventually accumulate in the lymph nodes (IARC, 1997). Experimental particle inhalation studies of laboratory animals, particularly Fischer 344 rats, have demonstrated a phenomenon known as "particle overload," which may occur when the pulmonary defences are overwhelmed by very high exposures (Donaldson & Borm, 1998) and which may reduce the accuracy of linear exposure–response extrapolations to low levels (US EPA, 1996). The implications of particle overload for non-rodent species, such as humans, are not known, but in rats it is characterized by the suppression of particle transport by alveolar macrophages and the development of concurrent events such as increased interstitial dust uptake and prolonged inflammatory response (Morrow, 1988, 1992).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

The biological response to quartz particles depends on a variety of factors. It is currently thought that the surface of the quartz particle is of prime importance in determining its biological effects because the surface makes contact with biological molecules and cell surfaces (Fubini et al., 1995; Fubini, 1997; Donaldson & Borm, 1998). Many experimental *in vitro* studies have investigated the surface characteristics of crystalline silica particles, including quartz, and their influence on fibrogenic activity and have found that a number of features may be related to cytotoxicity (Fubini et al., 1995; Bolsaitis & Wallace, 1996; Castranova et al., 1996; Fubini, 1997, 1998; Donaldson & Borm, 1998; Erdogdu & Hasirci, 1998). Some factors are inherent to the quartz particle itself (e.g., particle size, micromorphology, external surface defects, origin of the sample, thermal treatments, and grinding, ball milling, or etching of the particles), while other factors are external (e.g., contact, association, contamination, or coating by substances other than quartz) (Iler, 1979; Fubini, 1998). It has been suggested that intimate contact between quartz and carbon or metals could modify the nature of the surface sites (Fubini, 1998) and thus affect the biological response to quartz. Freshly fractured surfaces are more reactive than aged ones (IARC, 1997). Further research is needed to associate the surface characteristics with occupational exposure situations and health effects (Donaldson & Borm, 1998; NIOSH, forthcoming), such as work processes that produce freshly fractured silica surfaces (Vallyathan et al., 1995; Bolsaitis & Wallace, 1996) or where quartz may be contaminated with trace elements such as iron (Castranova et al., 1997). There is also a need for experimental studies to fully describe the sources and properties of quartz in products used in experimental studies (Mossman & Churg, 1998).

Experimental studies of the effects of other forms of crystalline silica, such as cristobalite, tridymite, stishovite, and coesite, as well as coal dust, diatomaceous earth, and amorphous silica, are not discussed because their *in vitro* toxicities differ from that of quartz (Parkes, 1982; Wiessner et al., 1988; Driscoll, 1995; Fubini et al., 1995; Donaldson & Borm, 1998; Hart & Hesterberg, 1998). Differences in induction of fibrogenicity of quartz, cristobalite, and tridymite were demonstrated *in vivo* in an early rat study (King et al., 1953).

8.1 Single exposure

No useful data are available on lethal doses of quartz in experimental animals.

8.2 Short-term exposure

Evidence of cellular proliferation and 3-fold (or higher) increases in the water, protein, and phospholipid content of male rat lungs were observed within 28 days after a single 50-mg intratracheal injection of quartz (i.e., Min-U-Sil with particle diameter less than 5 μm) (Dethloff et al., 1986a,b; Hook & Viviano, 1996). Discrete silicotic granulomas were observed in rats (both sexes) 21–30 days after administration of a single intratracheal instillation of 12 mg of quartz (Min-U-Sil; particle size <5 μm in diameter) (Saffiotti et al., 1996). When the same research team administered a single intratracheal instillation of 10 mg of quartz (Min-U-Sil; particle size <5 μm in diameter) to male mice, the histopathological changes were not as pronounced on day 30 as in the experimental rats, but silicotic nodules and some fibrosis were present (Saffiotti et al., 1996). However, hamsters at the same facility had silicotic granulomas, but not fibrosis or epithelial reactions, 30 days after a single intratracheal instillation of 20 mg of quartz (Min-U-Sil; particle size <5 μm in diameter) (Saffiotti et al., 1996).

A short-term inhalation bioassay of the pulmonary toxicity of acrosolized quartz particles (Berkeley Min-U-Sil® particles with mass median aerodynamic diameter of 3.7 μm; particle size range not reported) in rats found that brief exposure produced a persistent pulmonary inflammatory response and impairment of alveolar macrophage clearance functions (Warheit & Hartsky,

1997). Progressive lesions were observed within 1 month after a 3-day (6 h per day) aerosolized quartz exposure of 100 mg/m^3. Two months after exposure, the lesions had progressed and developed into a multifocal, granulomatous-type pneumonitis. Rats with a 3-day exposure (6 h per day) to 100 mg carbonyl iron particles/m^3 (negative controls) had no cellular, cytotoxic, or membrane permeability changes at any time after exposure (Warheit & Hartsky, 1997).

Silica-induced apoptosis (i.e., programmed cell death) was observed in three *in vivo* experiments with 60 (Leigh et al., 1998a) or 20 (Leigh et al., 1997; Wang et al., 1997a) male Wistar rats that were divided into groups of equal size and intratracheally instilled with 0.5 ml saline as a control or doses of Min-U-Sil 5 quartz suspended in 0.5 ml saline and ranging from 2.5 to 22.5 mg per group. Apoptotic cells were observed among lavaged cells (both alveolar and granulomatous) at various time periods, ranging from 1 to 56 days after instillation. The proportion of apoptotic cells generally appeared to increase with increasing quartz dose (Leigh et al., 1997), and it was proposed that apoptosis and subsequent engulfment of apoptotic cells by macrophages may be involved in the silica-induced inflammatory response, both acutely and chronically (Leigh et al., 1997; Wang et al., 1997a).

8.3 Long-term exposure and carcinogenicity

Several end-points have been selected to measure the fibrogenic potential of quartz in animals: pulmonary toxicity, lung weight, development of fibrous tissue, collagen content, cytotoxicity, and biochemical changes in the lungs (US EPA, 1996; Gift & Faust, 1997). Table 1 presents critical non-cancer effects found in subchronic and chronic quartz inhalation studies of rats and mice (US EPA, 1996; Gift & Faust, 1997). All studies showed either fibrosis, increased collagen, and increased elastin content of lungs or impaired phagocytic ability of alveolar macrophages. (Table 1 also presents estimates of human equivalent concentrations [HECs] for environmental exposures, which are discussed in section 11.1.1.)

Tests of the carcinogenicity of quartz by different routes of exposure have been conducted. Different quartz specimens (i.e., Min-U-Sil 5, Novaculite, DQ 12, hydrogen fluoride-etched Min-U-Sil 5, Min-U-Sil with polyvinylpyridine-*N*-oxide, DQ 12 with polyvinylpyridine-*N*-oxide, and Sikron F-300 quartz) with particle sizes in the respirable range were tested in five experiments with rats by inhalation (Holland et al., 1983, 1986; Dagle et al., 1986; Muhle et al., 1989, 1991, 1995; Reuzel et al., 1991; Spiethoff et al., 1992) and in four experiments with rats by intratracheal instillation (Holland et al., 1983; Groth et al., 1986; Saffiotti, 1990, 1992; Pott et al., 1994; Saffiotti et al., 1996). The results of these experiments and others are summarized in Tables 2–4. Significant increases in the incidence of adenocarcinomas and squamous cell carcinomas of the lung were found in eight of the nine experiments. Marked, dense pulmonary fibrosis was part of the response (IARC, 1997). (The IARC Working Group noted that the experiment by Reuzel et al. [1991], in which only one respiratory tract tumour was observed, had a short duration and lacked information on survival; in addition, only a small proportion of the quartz particles was respirable by rats.) (Note: Level of statistical significance of tumour incidence in treated animals compared with control animals was reported only by Groth et al. [1986]. *P*-value was less than 0.001 for their Min-U-Sil 5 and Novaculite experiments.)

Although pulmonary granulomatous inflammation and slight to moderate fibrosis of the alveolar septa were observed in three experiments on hamsters that used repeated intratracheal instillation of quartz dusts, no pulmonary tumours were observed (Holland et al., 1983; Renne et al., 1985; Niemeier et al., 1986).

In experiments with mice, no statistically significant increase was seen in the incidence of lung tumours in a strain A mouse (i.e., male A/J mice from Jackson Laboratories, Bar Harbor, ME, USA) lung adenoma assay with one sample of quartz (McNeill et al., 1990) or with a sample of quartz in a limited inhalation study of BALB/cBYJ female mice (Wilson et al., 1986). Fibrosis was not observed; however, the lungs of quartz-treated mice did have silicotic granulomas, and lymphoid cuffing was observed around airways (IARC, 1997).

Thoracic and abdominal malignant lymphomas, primarily of the histiocytic type, were found in several studies in rats using single intrapleural or intraperitoneal injection of suspensions of several types of quartz (Wagner & Berry, 1969; J.C. Wagner, 1970; Wagner & Wagner, 1972; M.M.F. Wagner, 1976; Wagner et al., 1980; Jaurand et al., 1987; IARC, 1997).

It is important to note the species differences observed in the tumour response to quartz particles. In rats, quartz is clearly carcinogenic, but there is less or no malignant tumour response in mice and hamsters (Donaldson & Borm, 1998). Particle-induced lung tumours have been noted in rats, but not to the same degree in mice or hamsters (IARC, 1997). Currently, there is a limited understanding of the mechanisms of quartz toxicity, including mechanisms of the rat lung response (IARC, 1997). Several mechanisms for the carcinogenicity of quartz in rats have been proposed, included the hypothetical inflammation-based

Table 1: Human equivalent concentrations (HECs) for environmental exposures and non-cancer and non-tumour effects for LOAELs[a] reported in subchronic (≠3 months) and chronic quartz inhalation studies in experimental animals.[b]

Species, strain, number, sex	Exposure, dose, duration	LOAEL (mg/m^3)	$LOAEL_{HEC}$[c] (mg/m^3)	Critical effect	Reference
Rat Fischer 344 50/sex	1 mg/m^3 of DQ 12 for 6 h/day, 5 days/week, for 24 months	1	0.18	Subpleural and peribronchial fibrosis, focal lipoproteinosis, cholesterol clefts, enlarged lymph nodes, and granulomatous lesions in the walls of large bronchi; doubling of lung collagen content. (Quantitative data were not reported for these effects.)	Muhle et al., 1989
Mouse BALB/c Female	2 mg/m^3 of Min-U-Sil for 8 h/day, 5 days/week, for 150, 300, or 570 days	2	0.36	Suppressed response to aerosol of *Escherichia coli* (i.e., formation of plaque-forming cells in spleen) at 150, 300, and 570 days; reduced ability of alveolar macrophages to phagocytize *Staphylococcus aureus* at 570 days; reduced T-lymphocyte-mediated cytolysis of allogeneic tumour cells at 185 days.	Scheuchen-zuber et al., 1985
Mouse BALB/c Female	4932.4 ± 235.4 $\mu g/m^3$ of Min-U-Sil 5 for 6 h/day, 5 days/week, for 3, 9, 15, 27, 33, or 39 weeks	5	0.90	Suppressed response to aerosol of *Escherichia coli* (i.e., formation of plaque-forming cells in spleen) at 15, 27, 33, and 39 weeks; increased spleen/body ratios at 15, 21, and 27 weeks; induced pulmonary fibrosis (fibrotic nodules of collagen, fibroblasts, lymphocytes, silica-filled macrophages) at 39 weeks.	Burns et al., 1980
Rat Fischer 344 Both sexes	0, 2, 10, or 20 mg/m^3 of Min-U-Sil 5 for 6 h/day, 5 days/week, for 6 months	2	0.36	Increased collagen and elastin content of lungs; caused birefringent crystals in foamy cytoplasm of macrophages that had accumulated in end airway luminal spaces; induced Type II cell hyperplasia in alveolar compartment and intralymphatic micro-granulomas around bronchioles in some animals. Quartz-dependent increases in collagen and elastin were 110%, 111%, and 116% for collagen (as hydroxyproline) and 102%, 109%, and 109% for elastin, respectively, for each exposure group relative to controls (US EPA, 1996).	Drew & Kutzman, 1984b
Rat Fischer 344 Both sexes	0, 2, 10, or 20 mg/m^3 of Min-U-Sil 5 for 6 h/day, 5 days/week, for 6 months, plus 6-month incubation period	2	0.36	Increased weight and collagen, elastin, deoxyribo-nucleic acid, and protein content of lungs (particularly at higher exposures of 10 and 20 mg/m^3), indicating continued tissue proliferation and fibrogenesis during incubation; increased number of silica particles and inflammation at end airways, focal fibrosis and intralymphatic granulomata, and overall severity and frequency of lesions. Alveolar proteinosis observed in the 20 mg/m^3 group. Quartz increases in collagen and elastin were 116%, 128%, and 136% for collagen (as hydroxyproline) and 107%, 119%, and 130% for elastin, respectively, for each exposure group relative to controls (US EPA, 1996).	Drew & Kutzman, 1984a

[a] LOAEL = lowest-observed-adverse-effect level. No-observed-adverse-effect levels (NOAELs) were not reported;
[b] Adapted from Gift & Faust (1997); [c] HEC calculated using methods described in US EPA (1994) and summarized in section 11.1.1.

mechanism (Figure 1; IARC, 1997). The rat model is the best model currently available for studying the effects of quartz, because it demonstrates the carcinogenic response observed in some human studies (Donaldson & Borm, 1998).

8.3.1 Interaction with other compounds

Other tests of carcinogenicity have been conducted using mixtures of quartz with known carcinogens. When aerosol concentrations of quartz (Dörentrup DQ 12) were administered by inhalation to rats for 29 days and followed by a single intravenous injection of Thorotrast (an "-radiation-emitting material) at the end of the inhalation period, there was a pronounced interactive effect of Thorotrast with quartz (DQ 12) that included the occurrence of tumours in the lung (i.e., bronchioloalveolar adenomas, bronchioloalveolar carcinomas, and squamous cell carcinomas), liver, and spleen (Spiethoff et al., 1992; IARC, 1997). In experiments with hamsters, benzo[*a*]pyrene with quartz and ferric oxide with quartz were administered by intratracheal instillation. No pulmonary tumours were observed in hamsters given

Table 2: Summary of data on lung tumours induced in rats by quartz.[a]

Treatment sample	Exposure conditions	Rat strain	Sex	Incidence of lung tumours[b]		Reference
				Treated	Controls	
Quartz (Min-U-Sil 5)	Intratracheal instillation (suspended in 0.2 ml saline) of 7 mg weekly for 10 weeks	Sprague-Dawley	not reported	6/36[c]	0/58	Holland et al., 1983
	Inhalation (nose only), 12 ± 5 mg/m³ for up to 2 years	Fischer 344	F	20/60[d]	0/54	Holland et al., 1986
	Inhalation of 51.6 mg/m³ for various durations; sacrificed at 24 months	Fischer 344	F M	10/53[e] 1/47[f]	0/47 0/42	Dagle et al., 1986
	Intratracheal instillation (volume of suspension not reported) of 20 mg in left lung, sacrificed at 12, 18, or 22 months or found dead	Fischer 344	M	30/67[g]	1/75[h]	Groth et al., 1986
Novaculite (i.e., microcrystalline quartz)	Intratracheal instillation of 20 mg (volume of suspension not reported) in left lung, sacrificed at 12, 18, or 22 months or found dead	Fischer 344	M	21/72[i]	1/75[h]	Groth et al., 1986
Quartz (DQ 12)	Inhalation of 1 mg/m³ for 24 months	Fischer 344	F M	12/50[j] 6/50[l]	3/100[k] (male and female)	Muhle et al., 1989
	Inhalation (nose only) of 6 mg/m³ for 29 days, followed by lifetime observation	Wistar	F	62/82[m]	0/85	Spiethoff et al., 1992
	Inhalation (nose only) of 30 mg/m³ for 29 days, followed by lifetime observation	Wistar	F	69/82[n]	0/85	Spiethoff et al., 1992
Quartz[o] (Sikron F300 from Quartz Werke, Frechen, Germany)	Inhalation of 58.5 ± 0.7 mg/m³, 6 h/day, 5 days/week, for 13 weeks	Wistar	F M	1/70[p] 0/70	0/70 0/70	Reuzel et al., 1991

[a] Adapted from Saffiotti et al. (1996); IARC (1997).
[b] Number of lung tumours per number of rats observed.
[c] One adenoma and five carcinomas.
[d] Six adenomas, 11 adenocarcinomas, and three epidermoid carcinomas.
[e] All epidermoid carcinomas.
[f] One epidermoid carcinoma.
[g] All adenocarcinomas.
[h] One adenocarcinoma.
[i] Twenty adenocarcinomas and one epidermoid carcinoma.
[j] Two keratinizing cystic squamous cell tumours, two adenomas, and eight adenocarcinomas.
[k] Two adenomas and one adenocarcinoma.
[l] Two keratinizing cystic squamous cell tumours, two adenocarcinomas, one adenosquamous carcinoma, and one epidermoid carcinoma.
[m] Eight adenomas, 17 bronchioloalveolar carcinomas, and 37 squamous cell carcinomas.
[n] Three adenomas, 26 bronchioloalveolar carcinomas, and 30 squamous carcinomas.
[o] IARC Working Group noted that only a small proportion of particles were respirable in rats.
[p] One squamous cell carcinoma, 1 year after the end of the exposure period.

Table 3: Lung tumours induced in Fischer 344 rats by a single intratracheal instillation of quartz.[a]

Treatment sample	Treatment dose[b]	Sex	Observation time	Incidence of lung tumours[c]	Total number of lung tumours[d]	Histological types
Untreated	None	M	Died after 17 months	0/32	0	
	None	F	Died after 17 months	1/20 (5%)	1	1 adenoma
Quartz (Min-U-Sil 5)	12 mg	M	Sacrificed 11 months	3/18 (17%)	37	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, and 3 epidermoid carcinomas
			Sacrificed 17 months	6/19 (32%)		
			Died after 17 months	12/14 (86%)		
	12 mg	F	Sacrificed 11 months	8/19 (42%)	59	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, and 3 epidermoid carcinomas
			Sacrificed 17 months	10/17 (59%)		
			Died after 17 months	8/9 (89%)		
	20 mg	F	Died after 17 months	6/8 (75%)	13	1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, and 1 epidermoid carcinoma
Quartz (hydrogen fluoride-etched Min-U-Sil 5)	12 mg	M	Sacrificed 11 months	2/18 (11%)	20	5 adenomas, 14 adenocarcinomas, and 1 mixed carcinoma
			Sacrificed 17 months	7/19 (37%)		
			Died after 17 months	7/9 (78%)		
	12 mg	F	Sacrificed 11 months	7/18 (39%)	45	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, and 5 epidermoid carcinomas
			Sacrificed 17 months	13/16 (81%)		
			Died after 17 months	8/8 (100%)		

[a] From Saffiotti et al. (1993, 1996).
[b] As mg quartz suspended in 0.3 ml saline.
[c] Number of rats with lung tumours per number of rats observed.
[d] At all observation times.

Table 4: Incidence of lung tumours in female Wistar rats after intratracheal instillation of quartz.[a]

Material	Surface area (m^2/g)	Number of instillations (× mg)[c]	Number of rats examined	Number and percentage of rats with primary epithelial lung tumours[b]					Other tumours[e]
				Adenoma	Adenocarcinoma	Benign CKSCT[d]	Squamous cell carcinoma	Total (%)	
Quartz (DQ 12)	9.4	15 × 3	37	0	1^z	11	$1 + 1^y$	38	1
Quartz (DQ 12) + PVNO[f]	9.4	15 × 3	38	0	$1 + 3^z$	$8 + 1^x$	$4 + 1^{\cdot} + 3^y + 1^z$	58	2
Quartz (DQ 12)	9.4	1 × 45	40	0	1	7	1	23	2
Quartz (Min-U-Sil)		15 × 3	39	1	$4 + 4^z$	6	$1 + 2^y + 2^z + 1^{y,z}$	54	3
Quartz (Min-U-Sil) + PVNO		15 × 3	35	1	$2 + 1^x$	8	$5 + 1^{\cdot} + 1^y + 1^z$	57	3
Quartz Sykron (F600)	3.7	15 × 3	40	0	3	5	$3 + 1^z$	30	1
0.9% sodium chloride	–	15	39	0	0	0	0	0	5

[a] From Pott et al. (1994); IARC (1997).
[b] If an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows: [x] adenoma; [y] adenocarcinoma; [z] benign CKSCT.
[c] Dusts were suspended in 0.9% sodium chloride solution with ultrasonication for 1–5 min.
[d] CKSCT, cystic keratinizing squamous cell tumour.
[e] Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites
[f] PVNO, polyvinylpyridine-*N*-oxide; PVNO was administered subcutaneously in seven injections of 2 ml each of 2% PVNO in saline. No PVNO control group was included.

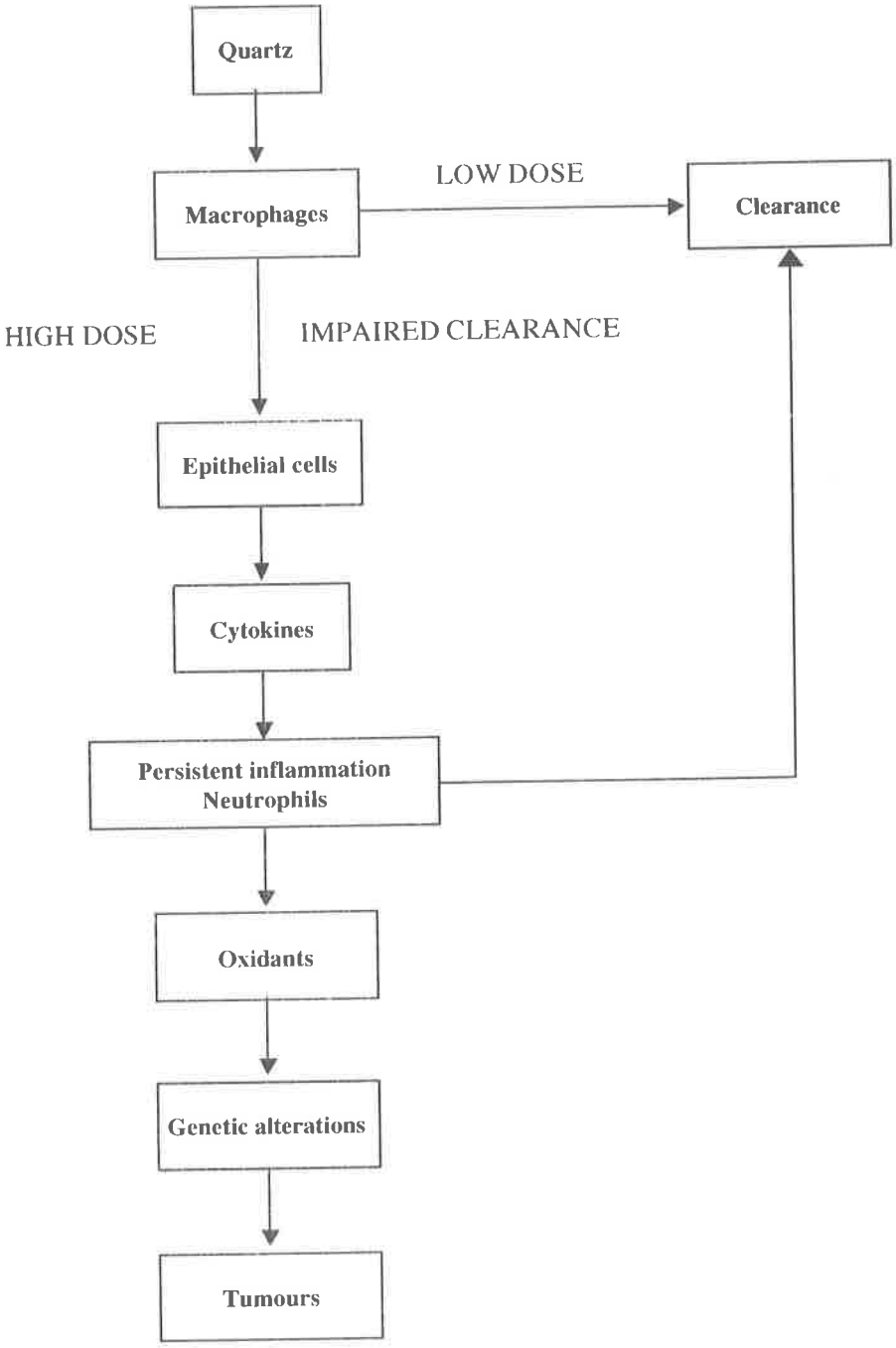


Figure 1: A hypothetical inflammation-based mechanism for carcinogenicity of quartz in rats. This hypothesis is supported by *in vitro* studies as well as *in vivo* studies in rats. Other pathways, such as a role for quartz surface-generated oxidants or a direct genotoxic effect, are not ruled out; however, at present, there is no convincing evidence for these alternative pathways (IARC, 1997, 1999).

mixtures of quartz and ferric oxide (1 : 1) (Niemeier et al., 1986). However, the number of respiratory tract tumours in hamsters given Min-U-Sil quartz and benzo[*a*]pyrene or Sil-Co-Sil and benzo[*a*]pyrene was significantly higher ($P < 0.01$) than the number found in hamsters that received saline and benzo[*a*]pyrene (Niemeier et al., 1986).

8.4 Genotoxicity and related end-points

Although silica (form not specified) has not tested positive in standard bacterial mutagenesis assays (IARC, 1987, 1997; Rabovsky, 1997), chromosomal changes, including DNA damage, have been observed in experimental systems, both *in vitro* and *in vivo*. (Study results are presented in Table 5.) Although the results of some studies (Daniel et al., 1993, 1995; Saffiotti et al., 1993; Shi et al., 1994) demonstrated that quartz caused

Table 5: Genetic and related effects of silica.[a]

Test system	Result[b]	Dose (LED/HID)[c]	Reference
DNA strand breaks, 8 *Hin*dIII-digested DNA	+	30 000[d]	Daniel et al., 1993
DNA strand breaks, herring sperm genomic DNA	+	10 000[d]	Daniel et al., 1993
DNA strand breaks, 8 *Hin*dIII-digested DNA	+	9 500[e]	Daniel et al., 1995
DNA strand breaks, PM2 supercoiled DNA	+	9 500[e]	Daniel et al., 1995
GIA, Gene mutation, *hprt* locus, rat RLE-6TN alveolar epithelial cells *in vitro*	!	NG	Driscoll et al., 1997
SIC, Sister chromatid exchange, Chinese hamster V79-4 cells *in vitro*	!	15[e]	Price-Jones et al., 1980
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	!	100[f]	Pairon et al., 1990
SIH, Sister chromatid exchange, human lymphocytes and monocytes *in vitro*	!	100[g]	Pairon et al., 1990
MIA, Micronucleus test, Syrian hamster embryo cells *in vitro*	!	18.75[f]	Oshimura et al., 1984
MIA, Micronucleus test, Syrian hamster embryo cells *in vitro*	+	70[e]	Hesterberg et al., 1986
MIA, Micronucleus test, Chinese hamster lung fibroblasts (V79) *in vitro*	+	200[g]	Nagalakshmi et al., 1995
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts (V79) *in vitro*	!	1 600[g]	Nagalakshmi et al., 1995
CIS, Chromosomal aberrations, Syrian hamster embryo cells *in vitro*	!	18.75[f]	Oshimura et al., 1984
AIA, Aneuploidy, Chinese hamster lung cells (V79-4) *in vitro*	!	15[e]	Price-Jones et al., 1980
AIA, Aneuploidy, Syrian hamster embryo cells *in vitro*	!	18.75[f]	Oshimura et al., 1984
AIA, Tetraploidy, Syrian hamster embryo cells *in vitro*	!	70[e]	Hesterberg et al., 1986
TBM, Cell transformation, BALB/3T3/31-1-1 mouse cells *in vitro*	+	30[e,h,i]	Saffiotti & Ahmed, 1995
TBM, Cell transformation, BALB/3T3/31-1-1 mouse cells *in vitro*	+	60[k]	Saffiotti & Ahmed, 1995
TCS, Cell transformation, Syrian hamster embryo cells *in vitro*	+	18[e]	Hesterberg & Barrett, 1984
TCS, Cell transformation, Syrian hamster embryo cells *in vitro*	+	70[l]	Hesterberg & Barrett, 1984
TCL, Cell transformation, fetal rat lung epithelial cells *in vitro*	(+)	NG[d]	Williams et al., 1996
MIH, Micronucleus test, human embryonic lung (Hel 299) cells *in vitro*	+	800[g]	Nagalakshmi et al., 1995
CIH, Chromosomal aberrations, human embryonic lung (Hel 299) cells *in vitro*	!	1 600[g]	Nagalakshmi et al., 1995
DVA, 8-hydroxy-2'-deoxyguanosine DNA extract from lung tissue, male Wistar rats	+	50 x 1 it[d]	Yamano et al., 1995
DVA, 8-hydroxy-2'-deoxyguanosine DNA extract from peripheral blood leukocytes, male Wistar rats	!	50 x 1 it[d]	Yamano et al., 1995
GVA, Gene mutation, *hprt* locus, rat alveolar epithelial cells *in vivo*	+	100 x 1 it	Driscoll et al., 1995
GVA, Gene mutation, *hprt* locus, rat alveolar epithelial cells *in vivo*	+	5 x 2 it	Driscoll et al., 1997
MVM, Micronucleus test, albino mice *in vivo*	!	500 ip	Vanchugova et al., 1985
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	+	NG	Sobti & Bhardwaj, 1991
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+	NG	Sobti & Bhardwaj, 1991
BID, Calf thymus DNA binding *in vitro*	+	200[l]	Mao et al., 1994
ICR, Metabolic cooperation using 8-azaguanine-resistant cells, Chinese hamster lung cells (V79-4) *in vitro*	!	50	Chamberlain, 1983

[a] Source: IARC (1997). See Appendix 1 of IARC (1997), Test system code words, for definitions of the abbreviations used in column 1.
[b] Results without exogenous metabolic system: +, positive; (+), weakly positive; !, negative.
[c] LED, lowest effective dose; HID, highest ineffective dose; *in vitro* tests, µg/ml; *in vivo* tests, mg/kg body weight per day; NG, not given; it, intratracheal; ip, intraperitoneal.
[d] Min-U-Sil 5.
[e] Min-U-Sil unspecified.
[f] "-Quartz.
[g] Min-U-Sil 5 and Min-U-Sil 10.
[h] Min-U-Sil 5, hydrofluoric acid-etched.
[i] A Chinese standard quartz sample.
[j] DQ 12, a standard German quartz sample.
[k] F600 quartz.
[l] Min-U-Sil 5 or Chinese standard quartz.

damage (i.e., strand breakage) to isolated DNA in acellular systems, the IARC Working Group (IARC, 1997) stated that the relevance of these assays to assess quartz-related genetic effects *in vivo* was "questionable." Uncertainties existed because the non-physiological experimental conditions did not apply to intracellular silica exposure and because very high doses of silica were used in the DNA breakage assays (IARC, 1997). However, a recent study not included in the IARC review found that by using the alkaline single cell gel/comet assay, crystalline silica (Min-U-Sil 5) induced DNA damage (i.e., DNA migration) in cultured Chinese hamster lung fibroblasts (V79 cells) and human embryonic lung fibroblasts (Hel 299 cells) at concentrations ranging from 17.2 to 103.4 $\mu g/cm^2$ (Zhong et al., 1997). Since the time of the IARC review, Liu et al. (1996, 1998) applied experimental conditions (i.e., Chinese hamster lung fibroblasts challenged with dusts pretreated with a phospholipid surfactant) to simulate the condition of particles immediately after deposition on the pulmonary alveolar surface. Results of the experiments showed that untreated Min-U-Sil 5 and Min-U-Sil 10 induced micronucleus formation in a dose-dependent manner, but surfactant pretreatment suppressed that activity (Liu et al., 1996). A subsequent experiment found that surfactant pretreatment suppressed quartz-induced DNA damage in lavaged rat pulmonary macrophages, but DNA-damaging activity was restored with time as the phospholipid surfactant was removed by intercellular digestion (Liu et al., 1998).

In vitro cellular transformation systems model the *in vivo* process of carcinogenesis (Gu & Ong, 1996; Gao et al., 1997). The ability of quartz to induce dose-dependent morphological transformation of cells *in vitro* has been demonstrated in experiments with Syrian hamster embryo cells (Hesterberg & Barrett, 1984) and mouse embryo BALB/c-3T3 cells (Saffiotti & Ahmed, 1995). Gu & Ong (1996) also reported a significant increase in the frequency of transformed foci of mouse embryo BALB/c-3T3 cells after treatment with Min-U-Sil 5 quartz. These studies indicate that quartz can morphologically transform mammalian cells. However, further studies are needed to determine whether the transforming activity of quartz is related to its carcinogenic potential.

Some studies have demonstrated the ability of quartz to induce micronuclei in mammalian cells in culture (i.e., Oshimura et al., 1984; Hesterberg et al., 1986; Nagalakshmi et al., 1995) and were reviewed by IARC (Table 5). However, other *in vitro* studies did not observe chromosomal aberration (Oshimura et al., 1984; Nagalakshmi et al., 1995), *hprt* (hypoxanthine-guanine phosphoribosyl transferase) gene mutation (Driscoll et al., 1997), or aneuploid or tetraploid cells (Price-Jones et al., 1980; Oshimura et al., 1984; Hesterberg et al., 1986).

Pairon et al. (1990) tested quartz (i.e., Min-U-Sil 5) particles for their ability to induce a significant number of sister chromatid exchanges in cultures of human lymphocytes plus monocytes or of human purified lymphocytes. The results were not "clear cut" for any of the three doses tested (i.e., 0.5, 5.0, and 50 $\mu g/cm^2$) (Pairon et al., 1990) (Table 5).

An *in vivo* treatment of rats with quartz induced mutation in rat alveolar epithelial cells (Table 5) (Driscoll et al., 1995, 1997). Nehls et al. (1997) reported results of tests for DNA modifications by quartz that were not reviewed by IARC (1997). Quartz (2.5 mg of DQ 12 suspended in 0.5 ml of physiological saline) or corundum (2.5 mg), a non-carcinogenic particle, was intratracheally instilled into the lungs of Wistar rats (10 rats per exposure and per time period). Control animals were exposed to saline solution or not treated. Rats were sacrificed 7, 21, and 90 days after treatment, then lung tissue sections were analysed with immunocytological assay to determine the level of 8-hydroxydeoxyguanosine in DNA extracts. Reactive oxygen species can induce 8-hydroxydeoxyguanosine and other mutagenic DNA oxidation products, which may be converted to mutations in proliferating cells (Nehls et al., 1997). Exposure to quartz induced levels of 8-hydroxydeoxyguanosine in the DNA of alveolar lung cells that were significantly higher (*P*-value not reported) at all time points than levels found in cells of untreated rats or rats treated with corundum or saline. The number of total cells in bronchoalveolar lavage fluid was 3–4 times higher in the quartz-treated groups at all time points than in corundum-exposed rats and control rats exposed to saline.

Other *in vivo* studies not reviewed by IARC (1997) found that quartz induced micronuclei in pulmonary alveolar macrophages of male Wistar rats in a time-dependent (Leigh et al., 1998b) and dose-dependent manner (Wang et al., 1997b).

In summary, results of genotoxicity studies of quartz conflict, and a direct genotoxic effect for quartz has not been confirmed or ruled out.

8.5 Reproductive and developmental toxicity

There are no data available on the reproductive or developmental effects of quartz in laboratory animals (IARC, 1997).

8.6 Immunological and neurological effects

Data on the neurological effects of quartz have not been identified. *In vitro* studies have shown that quartz can stimulate release of cytokines and growth factors from macrophages and epithelial cells, and there is evidence that these events may occur *in vivo* and contribute to disease (IARC, 1997). The immunological response to quartz in experimental animals is a complex subject with uncertain implications for humans, and detailed reviews are available elsewhere (i.e., Davis, 1991, 1996; Haslam, 1994; Heppleston, 1994; Weill et al., 1994; Driscoll, 1996; Gu & Ong, 1996; Hook & Viviano, 1996; Iyer & Holian, 1996; Kane, 1996; Sweeney & Brain, 1996; Weissman et al., 1996; Mossman & Churg, 1998).

9. EFFECTS ON HUMANS

9.1 Case reports

There are many published case reports of adverse health effects from occupational exposure to quartz. These health effects include silicosis (acute and chronic) and lung cancer. Case reports of silicosis and lung cancer are not mentioned further, because these diseases have been researched in depth in epidemiological studies (section 9.2).

There are numerous published case reports of several autoimmune disorders in workers or patients who had been occupationally exposed to crystalline silica, including quartz dust (NIOSH, forthcoming). The most frequently noted autoimmune diseases in those reports were scleroderma, systemic lupus erythematosus (i.e., lupus), rheumatoid arthritis, autoimmune haemolytic anaemia (Muramatsu et al., 1989), and dermatomyositis or dermatopolymyositis (Robbins, 1974; Koeger et al., 1991). Case reports have also described health effects that may be related to the immunological abnormalities observed in patients with silicosis, such as chronic renal disease (Saita & Zavaglia, 1951; Giles et al., 1978; Hauglustaine et al., 1980; Bolton et al., 1981; Banks et al., 1983; Slavin et al., 1985; Bonnin et al., 1987; Osorio et al., 1987; Arnalich et al., 1989; Sherson & Jorgensen, 1989; Dracon et al., 1990; Pouthier et al., 1991; Rispal et al., 1991; Neyer et al., 1994; Wilke et al., 1996), ataxic sensory neuropathy (Tokumaru et al., 1990), chronic thyroiditis (Masuda, 1981), hyperthyroidism (i.e., Graves' disease) (Koeger et al., 1996), monoclonal gammopathy (Fukata et al., 1983, 1987; Aoki et al., 1988), and polyarteritis nodosa (Arnalich et al., 1989).

9.2 Epidemiological studies

9.2.1 *Silicosis*

Most, if not all, of the several hundred epidemiological studies of exposure to quartz dust are studies of occupational cohorts. The majority of studies investigated the occurrence of silicosis morbidity or mortality. These studies have conclusively linked occupational quartz dust exposure with silicosis. Silicosis (i.e., nodular pulmonary fibrosis) is a fibrotic lung disease, sometimes asymptomatic, that is caused by the inhalation and deposition of respirable crystalline silica particles (i.e., particles <10 μm in diameter) (Ziskind et al., 1976; IARC, 1987).

A worker may develop one of three types of silicosis, depending on the airborne concentration of respirable crystalline silica: (1) chronic silicosis, which usually occurs after 10 or more years of exposure at relatively low concentrations; (2) accelerated silicosis, which develops 5–10 years after the first exposure; or (3) acute silicosis, which develops after exposure to high concentrations of respirable crystalline silica and results in symptoms within a few weeks to 4 or 5 years after the initial exposure (Ziskind et al., 1976; Peters, 1986; NIOSH, 1992a,b, 1996). Acute silicosis is a risk for workers with a history of high exposures from performing occupational processes that produce small particles of airborne dust with a high silica content, such as during sandblasting, rock drilling, or quartz milling, or any other process with high exposures to small particles of airborne dust with a high quartz content (Davis, 1996).

A recent study of 67 paraffin-embedded lung tissue samples from silicotic patients found a significant linear relationship ($P < 0.001$) between lung quartz concentration and silicosis severity in gold miners; although several types of mineral particles were found in the lungs, quartz was the only significant indicator of silicosis severity. The silicosis cases included 39 patients without lung cancer and 28 patients with lung cancer. All of the cases were gold miners in Canada (Dufresne et al., 1998a,b).

The epidemiological studies of silicosis usually define the profusion of small opacities present in the disease according to a standard system used by trained readers and developed by the International Labour Organization for classification of chest radiographs of pneumoconioses (ILO, 1980). Each reader assesses the profusion according to a 12-point scale of severity. Categories 0/! and 0/0 are the first and second points on the scale and represent a normal chest radiograph. The third point, category 0/1, represents the borderline

between normality and abnormality, and category 1/0, the fourth point, represents definite, but slight, abnormality (Love et al., 1994). The shape (rounded or irregular) and size of the opacities can also be described by the readers.

The critical studies of chronic silicosis, a progressive disease, are those occupational epidemiological studies where (1) quantitative quartz exposure data were available and used for risk analysis, (2) exposure–response relationships were investigated, or (3) the exposure–response relationships were documented with sufficient detail for a health effects benchmark, including (4) application of data to mathematical models that predicted silicosis prevalence at increasing concentrations of cumulative quartz exposure. (The *predicted* prevalences reported in the studies are discussed in section 11.1.3.) Studies that selected workers from a broad spectrum of occupations and included many workers that were exposed to different combinations of various minerals, such as studies of "dusty trades" workers (i.e., Rice et al., 1986), were excluded from consideration for risk assessment of quartz and silicosis. Epidemiological studies that provided evidence of an exposure–response relationship for silica and silicosis based on other kinds of exposure data (e.g., there is a positive relationship between development of chronic silicosis and duration of exposure) have been reviewed elsewhere (WHO, 1986; Goldsmith, 1994; Hughes, 1995; Rice & Stayner, 1995; Seaton, 1995; Steenland & Brown, 1995a; Davis, 1996; US EPA, 1996).

The two critical cross-sectional studies (i.e., Kreiss & Zhen, 1996; Rosenman et al., 1996 — see Table 6) found that the prevalence of radiographic silicosis (ILO category $ 1/0 or $ 1/1) was dose-related. That is, the prevalence of radiographic silicosis increased with average silica dust exposure, cumulative quartz exposure, duration of employment, or all of these measures. The actual prevalences varied greatly among the studies, and conclusions concerning quartz dust concentrations that may or may not induce silicosis cannot be drawn from simple "eyeball" analysis of the prevalences in the following two worker populations:

- Kreiss & Zhen (1996) conducted a community-based random sample survey of 134 male residents at least 40 years old, living in a hardrock (i.e., molybdenum, lead, zinc, and gold) mining town in Colorado, USA. Of the 134 residents, 100 were silica-exposed hardrock miners (including 32 silicosis cases) and 34 were community "controls" without occupational dust exposure. Nearly all (97%) of the dust-exposed subjects were 20 years since first exposure. The estimated crystalline silica content (polymorph not reported) of the total dust was 12.3%. Exposure was assessed with information from occupational histories, gravimetric dust exposure data from 1974–1982, and a cumulative silica exposure index. Pre-1974 exposure estimates were based on job-specific gravimetric data collected after 1974. Exposures were also estimated for mines where no exposure data were available (17.1% of person-years of follow-up). Thirty-two per cent of the 100 dust-exposed subjects had silicosis (defined as radiological profusion of small opacities of ILO category $ 1/0). Prevalence of silicosis was related to average silica dust exposure. Among the 94 dust-exposed subjects with data on cumulative and average dust exposures, those subjects with average silica exposure <0.05 mg/m^3 had 10% prevalence of silicosis; subjects with >0.05–0.10 mg/m^3 had a prevalence of 22.5%; subjects with greater than 0.10 mg/m^3 average silica exposure had a silicosis prevalence of 48.6% ($P = 0.01$). (See Table 6 for *predicted* prevalences when silicosis was defined as radiological profusion of small opacities of ILO category $ 1/1.) It is not known whether the small sample of 134 residents was representative of all miners or if the exposure estimates for mines where no exposure data were available (17.1% of person-years of follow-up) were representative.

- Rosenman et al. (1996) conducted a cross-sectional study in 1991 of 549 current, 497 retired, and 26 current salaried workers that were former production workers in a US grey iron foundry that produced automotive engine blocks (total workers = 1072). Twenty-eight cases (2.9%) of silicosis, defined as rounded opacities $ ILO category 1/0, were identified by at least two of three "B" readers of a total of 952 chest radiographs. More than half (18/28) of the cases were found in retired workers. Silicosis prevalence was positively related to mean silica (i.e., quartz) exposure ($P < 0.0001$). Of the workers with mean quartz exposure less than 0.05 mg/m^3, 0.8% had silicosis, while 6.3% of foundry workers with mean quartz exposure greater than 0.45 mg/m^3 had silicosis. Silicosis prevalence also increased with years of employment at the foundry, cumulative silica exposure, work area within the foundry, and cigarette smoking (i.e., smoker vs. non-smoker). Exposure estimates were derived from conversions of "early silica exposure data" collected by impingers. Quartz content of total dust was not reported. Weighted total dust exposure from impinger data was converted to an estimate of silica exposure in mass units (mg/m^3) by multiplying it by the average percentage of quartz in bulk samples.

Table 6: Predicted prevalence of silicosis (ILO category ≥ 1/1) following exposure to respirable quartz dust based on modelling of cumulative exposure at mean concentrations of 0.05 or 0.10 mg/m³ over a 45-year working lifetime.

Cross-sectional study and cohort	Mean concentration of respirable quartz dust (mg/m³)	Predicted prevalence of silicosis, ILO category ≥ 1/1 (cases per 100 workers)	Cohort's mean time since first quartz exposure (years)	Cohort's maximum time since first quartz exposure (years)
Kreiss & Zhen, 1996 100 US hardrock miners and 34 community controls	0.05 0.10	~30[a] ~90[a]	silicotic miners: 41.6 non-silicotic miners: 33.5	silicotic miners: 66 non-silicotic miners: 68
Rosenman et al., 1996 1072 US grey iron foundry workers	0.05 0.10	2[b,c] 3[b,c]	28	>30

[a] Based on cumulative silica exposure model with 10 years of post-employment follow-up.
[b] ILO category ≥ 1/0.
[c] Based on a 40-year working lifetime and controlling for pack-years of cigarette smoking, race, and silica exposure other than in the foundry under study.

Table 7: Predicted number of silicosis cases (ILO category ≥ 1/1) following exposure to respirable quartz dust based on modelling of cumulative exposure at mean concentrations of 0.05 or 0.10 mg/m³ over a 45-year working lifetime.

Cohort study and population	Mean concentration of respirable quartz dust (mg/m³)	Silicosis cases, ILO category ≥ 1/1, per 100 workers	Mean time since first quartz exposure (years)	Maximum time since first quartz exposure (years)
Hnizdo & Sluis-Cremer, 1993 2235 South African gold miners	0.05 0.10	13[a] ~70	silicotic miners: 36	silicotic miners: 50
Muir et al., 1989a,b; Muir, 1991 2109 Canadian gold and uranium miners	0.05	0.09–0.62[a,b]	18	silicotic miners: 38
Steenland & Brown, 1995a 3330 US gold miners	0.05 0.09	10[c] 47[c]	37	73[d]

[a] Estimate was reported in Rice & Stayner (1995).
[b] No post-employment follow-up and no retired miners included. The range includes five estimates (one for each reader).
[c] The predicted number of silicosis cases does not account for effects of age or calendar time (K. Steenland, personal communication, 1997).
[d] K. Steenland, personal communication, 1998.

Results of cohort studies of gold miners in South Africa, Canada, and the USA (see Table 7) also demonstrated an exposure–response relationship for radiographic silicosis (US EPA, 1996):

- A cohort study was conducted of 2235 white South African underground gold miners, 45–54 years old at the time of medical examination in 1968–1971, who started working after 1938, worked ≥ 10 years, and were followed until 1991 (Hnizdo & Sluis-Cremer, 1993). More than 300 (n = 313) of the 2235 miners were followed to the time when radiological signs developed, 658 miners were followed up to death, and 1264 miners were followed to the year of the most recent radiograph. Radiographs were read blindly by two independent readers. Silicosis was defined as the presence of rounded opacities of ILO category ≥ 1/1. Radiographs were read blindly by two readers initially, then one reader was chosen because his readings more closely matched the autopsy data. Mean respirable dust concentrations, after heat and acid treatment, in milligrams per cubic metre per shift were calculated for nine gold mining occupations. The concentrations were based on a study of shift-long dust exposure that measured the surface area of the respirable mine dust and the number of respirable particles (i.e., incombustible and acid-insoluble dust particles) per cubic metre in a random sample of 20 South African gold mines (Beadle, 1965, 1971). After heat and acid treatment, the respirable dust in South African gold mines was found to contain about 30% quartz (Beadle & Bradley, 1970). Cumulative dust exposure for the miners was calculated in milligrams per cubic metre-year by using data for mean mass respirable dust concentrations for the nine occupational categories, the average number of hours underground, and the number of dusty 8-h shifts.

  Of the 2235 miners studied by Hnizdo & Sluis-Cremer (1993), 313 developed radiologically diagnosed silicosis (rounded opacities with profusion of ILO category ≥ 1/1) during the follow-up period (i.e., 1968–1971 to 1991). The onset of silicosis occurred after an average (i.e., mean) of 27 years of net service, at a mean age of 56 years. For more than half of the miners (n = 178; 57%), the onset occurred an average of 7.4 years (standard deviation 5.5; range 0.1–25 years) after their employment at the mines, at 59 years of age (range 44–74 years). For the other miners (n = 135; 43%), the onset of silicosis occurred while they were still mining, at 51 years of age (range 39–61 years). These results show that the majority of the cases occurred in miners who were no longer employed at the mine and who were at least 50 years old (Hnizdo & Sluis-Cremer, 1993).

- Muir and colleagues conducted a study of 2109 current Ontario miners from 21 gold and uranium mines who started working and worked more than 5 years between 1940 and 1959 and were followed to 1982 or to the end of their dust exposure, whichever came first (Muir et al., 1989a,b; Muir, 1991). Any uranium miner with more than 2 weeks of exposure was also included (Muir et al., 1989a). The quartz content of respirable gold mine dust was 6.0%, and that of uranium mine dust was 8.4%. Retired and former miners were not included in the study. Sources of data for this study were full-sized annual chest radiographs taken for all miners after 1927 and periodic (pre-1959) and semi-annual mine dust measurements obtained with a konimeter (which is an instantaneous dust sampler that measures the number of particles per unit volume of air; Verma et al., 1989). Konimeter dust measurements taken from 1940 to 1952 were expressed in particles per cubic centimetre of air (ppcc). Verma et al. (1989) initiated an extensive, side-by-side comparison of the konimetric and gravimetric (i.e., milligrams of silica per cubic metre) sampling to derive a konimetric/gravimetric silica conversion curve. A total of 2360 filter (i.e., nylon cyclone-filter assembly in a constant-flow pump) samples and 90 000 konimeter samples were taken in a 2-year period in two gold and uranium mines, in existing conditions as well as in an experimental simulation of the high-dust conditions of the past caused by dry drilling (Verma et al., 1989). The results of the conversion relationship were non-linear and may have reflected the limitations of the konimeter in measuring high dust (i.e., high count) concentrations and the limitations of the gravimetric sampler in measuring low dust concentrations. There were different relationships for the gold and uranium mines, possibly because of the different fractional silica concentrations in the host rock. The conversion of the historical konimeter counts to gravimetric respirable silica equivalents was used to derive a cumulative respirable silica dose for each miner based on the miner's respirable silica dose for each year, mine, and task in his work history (Verma et al., 1989).

  Thirty-two of the 2109 hardrock miners studied by Muir and colleagues were considered by at least one of five readers to have silicosis (small, rounded opacities with profusion of ILO category ≥ 1/1). However, the results differed

among the five readers and "complicated the analysis" (Muir et al., 1989b). One of the five readers identified only seven cases of silicosis (Muir et al., 1989b). The results were presented by individual reader and by consensus. A consensus of all of the five readers with respect to identification of silicosis was reached on only six cases (Muir et al., 1989b). Average respirable quartz dust exposure for the cases was not reported.

- A cohort study of 3330 white male underground gold miners from South Dakota employed for at least 1 year between 1940 and 1965 and followed through 1990 found 170 cases of silicosis (128 cases were identified on death certificates, 29 cases were found during X-ray surveys of workers conducted in 1960 and 1976, and 13 cases were identified on both X-ray and death certificate). Cases were defined as (1) an underlying or contributing cause of death of silicosis, silicotuberculosis, respiratory tuberculosis, or pneumoconiosis, and/or (2) ILO category $\geq$ 1/1 silicosis identified in the 1976 radiographic survey or "small opacities" or "large opacities" identified in the 1960 radiographic survey (Steenland & Brown, 1995a). The miners were exposed to a median quartz level of 0.05 mg/m^3 (0.15 mg/m^3 for workers hired prior to 1930). The average length of follow-up was 37 years, and the average length of employment underground was 9 years. Quartz exposure was estimated by converting dust particle counts to gravimetric measurements (i.e., mg/m^3), based on an estimate of 13% quartz content of total dust. A job-exposure matrix was created to estimate dust exposures for each job over time, then average dust exposures for the job categories were calculated using existing measurements for each year from 1937 to 1975. The estimated daily dust exposures (constant over each year) were weighted to account for daily time spent underground. Summation of the estimated daily dust levels over time provided an estimate of cumulative quartz exposure (Steenland & Brown, 1995a). The risk of silicosis was less than 1% for miners with a cumulative exposure less than 0.5 mg/m^3-years. The risk increased to 68–84% for the highest cumulative exposure category (i.e., 4 mg/m^3-years) (Steenland & Brown, 1995a). Silicosis risk estimates could have been affected by (1) combining silicosis deaths with silicosis cases detected by cross-sectional radiographic surveys, (2) differences in quartz content of dust in early years, and (3) lack of dust measurements before 1937.

  A cohort study of a subcohort of the South Dakota gold miners described above analysed cases of silicosis that were reported as the underlying cause of death on the death certificates. Forty cases of silicosis, as well as 49 cases of tuberculosis, were ascertained among the 1321 miners employed for at least 21 years and followed through 1973. There was a linear trend in risk of about 2.4% for each 0.1 mg/m^3 of silica exposure. However, this study does not meet the criteria for a critical study because risk by cumulative quartz exposure was not calculated (McDonald & Oakes, 1984).

In the five critical studies described above, the number of cases identified depended upon the definition of silicosis (radiographic category and whether irregular opacities were included), the quality of the evaluation of the chest radiographs (e.g., number and training of readers), the duration of dust exposure, and the duration of follow-up after the end of exposure. Interstudy variation exists for each of these factors. In addition, exposure assessments in these studies were accompanied by uncertainties, such as the use of conversion equations (i.e., converting particle count data to mass concentrations; application of equations from one industry to a different industry) and estimation of quartz content of the dust. It is not uncommon for epidemiological studies to lack characterization of the source and properties of the mineral dusts collected in the workplace (Mossman & Churg, 1998). Nevertheless, the critical studies found an exposure–response relationship for respirable quartz dust that, when modelled, predicts the occurrence of silicosis cases in various industries at exposures close to regulatory levels.

9.2.2 Pulmonary tuberculosis and other infections

The association between tuberculosis and silicosis has been firmly established by the results of epidemiological studies conducted during this century (Balmes, 1990). In recent studies of silicotics, the association was well supported by the results of a survey of tuberculosis deaths among silicotics in the USA for the period 1979–1991 (Althouse et al., 1995), a mortality study of 590 California silicosis claimants (Goldsmith et al., 1995a), and a retrospective study of silicotic miners from the Freegold mines in South Africa (Kleinschmidt & Churchyard, 1997).

In studies of workers without silicosis, there is some limited evidence that long exposures or high cumulative exposures to quartz dust may increase the risk of developing tuberculosis. Two epidemiological studies reported 3-fold higher incidences of pulmonary tuberculosis cases in 5424 non-silicotic silica-exposed Danish foundry workers employed 25 or more years (Sherson & Lander, 1990) and among 335 non-silicotic

black South African gold miners with a median underground employment of 26 years (Cowie, 1994). Westerholm et al. (1986) found 13 cases of tuberculosis among 428 silicotic Swedish iron and steel workers and one case of tuberculosis in a comparison group of 476 Swedish iron and steel workers with normal chest radiographs (level of statistical significance not reported). Both groups had been exposed to silica for at least 5 years.

A study of tuberculosis incidence in 2255 white South African gold miners included 1296 miners who had an autopsy. The smoking-adjusted relative risk for pulmonary tuberculosis in miners without silicotic nodules on autopsy examination (n = 577) increased slightly with quartiles of cumulative dust exposure (relative risk [RR] = 1.38; 95% confidence interval [CI] = 0.33–5.62) for the highest quartile of cumulative exposure). For miners without radiologically diagnosed silicosis (n = 1934), the smoking-adjusted relative risk increased to 4.01 (95% CI = 2.04–7.88) in the highest quartile of cumulative dust exposure (Hnizdo & Murray, 1998, 1999). Radiological silicosis was defined as ILO category $\geq$ 1/1; detailed ILO grading was not performed (Hnizdo & Murray, 1998, 1999). Tuberculosis was diagnosed on average 7.6 years after the end of dust exposure and 6.8 years after the onset of radiological silicosis — a result that supports the need for medical surveillance of workers after the end of exposure to silica dust (Hnizdo & Murray, 1998). (Miners who developed tuberculosis before completing 10 years of underground employment were excluded because they were not allowed to continue working underground after diagnosis) (Hnizdo & Murray, 1998). It is not clear whether "dust" exposure refers to quartz exposure or exposure to gold mine dust.

Chen et al. (1997) conducted a case–control study (8740 cases; 83 338 controls) with US National Occupational Mortality Surveillance data for the years 1983–1992 that controlled for confounding from age, gender, race, socioeconomic status, potential exposure to active tuberculosis, and the presence of silicosis and other pneumoconioses. The potential for exposure to silica was based on potential exposure data from the National Occupational Exposure Survey (Seta et al., 1988) and the National Occupational Health Survey of Mining (Greskevitch et al., 1996) and was categorized as "high," "intermediate," or "low or no" potential exposure. The study found that decedents with potential high exposure to silica and with no documentation of silicosis on the death certificate had a 30% greater odds of mortality from respiratory tuberculosis than decedents with no potential exposure to silica after adjustment by logistic regression for the possible confounders mentioned above (odds ratio [OR] = 1.3; 95% CI = 1.14–1.48). The results also suggested the presence of an exposure–response relationship of silica exposure, in the absence of silicosis, with death from respiratory tuberculosis (Chen et al., 1997).

In summary, the relationship between quartz exposure and tuberculosis risk in the absence of radiographic silicosis in silica-exposed workers has not been well defined or quantitatively described by existing epidemiological studies.

A recent case–control study of tuberculosis and pulmonary disease caused by non-tuberculous mycobacteria (NTM) in South African gold miners found that radiographic silicosis, focal radiological scarring, and human immunodeficiency virus (HIV) infection were significant risk factors for NTM disease and for tuberculosis (Corbett et al., 1999). Past medical history of tuberculosis treatment (OR = 15.1; 95% CI = 7.64–29.93) and current employment in a "dusty job" at the mines (OR = 2.5; 95% CI = 1.46–4.44) were significant risk factors for NTM. The study included 206 NTM patients and 381 tuberculosis patients of known HIV status admitted to a South African hospital and 180 controls that were HIV-tested surgical or trauma patients admitted to that hospital during the same time period. Odds ratios for NTM and tuberculosis increased with increasing years of employment (range of ORs: 1.0–9.4 for NTM, and 1.0–4.1 for tuberculosis).

9.2.3 Lung cancer

Lung cancer is associated with occupational exposures to inhaled quartz (IARC, 1997).

Following a comprehensive review of the large body of published epidemiological studies, IARC (1997) found that the following epidemiological studies provide the least confounded investigations of an association between occupational crystalline silica exposure and lung cancer risk:

- US gold miners (Steenland & Brown, 1995b)
- Danish stone industry workers (Guenel et al., 1989)
- US granite shed and quarry workers (Costello & Graham, 1988)
- US crushed stone industry workers (Costello et al., 1995)
- US diatomaceous earth industry workers (Checkoway et al., 1993, 1996)
- Chinese refractory brick workers (Dong et al., 1995)
- Italian refractory brick workers (Puntoni et al., 1988; Merlo et al., 1991)

- United Kingdom pottery workers (Cherry et al., 1995, 1997; McDonald et al., 1995, 1997; Burgess et al., 1997)
- Chinese pottery workers (McLaughlin et al., 1992)
- cohorts of registered silicotics from North Carolina (Amandus et al., 1991, 1992) and Finland (Kurppa et al., 1986; Partanen et al., 1994)[1]

Although a few of those studies did not find a statistically significant association between occupational crystalline silica exposure and lung cancer risk, most of the studies did. Some non-uniformity of results is not unusual when a large number of epidemiological studies are reviewed and a variety of populations and work environments are studied (IARC, 1997). In addition, IARC noted that the carcinogenicity of quartz (or cristobalite) "may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs" (IARC, 1997). (A detailed critique of the studies listed above is available in Soutar et al., 1997.)

Some of the least-confounded studies reported that lung cancer risk tended to increase with:

- cumulative exposure to respirable silica (i.e., Checkoway et al., 1993, 1996)
- duration of exposure (i.e., Costello & Graham, 1988; Merlo et al., 1991; Partenen et al., 1994; Costello et al., 1995; Dong et al., 1995)
- peak intensity of exposure (Burgess et al., 1997; Cherry et al., 1997; McDonald et al., 1997)
- the presence of radiographically defined silicosis (Amandus et al., 1992; Dong et al., 1995)
- length of follow-up time from date of silicosis diagnosis (Partenen et al., 1994)

The observed associations noted above, including the exposure–response associations, are unlikely to be explained by confounding or other biases; therefore, the epidemiological studies, overall, support increased lung cancer risks from occupational exposure to inhaled respirable crystalline silica (i.e., quartz and cristobalite) (IARC, 1997).

[1] This list includes studies of diatomaceous earth industry workers and workers in the ceramics, refractory brick, and pottery manufacturing industries where the primary silica exposure may have been to cristobalite rather than quartz. In most studies, exposure data for quartz as well as cristobalite or tridymite were not available to support that assumption.

Three studies published since the IARC review investigated exposure–response associations for lung cancer and occupational exposure to quartz.

Cherry et al. (1998) published a final report of the preliminary results of a nested case–control study of 52 lung cancer deaths in a cohort of 5115 pottery workers (i.e., Burgess et al., 1997; Cherry et al., 1997; McDonald et al., 1997). After adjustment for smoking and inclusion of a 20-year-, 10-year-, or 0-year lag period, mean silica concentration (i.e., estimated daily 8-h time-weighted airborne concentrations in $\mu g/m^3$; polymorph not specified) was associated with lung cancer (OR = 1.60, 95% CI = 1.11–2.31; OR = 1.66, 95% CI = 1.14–2.41; OR = 1.67, 95% CI = 1.13–2.47, for 20-year, 10-year, and 0-year lag periods, respectively; $P < 0.008$ for each lag period). However, duration of exposure and cumulative silica dust exposure were not significantly associated with lung cancer mortality, regardless of lag time (Cherry et al., 1998). The presence of small parenchymal radiographic opacities (category $\geq$ 1/0; shape not reported) was not related to lung cancer mortality, before ($P = 0.78$) or after ($P = 0.68$) adjustment for smoking. The authors concluded that the results imply "that crystalline silica may well be a human carcinogen" (Cherry et al., 1998). The study did not differentiate quartz exposures from cristobalite exposures.

De Klerk & Musk (1998) conducted a cohort study of 2297 surface and underground gold miners in western Australia who participated in surveys of respiratory symptoms, smoking habits, and lung function in 1961, 1974, and 1975. Eighty-nine per cent of the cohort was traced to the end of 1993 for trachea, bronchus, and lung cancer mortality and incidence of compensated silicosis (i.e., compensation awarded by the Pneumoconiosis Medical Board). A nested case–control analysis of the 138 lung cancer deaths found that lung cancer mortality was related to log total cumulative silica dust exposure after adjustment for smoking (cigarette, pipe, or cigar) and for the presence of bronchitis at survey (relative rate = 1.31; 95% CI = 1.01–1.70). However, the effect of total cumulative silica dust exposure on lung cancer mortality was not significant after adjustment for smoking, bronchitis, and compensation for silicosis (relative rate = 1.20; 95% CI = 0.92–1.56). Lung cancer mortality was not significantly related ($P > 0.15$) to other silica exposure variables (i.e., duration of underground or surface employment, intensity of underground or surface exposure) after adjustment for smoking and bronchitis. Cigarette smoking (relative rate = 32.5; 95% CI = 4.4–241.2 for $\geq$ 25 cigarettes smoked per day), incidence of a compensation award for silicosis after lung cancer diagnosis (relative rate = 1.59; 95% CI = 1.10–2.28), and presence of bronchitis at survey (relative rate = 1.60; 95% CI = 1.09–2.33) were significantly related to lung

cancer mortality (de Klerk & Musk, 1998). The results of this study do not support a relationship between lung cancer and silica exposure in the absence of silicosis (i.e., a compensation award for silicosis after lung cancer diagnosis).

Hnizdo et al. (1997) conducted a nested case–control study of lung cancer deaths in a cohort of 2260 white South African underground gold miners. (A lung cancer mortality cohort study was conducted earlier [Hnizdo & Sluis-Cremer, 1991].) The mineral content of the rock in the gold mines was mostly quartz (70–90%), silicates (10–30%), pyrite (1–4%), and heavy minerals with grains of gold and uranium-bearing minerals (2–4%). Seventy-eight lung cancer deaths (69 of the 78 miners had a necropsy) that occurred during 1970–1986 were matched by year of birth with 386 control subjects from the same cohort (Hnizdo et al., 1997). Lung cancer mortality risk and a relationship with cigarette smoking (i.e., pack-years), cumulative "dust" exposure (mg/m^3-years), years of underground mining, incidence of radiographic silicosis (i.e., ILO category $\geq$ 1/1 diagnosed up to 3 years before death of a matched case), and uranium production or uranium grade of the ore in the gold mine were analysed with conditional logistic regression models. Radon daughter measurements in the gold mines were not available.

Lung cancer mortality was associated with cigarette smoking, cumulative dust exposure (lagged 20 years from death), duration of underground mining (lagged 20 years from death), and silicosis. The best-fitting model predicted relative risks of 1.0, 3.5 (95% CI = 0.7–16.8), 5.7 (95% CI = 1.3–25.8), and 13.2 (95% CI = 3.1–56.2) for <6.5, 6.5–20, 21–30, and >30 pack-years of smoking, respectively, and 2.45 (95% CI = 1.2–5.2) for silicosis. The authors stated that variables representing uranium mining were not significantly related to lung cancer mortality (modelling results for these variables were not presented) (Hnizdo et al., 1997). The authors proposed three explanations for their results: (1) miners with high dust exposure who develop silicosis have increased lung cancer risk, (2) high silica dust exposure concentrations may be important in the pathogenesis of lung cancer, and silicosis is coincidental, and (3) high levels of silica dust exposure may be a surrogate measure of exposure to radon daughters (Hnizdo et al., 1997).

Meta-analyses of the epidemiological studies of silica exposure and lung cancer reported a moderate summary risk of 1.3 for silica-exposed workers (Steenland & Stayner, 1997) and higher summary relative risks of 2.2–2.3 for studies of silicotic workers (Smith et al., 1995; Steenland & Stayner, 1997). Tsuda et al. (1997) pooled lung cancer risk estimates from 32 mortality studies of pneumoconiosis or silicosis (excluding asbestosis) published from 1980 to 1994. The estimated rate ratios of 2.74 (95% CI = 2.60–2.90) for all studies, 2.77 (95% CI = 2.61–2.94) for cohort studies only (25 of 32 studies), and 2.84 (95% CI = 2.25–3.59) for case–control studies (5 of 32 studies) were similar to the estimates reported by Steenland & Stayner (1997) and Smith et al. (1995).

Reasons for the higher risks in silicotics are not known; similarly, the question of whether fibrosis is a precursor to the development of lung cancer in humans has not been resolved. Various hypothetical mechanistic pathways have been proposed to explain the occurrence of lung tumours in rats and lung cancer in humans; however, there is no convincing evidence for any specific proposed pathway (IARC, 1997).

Selection bias is a common criticism of epidemiological studies of lung cancer in compensated silicotics, because workers who sought compensation for their disease may differ from the group of all silicotics in symptoms, radiographic changes, social and psychological factors, and industry (McDonald, 1995; Weill & McDonald, 1996). However, Goldsmith (1998) reviewed this question and concluded that lung cancer risk estimates were not higher in compensated silicotics when results of studies of compensated silicotics were compared with results of studies of silicotics ascertained from other clinical sources (i.e., hospital or registry data).

9.2.4 Autoimmune-related disease

In humans, immune activation by occupational exposure to respirable quartz may be linked to scleroderma, rheumatoid arthritis, polyarthritis, mixed connective tissue disease, systemic lupus erythematosus, Sjögren's syndrome, polymyositis, and fibrositis (Haustein et al., 1990; Ziegler & Haustein, 1992; Otsuki et al., 1998). The cellular mechanism that leads from quartz dust exposure to autoimmune diseases is not known (Otsuki et al., 1998; NIOSH, forthcoming). One theory is that when respirable silica particles are encapsulated by macrophages, fibrogenic proteins and growth factors are generated, and ultimately the immune system is activated (Haustein et al., 1992; Ziegler & Haustein, 1992; Haustein & Anderegg, 1998).

Several epidemiological studies have reported statistically significant numbers of excess deaths or cases of autoimmune-related diseases such as scleroderma (Sluis-Cremer et al., 1985; Steenland & Brown, 1995b), rheumatoid arthritis (Sluis-Cremer et al., 1986; Klockars et al., 1987), and systemic lupus erythematosus (Steenland & Brown, 1995b) in silica-exposed workers.

9.2.5 Renal disease

Recent epidemiological studies have found statistically significant associations between occupational exposure to crystalline silica dust and renal diseases and subclinical renal changes (Steenland et al., 1992; Ng et al., 1993; Boujemaa et al., 1994; Hotz et al., 1995; Nuyts et al., 1995; Steenland & Brown, 1995b; Steenland & Goldsmith, 1995; Calvert et al., 1997).

9.2.6 Chronic obstructive pulmonary disease

Occupational exposure to respirable crystalline silica dust is associated with chronic obstructive pulmonary disease, including bronchitis and emphysema. Although these health effects are also associated with tobacco smoking, some epidemiological studies suggest that they may be present to a significant extent in non-smokers with occupational exposure to quartz (Wiles & Faure, 1977; Becklake et al., 1987; Holman et al., 1987; Kreiss et al., 1989; Cowie & Mabena, 1991).

9.2.7 Other adverse health effects

Cor pulmonale (i.e., enlargement of the right ventricle of the heart because of structural or functional abnormalities of the lungs) may occur as a complication of silicosis (Green & Vallyathan, 1996) and other pneumoconioses (Kusiak et al., 1993). It is usually preceded by pulmonary arterial hypertension. An epidemiological case–control study of 732 white South African autopsied gold miners reported a statistically significant association ($P < 0.05$) of cor pulmonale with "extensive" silicosis and "slight" silicosis (Murray et al., 1993).

Other adverse health effects or complications of silicosis have been studied or identified in epidemiological studies of workers that may have been exposed to quartz dust, but evidence of an association with quartz exposure is inconclusive. These adverse effects include dental abrasion (Petersen & Henmar, 1988), nasopharyngeal or pharyngeal cancer (Carta et al., 1991; Chen et al., 1992), salivary gland cancer (Zheng et al., 1996), liver cancer (Chen et al., 1992; Hua et al., 1992), bone cancer (Steenland & Beaumont, 1986; Forastiere et al., 1989), pancreatic cancer (Kauppinen et al., 1995), skin cancer (Partanen et al., 1994), oesophageal cancer (Belli et al., 1989; Xu et al., 1996; Pan et al., 1999), stomach cancer (Parent et al., 1998), cancers of the digestive system (Decoufle & Wood, 1979), intestinal or peritoneal cancer (Amandus et al., 1991; Costello et al., 1995; Goldsmith et al., 1995a), lymphopoietic or haematopoietic cancers (Silverstein et al., 1986; Steenland & Brown, 1995b), and bladder cancer (Bravo et al., 1987).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

Terrestrial mammals (i.e., horses, camels) and birds exposed to quartz in the natural environment, especially in desert or coastal areas, show pathological lesions sometimes described as "silicosis" that are similar to those seen in humans with silicosis (Schwartz et al., 1981; Evans et al., 1988; Hansen et al., 1989; Berry et al., 1991; Xu et al., 1993; Green & Vallyathan, 1996). Rats, hamsters, guinea-pigs, monkeys, and mice exposed to quartz under experimental conditions develop lung conditions and nodules similar to those found in humans (reviewed by Green & Vallyathan, 1996).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

The extensive body of *in vitro* and *in vivo* research evaluating the effects of quartz on mammalian cells is summarized here (IARC, 1997; NIOSH, forthcoming). Quartz deposited in the lungs causes epithelial and macrophage injury and activation, and it translocates to the interstitium and the regional lymph nodes. Recruitment of inflammatory cells occurs in a dose-dependent manner. Oxidative stress (i.e., increased formation of reactive oxygen species, including hydroxyl radicals, or reactive nitrogen species) has been observed in rats after intratracheal instillation (Blackford et al., 1994; Schapira et al., 1995) or inhalation (Vallyathan et al., 1995) of quartz. Several mechanisms have been proposed to explain the cause of the cellular damage by quartz particles (Lapp & Castranova, 1993): (1) direct cytotoxicity of quartz, (2) stimulation of the alveolar macrophages by quartz, which results in the release of cytotoxic enzymes or oxidants, (3) stimulation of the alveolar macrophages to release inflammatory factors (e.g., interleukin-8, leukotriene B_4, platelet-activating factor, tumour necrosis factor, platelet-derived growth factor) that recruit polymorphonuclear leukocytes, which may release cytotoxins, (4) stimulation of the alveolar macrophages to release factors that initiate fibroblast production and collagen synthesis (e.g., interleukin-1, tumour necrosis factor, platelet-derived growth factor, fibronectin, alveolar macrophage-derived growth factor), and, more recently, (5) induction by quartz of apoptosis and subsequent engulfment by macrophages to regulate

the evolution of inflammation and fibrosis (Leigh et al., 1997).

Silicosis is indisputably causally related to occupational quartz exposure, and the dose–response assessments of the adverse health effects of quartz are based on epidemiological studies of occupational cohorts with silicosis. To date, there are no known adverse health effects associated with non-occupational exposure to quartz dust. Silicosis is the critical effect for hazard identification and dose–response assessment, for two reasons. First, although IARC classified inhaled quartz from occupational sources as a Group 1 carcinogen, there are very few published risk assessments (toxicological or epidemiological) with a quantitative dose–response assessment of lung cancer risk at various levels of quartz exposure. A pooled exposure–response assessment of a number of epidemiological studies with quantitative data for quartz exposures and lung cancer is currently being conducted by IARC.

Secondly, epidemiological studies of quartz-exposed workers reported statistically significant numbers of excess deaths or cases of renal disease or subclinical renal changes (Steenland et al., 1992; Ng et al., 1993; Boujemaa et al., 1994; Hotz et al., 1995; Nuyts et al., 1995; Steenland & Brown, 1995b; Calvert et al., 1997), mycobacterial infections (tuberculous and non-tuberculous), or fungal infections (Ziskind et al., 1976; Parkes, 1982; Parker, 1994; Althouse et al., 1995; Goldsmith et al., 1995a; NIOSH, 1996; American Thoracic Society, 1997; Kleinschmidt & Churchyard, 1997; Hnizdo & Murray, 1998; Corbett et al., 1999), immunological disorders and autoimmune diseases (i.e., scleroderma) (Sluis-Cremer et al., 1985; Cowie, 1987; Steenland & Brown, 1995b), rheumatoid arthritis (Sluis-Cremer et al., 1986; Klockars et al., 1987), and systemic lupus erythematosus (Steenland & Brown, 1995b), but sufficient epidemiological or toxicological data do not currently exist for quantitative assessment of the exposure–response relationship for these health effects.

The US EPA calculated lowest-observed-adverse-effect level (LOAEL) human equivalent concentrations (HECs) for non-cancer effects reported in subchronic (#3 months) and chronic inhalation studies that administered less than 20 mg quartz/m^3 to experimental rats and mice (Table 1). The results varied widely — from 0.18 mg/m^3 (based on rat study) to 0.90 mg/m^3 (based on mouse study). Some of this variation may have been due to differences in dose, species, and the quartz specimens. The method for determining the HEC was based on a series of empirical equations described elsewhere (US EPA, 1994) and summarized here. It represents an example of the calculation of an HEC and may not necessarily be a method used worldwide. The equations estimate fractional deposition of relatively insoluble particles and adjust for dosimetric differences between species by incorporating normalizing factors such as body weight or surface area (US EPA, 1994). In summary:

$$NOAEL_{[HEC]}\ (mg/m^3) = NOAEL_{[ADJ]}\ (mg/m^3) \times RDDR_r$$

where:

- $NOAEL_{[HEC]}$ = the no-observed-adverse-effect level (NOAEL) human equivalent concentration, dosimetrically adjusted
- $NOAEL_{[ADJ]}$ = the NOAEL adjusted for duration: E (mg/m^3) × D (h/24 h) × W (days/7 days), where E = experimental exposure level
- $RDDR_r$ = the regional deposited dose ratio of particles for the respiratory tract region (r)
- $RDDR = (RDD_{TH}/\text{Normalizing Factor})_A / (RDD_{TH}/\text{Normalizing Factor})_H$, the ratio of regional deposited dose (RDD_r) in the thoracic (TH) region in the animal (A) species to that of humans (H) (US EPA, 1994)
- r = region of dose deposition, in this case thoracic
- $RDD_r = 10^{-6} \times C_i \times V_E \times F_r$, where:
  C_i = concentration (mg/m^3)
  V_E = minute volume (ml/min)
  F_r = fractional deposition in region r

The literature contains a few additional risk assessments of lung cancer and quartz, and all were based on results of inhalation studies of rats (Collins & Marty, 1995, 1997; Goldsmith et al., 1995b). However, human data introduce less uncertainty than extrapolation from animals to humans (Goldsmith et al., 1995b; Goldsmith & Hertz-Picciotto, 1997). For quartz, the uncertainty can be attributed in part to the lack of (1) experimental studies that systematically evaluated exactly the same material to which humans are exposed (IARC, 1997), (2) understanding of the mechanism for induction of rat lung tumours (IARC, 1997), (3) understanding of the species differences observed in the fibrogenic response (Gift & Faust, 1997), and (4) experimental studies that administered doses in concentrations similar to known occupational exposures (US EPA, 1996). Epidemiological studies that used cumulative exposure estimates represent the best currently available source of information for characterizing the dose–response relationship for silicosis or lung cancer in occupational, as well as non-occupational, cohorts.

Exposure–response models based on cumulative exposure data can provide predictions of silicosis risk for a particular silica dust exposure over a period of time. Table 6 presents results of logistic regression models of data from the cross-sectional epidemiological studies

described in section 9.2. The models predicted the prevalence of radiographic silicosis (ILO category $\geq$ 1/1 or $\geq$ 1/0) from cumulative exposure to respirable quartz. All models predicted the occurrence of at least one case of radiographic silicosis per 100 workers at cumulative respirable quartz dust exposures of 0.05 or 0.10 mg/m^3 over a 45-year working lifetime. Logistic regression assumes that the change in the level of quartz exposure affects risk (or predicted prevalence) in a multiplicative manner (as compared with linear models, which predict deviations from additivity) (Kleinbaum et al., 1982).

Table 7 displays the results of three studies that followed cohorts of miners for silicosis over time or retrospectively. In these studies, the miners with silicosis had their first quartz exposure 18–37 years (mean) prior to radiographic diagnosis. The models applied to the data collected in these studies predicted that the risk of chronic silicosis increases exponentially with increasing cumulative dose of silica dust (US EPA, 1996). Data from the study of South African gold miners (Hnizdo & Sluis-Cremer, 1993) and Canadian gold and uranium miners were analysed with models that assumed some risk of silicosis at any exposure. The study of US gold miners (Steenland & Brown, 1995a) estimated silicosis rates (cases per person-time at risk) for seven cumulative exposure categories, stratified by 5-year age and calendar time intervals. Poisson regression was used to adjust the crude rates for age and calendar time. Although age and calendar time were highly correlated with exposure, it is not likely that they confounded the exposure–response analysis, because silicosis has no background rate for non-exposed populations that changes with age or calendar time (US EPA, 1996).

In summary, the risk estimates for silicosis prevalence for a working lifetime of exposure to respirable quartz dust concentrations of about 0.05 or 0.10 mg/m^3 in the occupational environment vary widely (i.e., 2–90%). Epidemiological studies varied in the definition of silicosis cases, radiographic interpretation methods, cohort follow-up periods, and statistical methods. The variability in the risk estimates cannot be solely attributed to differences in follow-up periods; however, it must be recognized that chronic silicosis is a progressive disease. Therefore, the development of silicosis after a long latency period and after workers leave employment must be accounted for in epidemiological studies. Results of a study of autopsied South African gold miners found that the diagnostic sensitivity of radiological examination is particularly poor (Hnizdo et al., 1993). For example, when the radiological findings for profusion of rounded opacities (ILO category $\geq$ 1/1) were compared with pathological findings for silicosis in 326 miners with an average of 2.7 years between the radiological and pathological examination, silicosis was not diagnosed radiographically for at least 61% of the miners with slight to marked silicosis at autopsy. The probability of a false-negative reading increased with years of mining and the average concentration of respirable dust (Hnizdo et al., 1993). Experimental studies of rats also reported lack of agreement between histopathological indicators of silica dust exposure and radiographic readings (Drew & Kutzman, 1984a,b).

Improved exposure assessment methods and data analyses that account for variations and deficiencies in exposure data would improve the risk estimates for silica-exposed workers (Agius et al., 1992; Checkoway, 1995). Although epidemiological studies that used cumulative exposure estimates represent the best available source of information for characterizing the dose–response relationship in occupational cohorts, peak exposures may predict silicosis risk better than cumulative exposures (Checkoway & Rice, 1992), but data are rarely available.

11.1.2 Criteria for setting tolerable intakes or guidance values for quartz

Results of genotoxicity tests of quartz, as well as other *in vitro* and *in vivo* evidence, suggest that persistent inflammation and epithelial proliferation are related to the tumour response in rats. Other pathways for tumour induction, such as a direct genotoxic effect, have not been ruled out. Because a pathway has not been determined, and it is unclear from results of epidemiological studies whether silicosis is a precursor to lung cancer, it cannot be assumed that there is a threshold (i.e., tolerable concentration, or TC) at which exposure to quartz would not result in silicosis and/or lung cancer. In addition, available data indicate that occupational quartz exposure is associated with the development of tuberculosis, especially in workers with silicosis; however, the association has not been quantified for that outcome or for other quartz-related diseases. Therefore, occupational exposure to respirable quartz dust should be reduced to the extent possible.

11.1.3 Sample risk characterization

It is recognized that there are many different methods for assessing the risk to human health posed by environmental and occupational substances. The example presented here applies to healthy individuals not compromised by respiratory ailments and who breathe the ambient air in the USA. It is based on the results of the three cohort studies of miners presented in Table 7 (section 11.1.1). Using a high estimate of 10% crystalline silica content of particulate matter with a mass median aerodynamic diameter not greater than 10 μm (PM_{10}) from US metropolitan areas, the highest

cumulative crystalline silica exposure expected from continuous human lifetime exposure at or below the annual US national ambient air quality standard (NAAQS) for particulate matter of 50 $\mu g/m^3$ is 1 mg/m^3-year (US EPA, 1996).

The US EPA applied a mathematical model (i.e., benchmark dose [BMD] analysis) to determine a concentration and lower confidence bound associated with a predefined effect level (i.e., 1%, 5%, and 10% risk of silicosis) (US EPA, 1996). After consideration of cross-sectional, longitudinal, retrospective cohort, and case–control epidemiological studies, the BMD was conducted on data from the previously described study of radiographic silicosis in a cohort of 2235 South African gold miners (Hnizdo & Sluis-Cremer, 1993). This study was selected for several reasons: (1) continuous and longitudinal investigation of silicosis, (2) miners had multiple X-ray examinations, and (3) autopsy data were available for more accurate interpretation of the radiographic results, which lack sensitivity (US EPA, 1996).[1]

Using methods described by US EPA (1996), the BMD analysis predicted that the silicosis risk for a continuous 70-year lifetime exposure to 0.008 mg/m^3 (estimated high crystalline silica concentration in US metropolitan areas) is less than 3% for healthy individuals not compromised by other respiratory diseases or conditions and for ambient environment (US EPA, 1996). (Risks were not calculated for other groups, such as people with respiratory illnesses.) This risk estimate for exposure to ambient quartz may be conservative, because quartz particles in the occupational environment may be finer or "freshly fractured," occupational exposures may involve high "peak" exposures, and, thus, the potential for disease development may be greater.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC has classified inhaled crystalline silica (quartz or cristobalite) from occupational sources as a Group 1 carcinogen based on sufficient evident of carcinogenicity in humans and experimental animals. In addition, "in making the overall evaluation, the Working Group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs" (IARC, 1997).

In 1991, the ILO published a document describing methods for prevention and control of occupational lung diseases, including silicosis (ILO, 1991), and in 1993, the Office of Occupational Health of the World Health Organization (WHO) called for increased medical surveillance of workers exposed to mineral dusts to prevent pneumoconioses such as silicosis and asbestosis (WHO, 1993). WHO also recently published information about risk factors for pulmonary tuberculosis, including occupational exposure to respirable crystalline silica (WHO, 1996).

In 1986, a WHO study group recommended a limit of 40 $\mu g/m^3$ (time-weighted average of an 8-h shift) for occupational exposure to respirable crystalline silica dust (WHO, 1986).

[1] The cross-sectional studies described in Table 6 and sections 9.2.1 and 11.1.1 were not available at the time of the US EPA assessment. These studies modelled the cumulative quartz exposures of hardrock miners (Kreiss & Zhen, 1996) and grey iron foundry workers (Rosenman et al., 1996) and predicted a 30% prevalence of ILO category $\geq$ 1/1 silicosis over a 45-year working lifetime with 10 years of post-employment follow-up (Kreiss & Zhen, 1996) or a 2% prevalence of ILO category $\geq$ 1/0 silicosis over a 40-year working lifetime and controlling for pack-years of cigarette smoking, race, and silica exposure other than in the foundry under study (Rosenman et al., 1996). Both predictions are for a mean quartz dust concentration of 0.05 mg/m^3.

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APPENDIX 1 — SOURCE DOCUMENTS

IARC (1997)

Copies of *Silica, some silicates, coal dust and* para-*aramid fibrils* (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 68) may be obtained from:

International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

The members of the Working Group on the Evaluation of Carcinogenic Risks to Humans of silica (including quartz), some silicates, coal dust and *para*-aramid fibrils that met in Lyon on 15–22 February 1996 were:

M.D. Attfield, National Institute for Occupational Safety and Health, USA
P.J. Borm, University of Limburg, The Netherlands
H. Checkoway, University of Washington, USA
K. Donaldson, Napier University, United Kingdom
M. Dosemeci, National Cancer Institute, USA
V.J. Feron, TNO Nutrition and Food Research Institute, The Netherlands
B.J. Fubini, University of Torino, Italy
M. Gérin, Université de Montréal, Canada
E. Hnizdo, National Centre for Occupational Health, South Africa
A.B. Kane, Brown University, USA
J.C. McDonald, Imperial College, United Kingdom
H. Muhle, Fraunhofer Institute for Toxicology and Aerosol Research, Germany
S. Olin, International Life Sciences Institute, USA
J.-C. Pairon, INSERM, France
T. Partanen, Institute of Occupational Health, Finland
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D.B. Warheit, DuPont Haskell Laboratory for Toxicology and Industrial Medicine, USA
V. Yermilov, N.N. Petrov Research Institute of Oncology, Russia

US EPA (1996)

Copies of the US Environmental Protection Agency report entitled *Ambient levels and noncancer health effects of inhaled crystalline and amorphous silica: health issue assessment* (NTIS Publication PB97-188122) may be obtained from:

National Technical Information Service
Springfield, VA 22161
USA

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NIOSH (forthcoming)

When published, copies of the *NIOSH special hazard review: Health effects of occupational exposure to respirable crystalline silica* will be available from:

National Institute for Occupational Safety and Health
Publications Dissemination
4676 Columbia Parkway
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APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on crystalline silica, quartz was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

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APPENDIX 3 — CICAD FINAL REVIEW BOARD

Sydney, Australia, 21–24 November 1999

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CAS No: 14808-60-7	Crystalline silica, quartz
RTECS No: VV7330000	Crystalline silicon dioxide, quartz
UN No:	Silicic anhydride
EC No:	SiO_2
	Molecular mass: 60.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible.		In case of fire in the surroundings: all extinguishing agents allowed.
EXPLOSION			

EXPOSURE		**PREVENT DISPERSION OF DUST!**	
Inhalation	Cough.	Local exhaust or breathing protection.	
Skin			
Eyes		Safety goggles, or eye protection in combination with breathing protection.	
Ingestion			

SPILLAGE DISPOSAL	**PACKAGING & LABELLING**
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Wash away remainder with plenty of water. (extra personal protection: P3 filter respirator for toxic particles).	Symbol R: S:

EMERGENCY RESPONSE	**STORAGE**

IMPORTANT DATA

Physical State; Appearance
COLOURLESS, WHITE OR VARIABLE BLACK, PURPLE, GREEN CRYSTALS

Chemical Dangers
Reacts with strong oxidants causing fire and explosion hazard.

Occupational Exposure Limits
TLV: 0.1 mg/m^3 (respirable dust) (ACGIH 1997).
MAK: 0.15 mg/m^3; (1996)

Routes of Exposure
The substance can be absorbed into the body by inhalation.

Inhalation Risk
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

Effects of Long-term or Repeated Exposure
The substance may have effects on the lungs, resulting in fibrosis (silicosis). This substance is carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: 2230°C
Melting point: 1610°C

Relative density (water = 1): 2.6
Solubility in water: none

ENVIRONMENTAL DATA

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. CSQZ, DQ 12, Min-U-Sil, Sil-Co-Sil, Snowit, Sykron F300, Sykron F600 are trade names.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Le présent CICAD, relatif à la silice cristallisée ou quartz, est basé sur trois documents résultant d'un examen approfondi par des pairs des effets sanitaires de cette substance, à savoir : 1) une mise au point portant sur les études et rapports consacrés aux effets nocifs d'une exposition de l'organisme humain au quartz (NIOSH, à paraître); 2) une revue critique des études de cancérogénicité effectuées par le Centre international de recherche sur le cancer (IARC/CIRC, 1997) et 3) un examen des études consacrées aux effets sanitaires du quartz présent dans le milieu ambiant, à l'exclusion des cancers (US EPA, 1996). Ces différentes sources documentaires n'accordant pas la même attention aux divers points d'aboutissement toxicologiques, on s'est efforcé, dans ce CICAD, de prendre en compte l'ensemble des effets indésirables mentionnés dans les documents de base. Il est a noter à cet égard, que même si les trois documents ne traitent pas tous les effets de manière aussi détaillée, leurs conclusions finales n'en sont pas moins très voisines. On a utilisé plusieurs bases de données en ligne pour effectuer une recherche bibliographique très complète. Le dernier dépouillement remonte à mars 1999.

Le présent CICAD porte sur la forme la plus commune de silice cristallisée, c'est-à-dire le quartz. Il ne prend pas en compte les travaux résultant des études expérimentales consacrées aux effets des différentes autres formes de silice cristallisée comme la cristobalite, la tridymite, la stishovite ou la coésite, ni à d'autres variétés comme la terre d'infusoires ou la silice amorphe ni même à la poussière de charbon car leur toxicité *in vitro* est différente ce celle du quartz. Une ancienne étude effectuée sur des rats vivants a montré que l'induction de la fibrogénicité était différentes selon les différentes formes : quartz, cristobalite ou tridymite. Il n'existe toutefois pratiquement aucune étude expérimentale qui ait procédé à une évaluation systématique du risque que représentent des matériaux identiques à ceux auxquels l'Homme est exposé. Selon le groupe d'étude du CIRC, il est possible que les différentes formes cristallines de silice n'aient pas toutes le même pouvoir cancérogène. Il est vrai que dans beaucoup d'études, l'évaluation a porté sur les « environnements mixtes » dans lesquels le quartz a pu être chauffé – ce qui est susceptible d'avoir produit une conversion en cristobalite ou en tridymite dans des proportions diverses (par ex. dans l'industrie de la céramique, de la poterie et de la brique réfractaire) – et on n'a pas fait de distinction entre l'exposition au quartz et l'exposition à la cristobalite, par exemple. On peut penser, au vu de certaines données, que le risque de cancer varie selon le type d'industrie et de procédé, et ce, selon des modalités qui laissent supposer que ce risque est spécifique de chacune des formes cristallines, mais le Groupe n'a pu parvenir à une conclusion que dans le cas précis du quartz et de la cristobalite. Ce CICAD reprend l'exposé et les conclusions du document de ce Groupe, aussi l'évaluation qu'il donne de la cancérogénicité du quartz sur le lieu de travail ne fait-elle pas de distinction entre les études épidémiologiques portant sur le quartz et celles qui sont consacrées à la cristobalite.

Il a été convenu que l'examen par des pairs de la littérature consacrée au quartz en vue de la rédaction du présent CICAD comporterait un volet particulier, consistant en une étude critique par un groupe international de spécialistes choisis en fonction de leur connaissance des controverses actuelles au sujet du quartz. On trouvera à l'appendice 1 des indications sur la nature de l'examen par des pairs et sur les sources documentaires existantes. Des indications sur l'examen par des pairs du présent CICAD figurent à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Sydney (Australie) du 21 au 24 novembre 1999. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information internationale sur la sécurité chimique (ICSC No 0808) relative à la silice cristallisée est également reproduite dans l'appendice 4 (IPCS, 1993).

Le quartz (No CAS 14808-60-7) est un constituant solide souvent présent dans la plupart des poussières minérales naturelles. L'exposition humaine au quartz est la plupart du temps liée à des activités professionnelles qui impliquent le déplacement de masses de terre, la manipulation de matériaux qui contiennent de la silice (pierre à bâtir ou béton par ex.); elle peut aussi se produire lors de l'utilisation ou de la fabrication de produits à base de silice. Il peut y avoir exposition à la poussière de quartz présente dans l'environnement lors d'activités naturelles, industrielles ou agricoles. Les particules de quartz respirables peuvent être inhalées et se déposer dans les poumons; toutefois on n'a aucune certitude au sujet de la cinétique d'élimination des particules de quartz chez l'Homme.

Le quartz provoque une inflammation cellulaire *in vivo*. Des études expérimentales à court terme sur des rats, des souris et des hamsters ont montré que l'instillation intratrachéenne de particules de quartz conduisait à la formation de nodules silicotiques discrets. L'inhalation d'aérosols de particules de quartz gêne la fonction de nettoyage alvéolaire des macrophages et conduit à des lésions évolutives et à une pneumopathie inflammatoire. Un stress oxydatif (c'est-à-dire la formation accrue de radicaux hydroxyles et

d'espèces oxygénées ou azotées réactives) a été observé chez des rats après instillation intratrachéenne ou inhalation de particules de quartz. De nombreuses études expérimentales *in vitro* ont permis de constater que les propriétés de surface des particules de silice cristallisées influent sur leur activité fibrogène et sur un certain nombre de caractéristiques de leur activité cytotoxique. De nombreux mécanismes possibles sont décrits dans la littérature, mais en fait les lésions cellulaires provoquées par le quartz sont le résultat de mécanismes complexes dont la nature n'est pas encore totalement élucidée.

Les études d'inhalation à long terme effectuées sur des rats et des souris montrent que les particules de quartz entraînent une prolifération cellulaire, la formation de nodules, la dépression des fonctions immunitaires et une protéinose alvéolaire pulmonaire. Des études expérimentales sur des rats ont permis de mettre en évidence la formation d'adénocarcinomes et de carcinomes spinocellulaires consécutive à l'inhalation ou à l'instillation intratrachéenne de particules de quartz. Les études sur le hamster ou la souris n'ont pas permis de mettre en évidence ce genre de tumeurs pulmonaires. On ne dispose pas de données dose-réponse (par ex. dose sans effet nocif ou dose minimale produisant un effet nocif) satisfaisantes pour le rat ou d'autres rongeurs car peu d'études de cancérogénicité comportant une variété de doses ont été effectuées.

Les tests de mutagénicité classique sur bactérie ne donnent pas de résultat positif. Les résultats des études de génotoxicité sont contradictoires et il n'a pas été possible de confirmer ou d'infirmer l'existence d'un effet génotoxique direct.

Les résultats d'études sur les particules peuvent donner des résultats variables selon le matériau testé, la granulométrie, la concentration administrée aux animaux et l'espèce utilisée. Les essais effectués avec des particules de quartz ont porté sur diverses espèces avec échantillons d'origine, de concentration et de granulométrie variée, autant de facteurs qui ont pu avoir une influence sur les observations.

On ne dispose pas de données concernant les effets que le quartz pourrait avoir sur la reproduction ou le développement chez des animaux d'expérience.

Les effets indésirables du quartz sur les organismes aquatiques et les mammifères terrestres n'ont pas été étudiés non plus.

Il existe beaucoup d'études épidémiologiques portant sur des cohortes de divers professionnels exposés à des poussières respirables de quartz. L'exposition professionnelle à la poussière de quartz est associée à la silicose, au cancer du poumon et à la tuberculose pulmonaire. Le CIRC a classé la silice cristallisée (quartz ou cristobalite) inhalée sur le lieu de travail dans le groupe 1 des produits dont la cancérogénicité pour l'Homme et l'animal repose sur des preuves suffisantes. Dans son évaluation générale de cette substance, le Groupe de travail a noté qu'aucun signe de cancérogénicité n'avait été relevé au cours de toutes ses enquêtes dans l'industrie. Il est possible que la cancérogénicité de la silice cristallisée dépende de certaines propriétés intrinsèques de cette substance ou encore de facteurs extérieurs susceptibles d'influer sur son activité biologique ou sur la proportion relative des différentes formes (IARC/CIRC, 1997).

On a fait état d'une augmentation statistiquement significative des décès ou des cas de bronchite, d'emphysème, de broncho-pneumopathie chronique obstructive, de maladies à composante auto-immune (comme la sclérodermie, l'arthrite rhumatoïde ou le lupus érythémateux disséminé) ou encore de néphropathie.

En ce qui concerne l'identification du risque et la relation exposition-réponse, c'est la silicose qui constitue l'effet déterminant. On possède suffisamment de données épidémiologiques pour permettre une évaluation quantitative du risque de silicose, mais pas pour donner une estimation précise du risque des autres effets sanitaires indiqués plus haut (une évaluation groupée utilisant des études épidémiologiques consacrées à la silice et au cancer du poumon est en cours au CIRC).

Il y a de grandes variations (par ex. 2 à 90 %) dans les estimations du risque relatives à la prévalence de la silicose par suite d'une exposition tout au long de la vie professionnelle à des particules respirables de quartz de concentration comprise entre 0,05 et 0,10 mg/m^3 sur le lieu de travail. En ce qui concerne l'exposition aux particules présentes dans l'air ambiant de l'environnement général, une analyse de référence conclut que le risque de silicose pour une exposition continue pendant 70 ans à 0,008 mg/m^3 (c'est à dire la valeur estimative élevée de la concentration de silice cristallisée en milieu urbain aux États-Unis), est inférieur à 3 % pour les individus en bonne santé ne souffrant pas de pathologie respiratoire (US EPA, 1996). Le risque de silicose pour les personnes exposées dans les même conditions mais présentant une pathologie respiratoire n'a pas été évalué.

Il existe un certain nombre d'incertitudes concernant l'évaluation des études épidémiologiques et l'estimation du risque d'effets toxiques résultant de l'exposition à des poussières de quartz. Les difficultés,

qui pour une grande part sont liées à l'étude même des affections respiratoires dans les diverses professions, tiennent au nombre et à la qualité des données longitudinales d'exposition, à l'insuffisance des informations sur les facteurs de confusion possibles – comme le tabagisme à la cigarette, par ex. – et à l'interprétation des radiographies thoraciques en tant que preuves de l'exposition. En outre, l'exposition professionnelle à la poussière de quartz est complexe car les travailleurs sont fréquemment exposés à des mélanges qui contiennent du quartz à côté d'autres types de substances minérales. Les propriétés de ces poussières (par ex. la granulométrie, les caractéristiques de surface, la forme cristalline) peuvent varier selon leur origine géologique et se même se modifier lors des divers traitements industriels. Ces variations peuvent influer sur l'activité biologique des poussières inhalées. Le Groupe de travail du CIRC a évalué la cancérogénicité de la silice cristallisée (quartz, notamment) et a concentré son attention sur les études épidémiologiques les moins susceptibles d'être affectées par des facteurs de confusion et des biais de sélection et il en a tiré des relations dose-réponse (IARC/CIRC, 1997).

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la sílice cristalina, el cuarzo, se basa en los tres amplios documentos siguientes objeto de un examen colegiado sobre los efectos en la salud de la sílice cristalina, incluido el cuarzo: 1) un examen de los estudios e informes publicados sobre los efectos adversos en la salud humana de la exposición al cuarzo (NIOSH, de próxima aparición), 2) un examen de los estudios de carcinogenicidad realizados por el Centro Internacional de Investigaciones sobre el Cáncer (IARC/CIIC, 1997) y 3) un examen de los efectos en la salud distintos del cáncer del cuarzo presente en el medio ambiente (US EPA, 1996). En los documentos originales se prestó una atención diferente a los distintos efectos finales, y el CICAD se elaboró a fin de evaluar todos los efectos adversos para la salud identificados en esos documentos. Hay que señalar que, a pesar de esas diferencias, las conclusiones finales de todos los documentos originales fueron muy semejantes. Se realizó una búsqueda bibliográfica amplia de varias bases de datos en línea. El presente examen contiene los datos obtenidos hasta marzo de 1999.

En este CICAD se examina la forma más común de sílice cristalina (es decir, el cuarzo). No se tienen en cuenta los estudios experimentales de los efectos de otras formas de sílice cristalina (por ejemplo, la cristobalita, la tridimita, la estishovita o la coesita), el polvo de carbón, la tierra de diatomeas o la sílice amorfa, porque su toxicidad *in vitro* es diferente de la del cuarzo. En un estudio preliminar en ratas *in vivo* se pusieron de manifiesto diferencias en la capacidad de inducción de fibrogenicidad del cuarzo, la cristobalita y la tridimita. Sin embargo, apenas existen estudios experimentales en los que se evalúe de manera sistemática exactamente el mismo material al que está expuesto el ser humano. El Grupo de Trabajo del CIIC examinó la posibilidad de que hubiera diferencias en el potencial carcinogénico entre los distintos tipos polimórficos de la sílice cristalina. Sin embargo, en algunos de los estudios epidemiológicos se evaluó la presencia de cáncer de pulmón entre los trabajadores de "entornos mixtos", donde el cuarzo se puede calentar y se pueden producir diversos grados de conversión a cristobalita o tridimita (por ejemplo, en las industrias de cerámica, alfarería y ladrillos refractarios) y no se describieron específicamente las exposiciones al cuarzo o la cristobalita. Aunque hubo algunos indicios de que los riesgos de cáncer variaban en función de la industria y el proceso, de manera que parecía indicar riesgos específicos de los tipos polimórficos, el Grupo de Trabajo pudo llegar solamente a una conclusión única para el cuarzo y la cristobalita. El CICAD se hace eco del debate y la conclusión de ese documento original; por consiguiente, al examinar la carcinogenicidad del cuarzo en el entorno ocupacional no se distingue entre los estudios epidemiológicos del cuarzo y los de la cristobalita.

El proceso de examen colegiado para el presente CICAD tenía por objeto incluir el examen de un grupo internacional de expertos seleccionados por sus conocimientos acerca de las controversias y las cuestiones actuales en relación con el cuarzo. La información relativa al carácter del examen colegiado y a la disponibilidad de los documentos originales figura en el apéndice 1. La información relativa al examen colegiado de este CICAD se presenta en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Sydney, Australia, los días 21-24 de noviembre de 1999. En el apéndice 3 figura la lista de participantes en esta reunión. La Ficha internacional de seguridad química (ICSC 0808) para la sílice cristalina, cuarzo (IPCS, 1993), también se reproduce en el apéndice 4.

El cuarzo (CAS Nº 14808-60-7) es un componente sólido presente con frecuencia en la gran mayoría de los tipos de polvo mineral natural. La exposición humana al cuarzo se produce sobre todo durante las actividades laborales que requieren el desplazamiento de tierra, la alteración de productos con sílice (por ejemplo, obras de albañilería, hormigón) o el uso o fabricación de productos con sílice. Se puede producir exposición al polvo de cuarzo presente en el medio ambiente durante la realización de actividades físicas, industriales y agrícolas. Se pueden inhalar partículas de polvo de cuarzo respirables, que se depositan en el pulmón; sin embargo, no se ha llegado a ninguna conclusión acerca de su cinética de eliminación en el ser humano.

El polvo de cuarzo induce inflamación celular *in vivo*. En estudios experimentales de corta duración en ratas se ha observado que la instilación intratraqueal de partículas de cuarzo da lugar a la formación de nódulos silicóticos dispersos en ratas, ratones y hámsteres. La inhalación de partículas de cuarzo pulverizadas dificulta las funciones de limpieza de los macrófagos alveolares y provoca lesiones progresivas y neumonitis. Se ha observado una tensión oxidante (es decir, una mayor formación de radicales hidroxilo, especies de oxígeno reactivo o especies de nitrógeno reactivo) en ratas tras la instilación intratraqueal o la inhalación de cuarzo. Numerosos estudios experimentales *in vitro* han puesto de manifiesto que las características de la superficie de las partículas de sílice cristalina influyen en su actividad fibrogénica y en varias propiedades relacionadas con su citotoxicidad. Aunque en la bibliografía se han descrito muchos mecanismos que posiblemente contribuyan a esto, la manera en la cual las partículas de cuarzo

provocan el daño celular es compleja y no se conoce del todo.

En estudios de inhalación prolongados con ratas y ratones se ha comprobado que las partículas de cuarzo inducen proliferación celular, formación de nódulos, supresión de las funciones inmunitarias y proteinosis alveolar. En estudios experimentales con ratas se notificó la aparición de adenocarcinomas y carcinomas de las células escamosas tras la inhalación o la instilación intratraqueal de cuarzo. En experimentos con hámsteres o ratones no se observaron tumores en los pulmones. No se dispone de datos adecuados sobre la relación dosis-respuesta (por ejemplo, la concentración sin efectos adversos o la concentración mas baja con efectos adversos) para ratas u otros roedores, debido a que se han realizado escasos estudios de carcinogenicidad con dosis múltiples.

El cuarzo no dio resultado positivo en las valoraciones normales de mutagénesis en bacterias. Los resultados de los estudios de genotoxicidad del cuarzo son contradictorios y no se ha confirmado ni descartado un efecto genotóxico directo.

En estudios experimentales de partículas, los resultados pueden variar en función del material de prueba, el tamaño de las partículas, la concentración administrada y la especie objeto de examen. En los experimentos con partículas de cuarzo se utilizaron ejemplares de varios orígenes, con diversidad de dosis, tamaños de partículas y especies, que podrían haber afectado a las observaciones.

No se dispone de datos sobre los efectos reproductivos y en el desarrollo del cuarzo en animales de laboratorio.

No se han estudiado los efectos adversos del cuarzo en los organismos acuáticos y los mamíferos terrestres.

Hay numerosos estudios epidemiológicos de cohortes ocupacionales expuestas a polvo de cuarzo respirable. La silicosis, el cáncer de pulmón y la tuberculosis pulmonar son enfermedades asociadas con la exposición ocupacional al polvo de cuarzo. El CIIC clasificó la sílice cristalina (cuarzo o cristobalita) de procedencia ocupacional como carcinógeno del grupo 1, basándose en pruebas suficientes de carcinogenicidad en el ser humano y en los animales experimentales; "al hacer la evaluación general, el Grupo de Trabajo observó que no se había detectado carcinogenicidad en el ser humano en todas las circunstancias industriales estudiadas. La carcinogenicidad puede depender de características inherentes a la sílice cristalina o de factores externos que afectan a su actividad biológica o a la distribución de sus tipos polimórficos" (IARC/CIIC, 1997).

Se han notificado aumentos estadísticamente significativos de muertes o casos de bronquitis, enfisema, enfermedad pulmonar obstructiva crónica, enfermedades relacionadas con la autoinmunidad (es decir, escleroderma, artritis reumatoide, lupus eritematoso sistémico) y enfermedades renales.

La silicosis es el efecto decisivo para la determinación del peligro y la evaluación de la relación exposición-respuesta. Hay datos epidemiológicos suficientes para poder efectuar una estimación cuantitativa del riesgo de silicosis, pero no estimaciones precisas de los riesgos de otros efectos para la salud mencionados anteriormente. (En el CIIC se está realizando una evaluación agrupada del riesgo de estudios epidemiológicos de la sílice y el cáncer de pulmón.)

Las estimaciones del riesgo relativas a la prevalencia de la silicosis para la exposición durante toda la vida laboral a concentraciones de polvo de cuarzo respirable de 0,05 ó 0,10 mg/m^3 en el entorno de trabajo varían ampliamente (es decir, 2%-90%). Con respecto a la exposición al cuarzo presente en el medio ambiente general, a partir del análisis de una dosis de referencia se pronosticó que el riesgo de silicosis para una exposición continua durante una vida de 70 años a 0,008 mg/m^3 (concentración de sílice cristalina estimada alta en las zonas metropolitanas de los Estados Unidos) era inferior al 3% para las personas sanas sin otras enfermedades o trastornos del aparato respiratorio y para el medio ambiente (US EPA, 1996). No se evaluó el riesgo de silicosis para las personas con enfermedades respiratorias expuestas al cuarzo en el medio ambiente general.

Hay incertidumbres en la evaluación de los estudios epidemiológicos y en la evaluación del riesgo de los efectos para la salud relacionados con la exposición al polvo de cuarzo. Las dificultades, muchas de las cuales son inherentes al estudio de las enfermedades respiratorias en poblaciones ocupacionales, se deben a limitaciones en la cantidad y la calidad de los datos históricos de exposición, la falta de datos sobre posibles factores de confusión, como por ejemplo el humo de los cigarrillos, y dificultades en la interpretación de las radiografías del tórax como prueba de exposición. Además, las exposiciones ocupacionales al polvo de cuarzo son complejas, porque los trabajadores están expuestos con frecuencia a mezclas de polvo que contienen cuarzo y otras variedades minerales. Las propiedades del polvo (por ejemplo, el tamaño de las

partículas, las propiedades de la superficie, la forma cristalina) pueden variar en función del origen geológico y también pueden cambiar durante la elaboración industrial. Dichas variaciones pueden afectar a la actividad biológica del polvo inhalado. El Grupo de Trabajo del CIIC evaluó la carcinogenicidad de la sílice cristalina (incluido el cuarzo) y se concentró en los estudios epidemiológicos con menor probabilidad de verse afectados por sesgos de confusión y selección en los que se analizaban las relaciones exposición-respuesta (IARC/CIIC, 1997).