4 Experimental Studies

This section provides an abbreviated review of various experimental research studies. The reader is encouraged to consult the cited materials for complete information.

4.1 Biomarkers

A biomarker can indicate (1) the occurrence of exposure, (2) the effects of exposure, (3) the presence of early or frank disease, or (4) the susceptibility to disease or early effects of exposure [Committee on Biological Markers of the National Research Council 1987; Schulte 1995]. Useful biomarkers require (1) a definitive, validated link with the exposure or the risk of disease and (2) evidence of a dose-response relationship between the marker and the exposure [Schulte 1995]. The relationship between respirable silica dust exposure and silicosis is well established. However, the complex chain of cellular responses that leads to fibrosis and silicosis has not been fully discovered. The usefulness of biomarkers as a screening tool for silicosis risk will be realized when biomarkers in the chain of complex cellular responses are validated for their relationship to disease. In addition, the studies of blood, serum, sputum, bronchoalveolar lavage samples, and gene patterns of silica-exposed workers or silicotics (Table 20) are inconclusive for the following reasons:

1. The numbers of subjects are small, and few studies of similar markers exist for comparison.

2. The studies lack control for factors other than silica exposure that could change immunoglobulin concentrations.

3. The studies lack information about control groups, diagnostic criteria for silicosis, and baseline levels of markers.

4. Study results are inconsistent.

Further research on biomarkers in silica-exposed workers is needed to do the following:

1. Quantify the exact amount of soluble products in bronchoalveolar lavage in individual patients to provide more information about the mechanisms of fibrogenesis [Sweeney and Brain 1996]

2. Determine whether silicosis or silica-related lung cancers are associated with a specific gene or gene pattern

3. Determine whether a relationship exists between changes in immunoglobulin concentrations and silica exposure

4. Determine whether a dose-response relationship exists between changes in certain cellular components (lymphocytes and Clara cell protein) and silica exposure

Detailed reviews of the immunologic response to silica and other mineral dusts are available elsewhere (i.e., Heppleston [1994]; Haslam [1994]; Weill et al. [1994]; Davis [1991,1996]; Kane [1996]; Driscoll [1996]; Sweeney and Brain [1996]; Hook and Viviano [1996]; Gu and Ong [1996]; Iyer and Holian [1996]; Weissman et al. [1996]; Mossman and Churg [1998]).

Table 20. Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Bernard et al. [1994], Belgium	Belgium quarry workers who had worked <2 yr. Controls were manual workers without silica dust exposure, matched by smoking status, body mass index, and age.	86 quarry workers and 86 controls	Serum and sputum Clara cell protein (Clara cell 16)	Decreased concentrations of serum and sputum Clara cell protein in quarry workers (P=0.04) compared with controls.	Controls may have been exposed to silica dust. Short duration of exposure among quarry workers may have limited the analysis. Authors state that serum Clara cell 16 may be marker for toxic effects of silica particles on respiratory epithelium.
Borm et al. [1986], Netherlands	Male silicosis patients at a hospital in the Netherlands; exposed to silica for 10–38 yr. Controls were "healthy male, Caucasian blood donors" aged 50–65.	20 silicosis patients (15 coal miners, 4 ceramics workers, 1 foundry worker); 48 controls	Blood and plasma concentrations of hemoglobin, reduced and oxidized glutathione, glutathione peroxidase, and superoxide dismutase	Silicosis patients had significantly higher concentrations of red blood cell glutathione (P<0.0001).	Small number of subjects. Controls were not interviewed for their occupational history, and definition of "healthy" was not reported. Medication administered to patients may have been a confounder.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Brandt-Rauf et al. [1992], Finland	Prospective study of compensated pneumoconiosis patients; 91 blood samples were collected between 1983 and 1987. Cancer cases were identified in the Finnish Cancer Registry. 4 silicotics had worked as stone workers, 1 as a stone crusher, 2 as miners, and 3 as foundry workers. 3 silicotics with lung cancer were matched by age and smoking habits with 7 controls without cancer.	46 patients: 36 with asbestosis and 10 with ILO† category ≥1/1 silicosis	9 serum oncogene-related proteins or growth factors: growth factor PDGF-B (*sis*), TGF-β_1, *ras*, *fes, myb*, *int-1, mos, src, myc*	7/15 asbestosis patients had *ras* (p21) oncogene, but no oncogene-related proteins were found in the 10 silicosis patients. All silicosis patients had PDGF-B (*sis*) growth factor; only 42% of asbestosis patients had PDGF-B (*sis*).	Prospective study found that 3 of the 10 silicosis patients developed cancer during the study period (1983–1987). 2 patients had bladder cancer and 1 had lung cancer. PDGF may be a possible marker for development of severe or progressive silicosis. Study results suggest different pathogeneses for silicosis and asbestosis.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Calhoun et al. [1986], United States	Healthy, male, employed granite workers (non-smokers) with no clinical or radiographic evidence of silicosis. Volunteer controls of similar age and smoking history with no history of occupational exposure to dust. All workers and controls had BAL.	9 workers and 9 controls	IgG, IgM, IgA, albumin, and total protein (all were measured in BAL fluid and serum)	No significant differences in mean serum concentrations between workers and controls. Statistically significant differences (i.e., higher concentration) between IgG, IgA, IgM concentrations and lymphocyte counts in lavage fluid of workers compared with controls.	Authors concluded that inhalation of granite dust might initiate and sustain an immune-inflammatory response.
Gáliková [1982], Slovakia	Miners, drillers, and tunnelers, half with silicosis, aged 43–81, exposed 2–30 yr. Control group of healthy blood donors aged 42–82 with no history of exposure to inorganic dusts.	40 workers and 40 controls	Serum IgG, IgM,and IgA	No difference in IgM concentration. Significantly elevated average concentration of IgG in workers compared with controls ($P<0.001$). Significantly elevated average concentration of IgA in workers compared with controls ($P<0.05$). No significant differences in IgG, IgM, or IgA between silicotic and non-silicotic workers.	Method of silicosis diagnosis not reported.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Gualde et al. [1977], France	Caucasian silicosis patients (radiographic diagnosis) who had a silica-related occupation for 10–40 yr (38 gold, wolfram, and uranium miners; 35 porcelain workers; 2 quarry workers). "Normal and healthy" Caucasian controls plus second control group of porcelain workers employed 20–40 yr but with no clinical or radiographic signs of silicosis.	75 patients, 160 controls in first group, and 46 in control group of porcelain workers	27 HLA antigens (serum)	Prevalence of B7 antigen was significantly less ($P<0.05$ before correction for multiple comparisons of tested antigens) than in healthy or silica-exposed controls. No other significant differences found between silicotics and controls.	Small number of controls may have resulted in low statistical power to detect any differences after correction for multiple comparisons. Authors suggested that presence of B7 antigen may be related to resistance to development of silicosis. (See also Sluis-Cremer and Maier [1984] later in table.)
Honda et al. [1993], Japan	Japanese silicosis patients who had been sandblasters and who had radiographic evidence of silicosis. Controls were "healthy unrelated Japanese."	46 patients, 315 controls for HLA typing, and 94, 127, 100, or 128 controls for other analyses	HLA-DQ alleles, RFLP patterns, and IGLV gene extracted from peripheral granulocytes (medium not reported)	Some HLA-DQ alleles were more frequent in silicosis patients ($P<0.05$). RFLP pattern of C4A3–C4B5 allotype and IGLV more frequent in silicosis patients ($P<0.05$).	Source and occupational history of control group not reported. Definition of "healthy" not reported. Potential confounders of exposure and immunological outcomes not reported. Authors suggested that their findings indicate that a gene for silicosis may be near the HLA-B locus. Validation of these findings is needed.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Husgafvel-Pursiainen et al. [1997], Finland	Finnish white males with lung cancer (see comments).	5 patients with silicosis and 16 patients with asbestosis	Mutation of p53 gene and serum elevation of p53 protein (serum samples were not available for the silicosis patients)	Two of the five silicosis patients had lung tumors with DNA mutations of the p53 gene.	Subjects for study were drawn from cohort studied by Brandt-Rauf et al. [1992] (described earlier). The results of the serum tests do not support use of p53 assay by itself as a screening tool for lung cancer because only 36% of cancer cases tested positive for the mutant protein. The authors state that it may be a useful biomarker if combined with serum assays for altered oncoproteins as in the study by Brandt-Rauf [1992].
Karnik et al. [1990], India	Male slate pencil workers. Controls with no history of occupational exposure to dust or silica.	130 silica-exposed workers: 80 with ILO category 1, 2, or 3 silicosis and 50 controls	Serum IgG, IgM, and IgA	Higher concentrations ($P<0.05$) of IgG, IgM, and IgA in silicotic workers compared with controls.	Results may have been confounded by bacterial infections in some workers. Authors stated that an increase in immunoglobulin concentrations was not a marker for severity of silicosis.

See footnotes at end of table.

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Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Koskinen et al. [1983], Finland	Finnish male silicosis patients (ILO category ≥1/1) who had been exposed to silica dust ≥10 yr. Non-silicotic controls matched by age (±5 yr), duration of silica exposure (± 5 yr), and work environment. Additional control group of healthy Finnish blood donors.	27 patients; 27 non-silicotic, silica-exposed controls; and 900 blood donor controls	Serum HLA antigens	Higher prevalence of HLA-Aw19 in silicotics compared with non-silicotic, silica-exposed controls (P=0.02). Higher prevalence of HLA-Aw19 in unexposed blood donor group than in silica-exposed controls (P=0.04).	Authors state HLA-Aw19 may be marker for silicosis progression in Finnish population, but larger study groups are needed.
Kreiss et al. [1989a], United States	Silicotic residents from hardrock mining town in Colorado who had mined for 5–58 yr and were aged 30–59 when diagnosed with ILO category ≥1/0 silicosis. Published antigen prevalences of North American whites and international whites used for comparison.	49 silicotics, 1,029 North American controls, and 1,061–1,082 international controls	HLA-A, HLA-B, HLA-DR, and HLA-DQ antigens (blood)	Significantly higher prevalence of A29 and B44 in silicotics compared with two control groups (P<0.05 after correction for num-ber of antigens tested).	Population-based study design. A29 is a component of Aw19 (see Koskinen et al. [1983] above).

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Pevnitskiy et al. [1978], Russia	Male Russian patients aged 30–50 with "Stage I" silicosis who had been employed >10 yr in occupations with exposure to quartz dust (i.e., casting shop cleaners, sandblasters, and molders). Controls were "clinically healthy" Russian male blood donors aged 30–50.	32 silicosis patients and 32 controls	11 HLA antigens (6 on A locus and 5 on B locus) (serum)	Prevalence of HLA–B8 and HLA–B13 in silicotics was twice the prevalence in the control group (*P* value not reported).	Occupational history of control group not reported. Definition of "healthy" not reported. Definition of "Stage I" silicosis not reported. Small number of subjects and controls.
Sluis-Cremer and Maier [1984], South Africa	White South African gold miners who had been exposed to at least 20 "low-dust" years. Control group of Caucasian nonminers.	101 miners (45 silicotics of category ≥1/0 and 56 nonsilicotics) and 279 controls	29 HLA antigens (medium not reported)	Significantly fewer silicotics had B40 antigen compared with both silica-exposed and nonexposed comparison groups (P=0.02).	Source of control group not reported. No significant difference was found in the prevalence of B7, which does not agree with the findings of Gualde et al. [1977] (discussed earlier).
Sobti and Bhardwaj [1991], India	Male sandstone-crushing workers. Control group of local university teachers and students.	50 workers and 25 controls	Blood: SCE and CA	Higher proportion of SCE and CA in silica-exposed workers compared with controls (2.72% versus 1.28%; P<0.01). More SCEs (P<0.01) in smokers—both silica-exposed and nonexposed.	Dust contained 50%–60% crystalline silica, 14%–16% aluminum oxide, and 4%–5% iron oxide. Possible effect of socioeconomic differences between workers and control group not accounted for. No statistical test for correlation between duration of exposure and levels of SCE and CA. Silica exposure concentrations not reported.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Watanabe et al. [1987], Japan	Males aged 34–78, hospitalized with ILO category ≥2 silicosis and employed as tunnel workers or metal miners for a mean duration of 23.8 yr. "Normal" male controls aged 46–72 without silicosis.	82 patients and 25 controls	Total blood lymphocyte count and lymphocyte subsets: OKT3+, OKT4+, OKT8+, OKIa–1+ Serum IgG, IgM, IgA, IgD, and IgE	Silicosis patients with low lymphocyte counts (≤1,500 µl) had significantly increased IgG and IgA levels compared with controls (P<0.001). Decreased number of circulating T-cells in patients.	Source and occupational history of control group not reported. Definition of "normal" controls not reported. Potential confounders of exposure and immunological outcomes not reported. Need further study of relationship of silicosis with serum immunoglobulin levels and lymphocytes.

*Studies were cross-sectional unless otherwise indicated.

†Abbreviations: BAL = bronchoalveolar lavage; CA = chromosomal aberrations; HLA = human leukocyte antigen; Ig = immunoglobulin; IGLV = immunoglobulin lambda variable chain; ILO = International Labour Organization; PDGF = platelet-derived growth factor; RFLP = restriction fragment length polymorphism; SCE = sister chromatid exchange; TGF = transforming growth factor.

4.2 Cytotoxicity

Respirable crystalline silica is known to cause silicosis; however, the molecular mechanism responsible for the cellular injury that precedes the lung disease is unknown. Extensive in vitro and in vivo research has been conducted to evaluate the effects of crystalline silica on mammalian cells. Several mechanisms have been proposed to explain the cause of the cellular damage [Lapp and Castranova 1993]:

1. Direct cytotoxicity of crystalline silica

2. Stimulation of the alveolar macrophages by silica and subsequent 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, tumor necrosis factor, platelet-derived growth factor) that recruit polymorphonuclear leukocytes, which in turn may release cytotoxins

4. Stimulation of the alveolar macrophages to release factors that initiate fibroblast production and collagen synthesis (e.g., interleukin-1, tumor necrosis factor, platelet-derived growth factor, fibronectin, and alveolar macrophage-derived growth factor)

4.3 Genotoxicity and Related Effects

Some studies have demonstrated the ability of quartz to induce micronuclei in mammalian cells in culture [Hesterberg et al. 1986; Nagalakshmi et al. 1995; Oshimura et al. 1984] (Table 21). However, other in vitro studies did not observe chromosomal aberration [Nagalakshmi et al. 1995; Oshimura et al. 1984], *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]. An in vivo treatment of rats with quartz induced mutation in rat alveolar epithelial cells (Table 21) [Driscoll 1995; 1997].

Pairon et al. [1990] tested tridymite (i.e., Tridymite 118) and quartz (i.e., Min-U-Sil 5) particles for genotoxic effects. Tridymite induced a significant number of sister chromatid exchanges (SCEs) in co-cultures of human lymphocytes and monocytes ($P<0.05$ compared with control cells) at doses of 5 and 50 µg/cm^2 (87.9% of the tridymite particles had a diameter <1 µm). However, the number of SCEs in purified human lymphocytes that were treated with the same doses of tridymite particles did not differ significantly from control cells [Pairon et al. 1990]. Results of the same experiments with quartz did not yield a clear conclusion about the ability of quartz to induce a significant number of SCEs (Table 21) [Pairon et al. 1990].

In vitro cellular transformation systems model the in vivo process of carcinogenesis [Gao et al. 1997; Gu and Ong 1996]. 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 and Barrett 1984] and mouse embryo BALB/c-3T3 cells [Saffiotti and Ahmed 1995]. Gu and 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 crystalline silica can morphologically transform mammalian cells. However, further studies are needed to determine whether the transforming activity of silica is related to its carcinogenic potential.

Table 21. Summary of the genotoxic effects of quartz in mammalian cells

	In vitro studies		In vivo studies	
Genotoxic effect	Number of positive studies/number of studies available	Reference	Number of positive studies/number of studies available	Reference
Sister chromatid exchange	1*/3	Price-Jones et al. [1980] Pairon et al. [1990] (2 experiments)	1*/1	Sobti and Bhardwaj [1991]
Chromosomal aberrations	0/3	Nagalakshmi et al. [1995] (2 experiments) Oshimura et al. [1984]	1*/1	Sobti and Bhardwaj [1991]
Micronuclei	3/4	Oshimura et al. [1984] Hesterberg et al. [1986] Nagalakshmi et al. [1995] (2 experiments)†	0/1	Vanchugova et al. [1985]
Aneuploidy or tetraploidy	0/3	Price-Jones et al. [1980]; Oshimura et al. [1984]; Hesterberg et al. [1986]	0/0	
hprt mutation‡	0/1	Driscoll et al. [1997]	2/2§	Driscoll et al. [1995, 1997]

Source: IARC [1997].
*One questionably positive study available.
†One experiment by Nagalakshmi et al. [1995] showed an increase in the frequency of micronucleated cells at all concentrations tested, but the increase was statistically significant ($P<0.05$) only at the two highest concentrations tested.
‡*hprt* = hypoxanthine-guanine phosphoribosyl transferase.
§Mutagenic response associated with inflammation.

Researchers at the National Cancer Institute have examined the ability of quartz, cristobalite, and tridymite particles to cause deoxyribonucleic acid (DNA) damage (i.e., strand breakage) [Saffiotti et al. 1993; Shi et al. 1994; Daniel et al. 1993; Daniel 1993, 1995]. Although the results of those studies demonstrated the ability of crystalline silica to cause damage to isolated DNA in acellular systems, reviewers at IARC [1997] recently stated that the relevance of these assays to assess quartz-related genetic effects in vivo was "questionable" because (1) the nonphysiological experimental conditions did not apply to intracellular silica exposure and (2) very high doses of silica were used in the DNA breakage assays [IARC 1997].

Several studies conducted since the IARC review found that crystalline silica induced DNA damage (i.e., DNA migration). Zhong et al. [1997] found that by using the alkaline single cell gel/comet (SCG) assay, crystalline silica (Min-U-Sil 5) induced DNA damage in cultured Chinese hamster lung fibroblasts (V79 cells) and human embryonic lung fibroblasts (Hel 299 cells) [Zhong et al. 1997]. Amorphous silica (Spherisorb), but not carbon black, was also found to induce DNA damage in these mammalian cells. However, the DNA-damaging activity of amorphous silica was not as high as the damaging activity of crystalline silica [Zhong et al. 1997]. Liu et al. [1996, 1998] challenged Chinese hamster lung fibroblasts 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, Min-U-Sil 10, and noncrystalline silica 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 intracellular digestion [Liu et al. 1998].

Shi et al. [1998] recently reviewed published literature on (1) the generation of reactive oxygen species (ROS) directly from silica and from silica-stimulated cells, (2) the role of ROS in silica-induced DNA damage and silica-induced cell proliferation, and (3) other silica-mediated reactions. A proposed mechanism for silica-induced generation of ROS species and carcinogenesis is described by Shi et al. [1998]. Experimental research is continuing to determine whether crystalline silica particles have a direct genotoxic effect that could cause lung tumor formation in humans.

4.4 Carcinogenicity

Experimental evidence of the carcinogenicity of quartz particles is based on the results of long-term inhalation and intratracheal instillation studies of rats, which are summarized in Tables 22 and 23 [Saffiotti et al. 1996]. Several issues are apparent from the results of the rat studies [Holland 1995]:

1. The appearance of tumors (usually adenocarcinomas or epidermoid carcinomas) is a late phenomenon.

2. Lung fibrosis is usually present in the rats with tumors.

3. No adequate dose-response data exist because multiple-dose experiments have not been conducted in the rat except for the inhalation study by Spiethoff et al. [1992].

4. Comparability of the intratracheal instillation and inhalation studies is difficult because of notable differences in methods and materials.

Table 22. Summary of data on lung tumors induced in rats by crystalline silica

Sample and exposure conditions	Rat strain	Sex	Incidence of lung tumors*		Reference	Comments
			Treated rats	Controls		
Quartz (Min-U-Sil 5):						
Intratracheal instillation of 7 mg/wk for 10 wk	Sprague-Dawley	—†	6/36	0/58	Holland et al. [1983]	Treated rats had 1 adenoma and 5 carcinomas.
Inhalation (nose only) of 12 ± 5 mg/m^3 for up to 2 yr	Fischer 344	F	20/60	0/54	Holland et al. [1986]	Treated rats had 6 adenomas, 11 adenocarcinomas, and 3 epidermoid carcinomas.
Inhalation of 51.6 mg/m^3 for various durations; sacrificed at 24 months	Fischer 344	F M	10/53 1/47	0/47 0/42	Dagle et al. [1986]	Treated female rats had 10 epidermoid carcinomas. Treated male rats had 1 epidermoid carcinoma.
Intratracheal instillation of 20 mg in left lung; sacrificed at 12, 18, or 22 months, or found dead	Fischer 344	M	30/67	1/75	Groth et al. [1986]	Treated rats had 30 adenocarcinomas. Controls had 1 adenocarcinoma.
Novaculite (i.e., microcrystalline quartz):						
Intratracheal instillation of 20 mg in left lung; sacrificed at 12, 18, or 22 months, or found dead	Fischer 344	M	21/72	1/75	Groth et al. [1986]	Treated rats had 20 adenocarcinomas and 1 epidermoid carcinoma. Controls had 1 adenocarcinoma.
Raw shale dust:						
Inhalation (nose only) of 152 ± 51 mg/m^3 (average quartz content: 8%–12%)	Fischer 344	F	17/59	0/54 1/15‡	Holland et al. [1986]	Treated rats had 2 adenomas, 8 adenocarcinomas, and 7 epidermoid carcinomas. Controls had 1 adenoma.

See footnotes at end of table.

(Continued)

Table 22 (Continued). Summary of data on lung tumors induced in rats by crystalline silica

Sample and exposure conditions	Rat strain	Sex	Incidence of lung tumors* Treated rats	Incidence of lung tumors* Controls	Reference	Comments
Spent shale dust:						
Inhalation (nose only) of 176 ± 75 mg/m^3 (average quartz content: 8%–12%)	Fischer 344	F	11/59	0/54 1/15‡	Holland et al. [1986]	Treated rats had 2 adenomas, 8 adenocarcinomas, and 1 epidermoid carcinoma. Controls had 1 adenoma.
Quartz (DQ12):						
Inhalation of 1 mg/m^3 for 24 months	Fischer 344	F	12/50	3/100 (male and female)	Muhle et al. [1989]	Treated female rats had 2 keratinizing cystic squamous cell tumors, 2 adenomas, and 8 adenocarcinomas. Treated male rats had 2 keratinizing cystic squamous cell tumors, 2 adenocarcinomas, 1 adenosquamous carcinoma, and 1 squamous cell carcinoma. Controls had 2 adenomas and 1 adenocarcinoma.
	Fischer 344	M	6/50	—		
Inhalation (nose only) of 6 mg/m^3 for 29 days followed by lifetime observation	Wistar	F	62/82	0/85	Spiethoff et al. [1992]	Treated rats had 8 adenomas, 17 bronchioloalveolar carcinomas, and 37 squamous cell carcinomas.
Inhalation (nose only) of 30 mg/m^3 for 29 days followed by lifetime observation	Wistar	F	69/82	0/85	Spiethoff et al. [1992]	Treated rats had 13 adenomas, 26 bronchioloalveolar carcinomas, and 30 squamous cell carcinomas.

Source: Adapted from Saffiotti et al. [1996].
*Number of lung tumors per number of rats observed.
†Not reported.
‡Investigators used two control groups.

Table 23. Lung tumors induced in Fischer 344 rats by a single intratracheal instillation of quartz

Treatment sample and dose*	Sex	Observation time	Incidence of lung tumors		Total number of lung tumors‡	Histological types
			Number†	%		
Untreated:						
No dose	M	Died after 17 months	0/32	—	0	—
No dose	F	Died after 17 months	1/20	5	1	1 adenoma
Quartz (Min-U-Sil 5):						
12-mg dose	M	Sacrificed at 11 months	3/18	17	37	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, and 3 epidermoid carcinomas
		Sacrificed at 17 months	6/19	32		
		Died after 17 months	12/14	86		
12-mg dose	F	Sacrificed at 11 months	8/19	42	59	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, and 3 epidermoid carcinomas
		Sacrificed at 17 months	10/17	59		
		Died after 17 months	8/9	89		
20-mg dose	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 dose	M	Sacrificed at 11 months	2/18	11	20	5 adenomas, 14 adenocarcinomas, and 1 mixed carcinoma
		Sacrificed at 17 months	7/19	37		
		Died after 17 months	7/9	78		
12-mg dose	F	Sacrificed at 11 months	7/18	39	45	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, and 5 epidermoid carcinomas
		Sacrificed at 17 months	13/16	81		
		Died after 17 months	8/8	100		

Sources: Saffiotti et al. [1993; 1996].
*As mg quartz suspended in 0.3 ml saline.
†Number of rats with lung tumors per number of rats observed.
‡At all observation times.

Although new long-term carcinogenesis studies in animals may provide information about dose-response relationships and inhibition of quartz toxicity or reactivity in vivo, in vitro studies are needed to develop effective cellular and molecular models of carcinogenesis [Holland 1995; Saffiotti et al. 1996].