Arch Toxicol (2002) 75: 625–634
DOI 10.1007/s002040100266

REVIEW ARTICLE

R. Merget · T. Bauer · H. U. Küpper · S. Philippou
H. D. Bauer · R. Breitstadt · T. Bruening

Health hazards due to the inhalation of amorphous silica

Received: 31 May 2001 / Accepted: 21 June 2001 / Published online: 29 November 2001

Abstract Occupational exposure to crystalline silica dust is associated with an increased risk for pulmonary diseases such as silicosis, tuberculosis, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and lung cancer. This review summarizes the current knowledge about the health effects of amorphous (non-crystalline) forms of silica. The major problem in the assessment of health effects of amorphous silica is its contamination with crystalline silica. This applies particularly to well-documented pneumoconiosis among diatomaceous earth workers. Intentionally manufactured synthetic amorphous silicas are without contamination of crystalline silica. These synthetic forms may be classified as (1) wet process silica, (2) pyrogenic (''thermal'' or ''fumed'') silica, and (3) chemically or physically modified silica. According to the different physicochemical properties, the major classes of synthetic amorphous silica are used in a variety of products, e.g. as fillers in the rubber industry, in tyre compounds, as free-flow and anti-caking agents in powder materials, and as liquid carriers, particularly in the manufacture of animal feed and agrochemicals; other uses are found in toothpaste additives, paints, silicon rubber, insulation material, liquid systems in coatings, adhesives, printing inks, plastisol car undercoats, and cosmetics. Animal inhalation studies with intentionally manufactured synthetic amorphous silica showed at least partially reversible inflammation, granuloma formation and emphysema, but no progressive fibrosis of the lungs. Epidemiological studies do not support the hypothesis that amorphous silicas have any relevant potential to induce fibrosis in workers with high occupational exposure to these substances, although one study disclosed four cases with silicosis among subjects exposed to apparently non-contaminated amorphous silica. Since the data have been limited, a risk of chronic bronchitis, COPD or emphysema cannot be excluded. There is no study that allows the classification of amorphous silica with regard to its carcinogenicity in humans. Further work is necessary in order to define the effects of amorphous silica on morbidity and mortality of workers with exposure to these substances.

Keywords Non-crystalline · Amorphous · Silica, Silicosis · Bronchitis · Emphysema · Airway disease · Carcinoma

R. Merget (✉) · T. Bruening
Research Institute for Occupational Medicine (BGFA),
Buerkle-de-la-Camp-Platz 1, 44789 Bochum, Germany
E-mail: merget@bgfa.de
Tel.: +49-23-43074546
Fax: +49-23-43074505

T. Bauer
Bergmannsheil, University Hospital,
Department of Internal Medicine,
Division of Pneumonology,
Allergology and Sleep Medicine, Bochum, Germany

H. U. Küpper · R. Breitstadt
Degussa-Hüls Corporation,
Wesseling and Frankfurt am Main, Germany

S. Philippou
Department of Pathology,
Augusta Krankenanstalten, Bochum, Germany

H. D. Bauer
Research Institute for Hazardous Substances (IGF),
Bochum, Germany

Introduction

Recently, the American Thoracic Society has reviewed a great number of studies on the adverse health effects of crystalline silica (American Thoracic Society 1997). The most prominent effects of exposure to crystalline silica are silicosis, tuberculosis, chronic bronchitis/chronic obstructive pulmonary disease (COPD) and lung cancer. A review of the health effects of amorphous silica with particular reference to cancer has been published recently (McLaughlin et al. 1997). The authors concluded that epidemiological investigations for any potential cancer risk were not informative because the effects of

crystalline and amorphous silica have not been separated. In the same year, amorphous silicas were considered not classifiable with regard to their carcinogenicity in humans by the International Agency for Research on Cancer (1997). Both reviews focused on carcinogenicity. The present review concentrates on the definition, classification, uses and pulmonary effects of amorphous silica and describes in more detail the data on synthetic amorphous silica not contaminated with crystalline silica.

Definition and use of amorphous silica

Silica is the common name for silicon dioxide (SiO_2). Silica may have a crystalline or a non-crystalline (amorphous) structure. In crystalline silica, the silicon and oxygen atoms are arranged in a fixed geometric pattern. In contrast, in amorphous silica no spatial ordering of the atoms is present. The most common form of crystalline silica is quartz, but cristobalite, tridymite and others also have crystalline structures. Amorphous silica may be divided into (1) naturally occurring silica, (2) silica obtained under uncontrolled conditions, and (3) intentionally manufactured synthetic silica.

1. The most important naturally occurring amorphous silica is diatomaceous earth whose particles are the fossil skeletons of microscopic marine plants known as diatoms. Dust from uncalcined diatomaceous earth was reported to contain between 0.1 and 4% crystalline silica, whereas processing (particularly calcining) leads to contamination with crystalline silica such as cristobalite up to 60% (International Agency for Research on Cancer 1997; Hughes et al. 1998). Exposure to other naturally occurring biogenic (originating in living matter) amorphous silicas has been described in farmers during harvesting, crop burning or incineration (Rabovsky 1995).
2. ''Fused'' silica is silica heated to a liquid phase and cooled down without allowing it to crystallize (silica glass). The processing of these silicas leads to exposure to crystalline forms of silica. Contamination with crystalline silica occurs also in fly-ashes from power stations or silica fumes due to metallurgical processes such as the production of ferrosilicon.
3. The group of amorphous silica produced under controlled conditions may be classified as:
   i) Wet process silica, i.e. precipitated silica and silica gels
   ii) Pyrogenic (''thermal'' or ''fumed'') silica
   iii) After-treated silica, e.g. chemically modified, surface-coated or physically treated silica.

None of these intentionally manufactured synthetic amorphous silicas contain crystalline silica.

The wet manufacturing process carried out in aqueous solution or dispersion (alkali metal silicate solution) may provide two different kinds of synthetic amorphous silicas, namely precipitated silica and silica gels. Pyrogenic silicas are obtained by decomposition of a precursor from a vapour or gas phase at elevated temperature (Legrand 1998). All kinds of synthetic amorphous silicas can be after-treated either physically, chemically, or by surface modification. The methods of after-treatment are various and depend on the product application (Ferch and Toussaint 1996).

Depending on the manufacturing process, amorphous silicas have a wide range of physico-chemical properties (Table 1). The major applications depend upon the silica type (Table 2). Approximately 60% of precipitated silicas are used as fillers in the rubber industry. Increasing amounts are used in tyre compounds for reduced rolling resistance and better wet-grip ''green'' tyres. They are used as free-flow and anti-caking agents for powder materials and as carriers of liquids which are transformed into free-flowing powders, particularly in the manufacture of animal feed and agrochemicals. Toothpaste, paints, and silicon rubber represent further important applications. More than half of the worldwide pyrogenic silica production is used as reinforcing filler for silicon rubber, a particularly high and low temperature resistant elastomer with major applications in wires, cables and automotive components. High performance thermal insulation materials utilize the low heat conductivity of pyrogenic silica. These substances are also used as thickening and anti-setting agents in liquid systems of coatings, adhesives, printing inks, plastisol car undercoats, cosmetics and many other systems. The high purity makes pyrogenic silica a preferred carrier and free-flow agent for many pharmaceutical and food applications, for toners or fire extinguisher powders.

The estimated 1995 production of amorphous silica was about one million tons (Table 3). The table includes by-products generated in more or less uncontrolled procedures. About 2,400 subjects worldwide are exposed

Table 1 Properties of synthetic amorphous silica. Pyrogenic and precipitated silicas are wet process manufactured. Tables 1–3 were adapted with minor modifications from Ferch and Toussaint (1996) (with permission)

Property	Form of amorphous silica		
	Pyrogenic	Precipitated	Gels
Specific surface area (m^2/g)	50–400	30–800	250–1000
pH	3.6–4.3	5–9	3–8
Primary particle size (nm)	7–50	5–100	3–20
Aggregate size (μm)	< 1	1–40	1–20
Agglomerate size (μm)	1–100	3–100	not applicable
Pore size (nm)	–	> 30	2–20

to intentionally produced amorphous silica at work (European Chemical Industry Council 1996). The number of users exposed to these substances is not known, but it is obviously large.

Human data

Only few studies have evaluated the effects of synthetic amorphous silica with respect to airway or lung diseases. Workplace concentrations were assessed in quite a number of studies, among them a few older ones. The ranges of the median total dust concentrations were reported to be <1 to about 10 mg/m^3 (European Chemical Industry Council 1996; International Agency for Research on Cancer 1997). The following health effects of amorphous silica in humans are discussed in the literature: pneumoconiosis, chronic bronchitis and COPD, bronchiolitis obliterans (BO), and carcinoma.

Pneumoconiosis

Many older studies reported high numbers of workers with pneumoconiosis in the diatomite industry (Table 4). None of these studies can definitely differentiate between crystalline and amorphous silica. Recent studies in diatomaceous earth workers showed a low prevalence of radiographic abnormalities (Harber et al. 1998; Hughes et al. 1998). In one study, 5% of the subjects had profusion scores ≥1/0 according to the classification of the International Labour Office of 1980, and the authors concluded that the lower prevalence of pneumoconiosis compared to (=nowadays lower prev.) earlier studies was due to modern dust control measures (Harber et al. 1998). The hypothesis that contamination with crystalline silica is causative for pneumoconiosis in diatomite-exposed workers is strengthened by the finding that exposure to natural diatomite (little contamination) was associated with simple fibrosis while exposure to calcined diatomite (high contamination) was associated with progressive pulmonary fibrosis (Smart and Andersen 1952; Caldwell 1958; Dutra 1965; Beskow 1978; Omura et al. 1978; Brambilla et al. 1980).

In the few epidemiological studies on workers with long-term exposure to intentionally manufactured synthetic silica (precipitated or pyrogenic), no silicosis was found (Volk 1960; Plunkett and De Witt 1962; Wilson et al. 1979; Ferch et al. 1987a; Choudat et al. 1990). In one study, silicosis caused by amorphous silica obviously not contaminated with quartz was found in 4 of 28 workers (Mohrmann and Kann 1985). However, the authors cannot exclude contamination by small amounts of cristobalite, and detailed information about the amorphous silica origin is not included. In a further study, histological examination of lung biopsies of two subjects with exposure to amorphous silica and a clinical diagnosis of lung fibrosis disclosed non-birefringent material in the vicinity of fibrotic lesions, and birefringent particles were found to a much lesser degree (Philippou et al. 1992). One worker was also exposed to 1–3% of crystalline silica, and no exposure data were provided for the second worker.

Chronic bronchitis and COPD

Information about exposure to amorphous silica and the diagnosis of bronchitis or COPD is sparse. Ferch et al. (1987b) found obstructive and/or restrictive lung

Table 2 Major applications of amorphous silica

Form of amorphous silica	Application	Important properties
Pyrogenic	Silicone rubber reinforcement	Surface area, purity, structure
	Heat insulation	Aggregate size, purity
	Rheology control (numerous liquid systems)	Surface chemistry, aggregate/agglomerate size
Precipitated	Rubber reinforcement	Particle size, surface area, structure
	Free flow, anti-caking	Particle size, spherical form
	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size, particle size, structure
	Paints: matting	Particle size, structure
Gels	Desiccant, adsorbent	Porosity
	Paints: matting	Particle size, pore volume
	Toothpaste: cleaning, rheology control	Particle size, pore volume, hardness

Table 3 Worldwide shares of amorphous silica products (estimation for 1995)

Form of amorphous silica	Production in tons ×10^3	Percentage of total volume	Percentage of total value
Synthetic, produced under controlled conditions			
Pyrogenic	110	10	35
Precipitated	900	82	50
Gels	90	8	15
By-products of technical processes			
Silica fume and fly ashes	2000		

Table 4 Epidemiological studies and case reports on occupational respiratory morbidity in workers exposed to amorphous silica (*A.S.*). Studies on subjects with exposure to amorphous silica not contaminated with crystalline silica are indicated. Only studies reporting the number of the total workforce and those examined were considered cross-sectional. (*BAL* bronchoalveolar lavage, *PC* pneumoconiosis, *N.R.* not reported, *SMR* standardized mortality ratio)

Reference	Study type	Silica type	Study population	Exposure (duration)/ further exposure data	Results
Legge and Rosencrantz 1932	Case series	Diatomite	108 Miners	Detail of exposure N.R.	PC in 75%
Bruce 1937	Cross-sectional	Ferrosilicon alloy	38 (plant 1) 26 (plant 2)	4–8 years 9–22 years	PC in 24% PC in 19%
Vigliani and Mottura 1948	Case series	Diatomite (production of filter-candles)	20 Workers in 2 factories	Exposure duration N.R.; 400–500 particles/cm^3, particle size 0.5–2 μm	PC in 65%
Ebina et al. 1952	Cross-sectional	Diatomite	106 Workers	24 Workers > 10 years	PC in 11%; severe forms (I and II) occurred in 4 subjects exposed > 15 years
Smart and Andersen 1952	Case reports	Diatomite	6 Workers	Variable	PC
Motley et al. 1956	Case series	Diatomite	50 Workers	N.R.	No correlation between lung function and radiographic appearance
Caldwell 1958	Case reports	Diatomite	8 Workers	1–25 years	PC
Cooper and Cralley 1958	Cross-sectional	Diatomite	869 Workers	251 Workers > 5 years	No PC in workers exposed to raw diatomite; PC in 48% with exposure to calcined diatomite
Volk 1960[a]	Case series	Pyrogenic A.S. not contaminated with crystalline silica	215 Workers	Exposure duration N.R.; total dust: filling nozzle 15–100 mg/m^3, bagging room 2–6 mg/m^3, production room 3–7 mg/m^3	No PC in 720 X-rays of 215 workers
Motley 1960	Cross-sectional (selected)	Diatomite	98 Workers	Exposure duration N.R.	Severe changes of lung function in 6%, moderate changes in 14%
Plunkett and De Witt 1962[a]	Case series	Precipitated A.S. not contaminated with crystalline silica	78 Workers	4.7 (1–16) years	No PC
Dutra 1965	Case report	Diatomite	1 Worker	20 years in mill	Severe PC
Swensson et al. 1971	Case series, follow-up of the 1937 Bruce cohort	Ferrosilicon alloy	10 Workers with PC	Variable	PC validated in 1/10 cases X-ray findings of 1937; in 9/10 cases, transient and due to other diseases
Vitums et al. 1977	Cross-sectional	Metallurgical plant	40 Workers	11–18 years "at the previously acceptable atmospheric TLV" for A.S.	PC in 11/40 cases; of 3/11 studied in detail, 2 had impaired lung function, 2 had biopsies showing fibrosis

Cooper and Jacobson 1977	Follow-up of the 1953–54 cohort	Diatomite	428 of 617 Workers with > 5 yrs exposure	Exposure groups: 30% > 20 years	PC in 4.7% with profusion 1/1 or more
Beskow 1978	Case reports	Diatomite	6 Workers	3–20 years	PC
Omura et al. 1978	Case series	Diatomite	162 Workers 81 Controls	Exposure duration N.R.	Mild PC in 18%
Wilson et al. 1979[a]	Case series	Precipitated A.S. not contaminated with crystalline silica	165 Workers	Mean 8.6 years; total dust < 1 mg/m^3**–10 mg/m^3**	No PC in 143 workers with serial X-rays; lung function/symptoms not associated with exposure
Brambilla et al. 1980	Case reports	A.S. in a silicon factory	6 Workers	9–36 yrs	PC
Cooper and Sargent 1984	Follow-up of the 1953–1954 cohort	Diatomite	473 Workers	All workers > 5 years	PC in 2.3% with profusion 1/1 or more; ;PC not occurring before 20 years of service
Robalo-Cordeiro et al. 1985	Case series	Ferrosilicon alloy	14 Workers	Mean 15 years	9/14 with dyspnoe; fibrosis in lung biopsies; BAL: lymphocytic alveolitis
Mohrmann and Kann 1985[a]	Cross-sectional	A.S. not specified but not contaminated with crystalline silica	28 Workers	Mean 9 years; mean respirable dust: 1979, 1.23 mg/m^3**; 1984, 1.05 mg/m^3**	PC in 4 workers
Ferch et al. 1987a[a]	Case series	Pyrogenic A.S. not contaminated with crystalline silica	143 Workers	1–34 years	No correlation between symptoms and exposure; no PC; impaired lung function due to smoking
Puntoni et al. 1988	Cohort mortality	Refractory brick	231 Workers	N.R.	Excess of bronchial carcinoma; among silicotics excess of death, respiratory tract cancer (larynx), cardiovascular diseases, non-malignant respiratory diseases
Choudat et al. 1990[a]	Cross-sectional (selected)	Precipitated A.S. not contaminated with crystalline silica	41 Workers, 90 controls	8 (1–28) years; inhalable dust 0–10.5 mg/m^3**, respirable dust 0–3.4 mg/m^3**	Questionnaire, blood gas analyses, X-rays comparable; reduced expiratory flows not associated with exposure
Philippou et al. 1992	Case reports	A.S. not specified	2 Workers with lung fibrosis	12 and 15 years	Histological investigation: fibrosis due to A.S.
Checkoway et al. 1993	Cohort mortality	Diatomite	2570 Workers	4 (1–46) years	Increased SMR for non-malignant respiratory diseases and lung cancer
Corhay et al. 1995	Cross-sectional (only 26.8% participated)	Blast-furnace	47 Workers 45 controls	All > 15 years	Higher number of nonfibrous particles in BAL
Spain et al. 1995	Case report	Animal feed industry; A.S. not specified	1 Worker	N.R.	Bronchiolitis obliterans; silica in lung biopsy
Harber et al. 1998	Case series	Diatomite	492 Workers	14.4 ± 10.2 years	5% PC with profusion 1/0 or more; lung function not associated with exposure
Hughes et al. 1998	Case series	Diatomite	1809 Workers	Complex exposure assessment	Dose-response relationship for crystalline silica (PC)

[a] This reference did not consider A.S contaminated by crystalline silica

Table 5 Animal studies on inhaled amorphous silica (*A.S.*). Note that, in contrast to the human data in Table 4, only studies with amorphous silica probably not contaminated with crystalline silica were included. (*N.R.* not reported, *n.s.* not further specified, *BAL* bronchoalveolar lavage, *MMAD* mass median aerodynamic diameter)

Reference	Animals		Exposure				Effects		
	Species	*n* (controls)[a]	Silica type	Concentration (mg/m^3)	Particle Size (μm)	Maximal duration of exposure	Bronchitis/ Emphysema	Interstitial lung disease	Others/Comments
Gärtner 1952	Rabbits	50 (0)	Aerosil (n.s.)	N.R.	0.01–0.05	1100 days (5 days/week, 5 h/day)	Desquamative catarrh, significant emphysema, bronchiolitis obliterans (some)	Macrophage granulomas; no fibrosis	
Klosterkötter 1953	Rats	6 (0)	Aerosil (n.s.)	N.R.	N.R.	300 days (7 days/week, 2–3 h/day)	Small subpleural areas of atelectasis	Low grade perivascular fibrosis in 3 animals	One animal with purulent hilar lymph node
Schepers et al. 1957a	Rabbits	10 (50)	Pyrogenic silica	About 53	About 0.02[b]	12 months (5 days/week, 8 h/day)	Emphysema, peribronchial cellular catarrh	Mural cellular infiltration; some deposition of collagen; no radiographic PC	Regression after discontinuation of exposure, but persistent minor focal alveolar mural collagen; high fatality rate not due to pulmonary effects
Schepers et al. 1957b	Guinea-pigs	50 (0)	Pyrogenic silica	About 53	About 0.02[b]	24 months (5 days/week, 8 h/day)	Emphysema; bronchiolar and ductal stenosis	Reversible periductal and peribronchiolar intra-alveolar accumulation of giant cells; some cellular infiltration	No lymphoid tissue reaction; no disability of the animals
Schepers et al. 1957c	Rats	65 (0)	Pyrogenic silica	About 53	About 0.02[b]	24 months (5 days/week, 8 h/day)	High fatality rate due to emphysema without bronchitis or bronchiolitis	Complex tissue infiltration; some perivascular granulomas; some reticulum deposition	Reversal of emphysema after discontinuation of exposure
Schepers 1959	Rabbits	65 (controls n.s.)	Precipitated A.S.	28 135 364	about 0.02	24 months (5 days/week, 8 h/day)	Emphysema	Radiographs showed mottled shadows which disappeared after discontinuation of exposure	Effects dose-related, cardiac function suppressed also with lowest concentration
Schepers 1962	Monkeys	4 5 5 (15)	Quartz Fibre-glass Precipitated A.S.	245 164 15	3 8 0.02	27 months 8 months 12 months (5 days/week, 8 h/day)	Emphysema	Alveolar wall sclerosis; in contrast to quartz no PC	Lymph node enlargement; vascular occlusion; pleural adhesions; cor pulmonale
Klosterkötter 1965	Rats	235 (0) 120 (0)	Aerosil R 972 Standard Aerosil	80 45	About 0.02 0.01–0.05	12 months (4 h/day)	Desquamative catarrh, perifocal emphysema	Granulomas with small number of fibroblasts; some collagen formation; regression post-exposure	Lymph node enlargement; effects of standard Aerosil greater than with Aerosil R972

Schepers and Dunnom 1981	Rats Guinea-pigs Rabbits	Total 270 (226)	Precipitated A.S. (Hi-Sil 233)	126	0.0225–0.035[b]	24 months (8 h/day)	Transient alveolar hyperinflation especially in rats	Macrophage accumulation in various tissues especially in guinea-pigs and rabbits; some reticulum deposition in interstitial tissues disappeared on cessation of exposure	No radiographic signs of lung disease
Groth et al. 1981	Rats	Per group: 80 (80)	s. gel	15	0.27	18 months	Cell aggregates in respiratory bronchioles	Macrophage and mononuclear cell aggregates mainly in monkeys; collagen fibres mainly in monkeys, almost exclusively with fumed silica; early nodular fibrosis (rats and monkeys)	Lung function affected to variable degrees; more alterations in monkeys; fumed silica more potent
	Guinea-pigs	Per group: 20 (20)	Precipitated A.S.		0.38	(5 days/week, 6 h/day)			
	Monkeys	Per group: 10 (10)	Fumed silica		0.17				
Reuzel et al. 1991	Rats	Per group: 140 (140)	Aerosil 200 Aerosil R 974 Sipernat 22S Quartz	Up to 31.0 34.7 34.9 58.5	0.012[b] 0.012[b] 0.018[b] 8[b]	13 weeks (5 days/week, 6 h/day)	N.R.	Granulomas, macrophage aggregates; increase in fibrotic tissue	Changes with A.S. reversed, but not with quartz; silicotic nodules only with quartz
Lee and Kelly 1993	Rats	Per group: 25 (25)	Ludox	10.1 50.5 154	3.7 (MMAD) 3.3 (MMAD) 2.9 (MMAD)	4 weeks (5 days/week, 6 h/day)	N.R.	1/10 animals and 3/10 animals in 50 and 150 mg/m^3 group showed silicotic nodules; no to minimal collagen fiber deposition	With the exception of few particle-laden macrophages no adverse effects with 10 mg/m^3
Lewinson et al. 1994	Rats	10 (0)	Aerosil R 972	Up to 477	2.9 (MMAD)	4 h	N.R.	N.R.	Only gross pathology
Warheit et al. 1995	Rats	Per group: 24 (0)	Cristobalite	10, 100	3.4–3.6	Several studies up to 4 weeks	N.R.	N.R.	Inflammatory markers in BAL less pronounced and transient with A.S.
			Quartz (Min-U-Sil)	100	3.3–3.5	(5 days/week, 6 h/day)			
			A.S. (Zeofree 80)	10, 100	2.4–3.4				
			Ludox	10, 50, 150	2.9–3.7 (all MMAD)				

[a]The number indicates the total number of exposed animals, with number of control animals in parentheses
[b]Additional information of the aggregate size was provided

function impairment associated with confounding factors (smoking) but not with exposure to Aerosil, a pyrogenic amorphous silica (Ferch et al. 1987b). Choudat et al. (1990) reported a reduction of forced expiratory flow in the group exposed to precipitated amorphous silica compared to a control group, but there was no correlation between the extent of exposure and pulmonary function. The authors concluded that smoking and exposure to amorphous silica have synergistic effects on the development of small airway diseases. Wilson et al. (1979) failed to show a significant association between the degree of exposure to precipitated amorphous silica and the annual change in lung function.

Bronchiolitis obliterans (BO)

Recently, a case report of BO was published by Spain et al. (1995). An animal feed worker was exposed to a large number of agents (microorganisms, proteolytic enzymes, various organic substances) including possibly amorphous silica. No information about exposure to crystalline silica was provided. The authors suspected amorphous silica as the cause of BO because silica was found in an open lung biopsy. However, it is not mentioned whether the silica in the lung tissue was of crystalline or amorphous origin.

Carcinoma

Two cohort mortality studies in the diatomaceous earth industry (Checkoway et al. 1993) and a refractory brick factory (Puntoni et al. 1988) found an increased risk of bronchial carcinoma. However, neither study examined mortality by the type of silica (amorphous or crystalline) or by the exposure level, thus an independent effect of amorphous silica cannot be determined.

Regulations

The regulatory issue of silica exposure has been reviewed by the IARC (International Agency for Research on Cancer 1997). There is a tendency to set separate limits for the various kinds of amorphous silicas. For intentionally produced synthetic amorphous silicas, the exposure limits in different countries vary between 4 mg/m^3 (Germany) and 10 mg/m^3 (USA, France). The threshold limit value (TLV) for amorphous silica has been set to 10 mg/m^3 of total dust in the USA, a value also assigned to nuisance dust (American Conference of Governmental Industrial Hygienists 1987). In Germany, two limit values for amorphous silica were stipulated at the end of the 1980s. The first one of 0.3 mg/m^3 for respirable dust applies to silica fume, calcined diatomaceous earth and silica produced under uncontrolled conditions (Deutsche Forschungsgemeinschaft 1989). For intentionally manufactured amorphous silica and uncalcined diatomaceous earth, the MAK (Maximale Arbeitsplatz-Konzentration, maximum workplace concentration) was set to 4 mg/m^3 for the inhalable dust fraction. The TLV for the avoidance of skin and eye irritation has been set to even lower values (0.2 mg/m^3, twice the value for quartz) (Ratney 1988). Whether these concentrations imply a health risk has to be shown by further epidemiological studies that are currently being performed in Germany.

Animal experiments

The health effects of amorphous silica with regard to carcinogenicity were reviewed recently (Lewinson et al. 1994; International Agency for Research on Cancer 1997; McLaughlin et al. 1997). The present review on animal experiments is therefore restricted to the adverse non-malignant effects of inhaled amorphous silica on the lung (Table 5).

Short-term inhalation studies on rats with amorphous silica showed transient pulmonary inflammatory responses at 24 h, but not 8 days after exposure (Warheit et al. 1995). This was in contrast to crystalline silica that produced persistent neutrophil recruitment and cytotoxic effects.

Long-term animal inhalation experiments performed with amorphous silica showed some differences between species. Inhalation studies in monkeys, rats and guinea-pigs with different amorphous silicas for about 1 year at concentrations of 15 mg/m^3 showed particle-laden macrophage and mononuclear cell infiltrates together with collagen formation in monkeys, but to a much lower extent in rats or guinea-pigs (Groth et al. 1981). Differences between animal species were confirmed in another study showing less macrophage reaction in rats than in guinea-pigs and rabbits, whereas guinea-pigs showed less alveolar hyperinflation (Schepers and Dunnom 1981). In addition, the location of macrophage accumulation differed between species, rabbits showing a more perivascular infiltrate and guinea-pigs a more peribronchial pattern (Schepers and Dunnom 1981). Few studies compared the effects of different amorphous silicas, but all found differences between substances (Klosterkötter 1965; Groth et al. 1981; Reuzel et al. 1991). However, no specific product properties were defined that may predict adverse effects. There are two important consistent findings. Firstly, emphysema or alveolar hyperinflation was present in many animal studies, and especially in rats, this was the cause of a high mortality. Interestingly, this process was partially reversible after discontinuation of exposure (Table 5). Secondly, inflammation and fibrogenic effects were less pronounced than following quartz inhalation (Schepers 1962; Reuzel et al. 1991; Warheit et al. 1995), and persistent or progressing silicotic nodules were not found after the discontinuation of exposure. Regression of granuloma and connective tissue formation after

discontinuation of exposure was found in all animals species.

Lung clearance is probably an important factor that determines the occurrence of silicosis. In contrast to quartz, a number of amorphous silica products have been shown to be almost completely eliminated from the lungs of various animal species after discontinuation of exposure within months. Also, the finding of amorphous silica accumulation in the lymph nodes (Klosterkötter and Einbrodt 1965; Reuzel et al. 1991) was at least partially reversible. The difference in clearance between crystalline and amorphous silica is not yet fully understood. Alveolar macrophages transport phagocytosed material from the alveoli to the lymph nodes (Lee and Kelly 1993; Lehnert et al. 1986). Amorphous silica have a surface area 10–1000 times larger than quartz and can therefore be expected to dissolve faster. This might explain that while amorphous silica is accumulated in macrophages and lymph nodes, it is eliminated much faster than crystalline silica (Pratt 1983; this study was performed with fused silica).

Conclusions

In summary, with the exception of few case reports with poorly described exposure quality, there is no evidence for a fibrogenic effect of intentionally manufactured synthetic amorphous silica to the human lung. Animal studies show no persistent silicotic nodules even in long-term inhalation experiments with high concentrations of amorphous silicas that are probably not encountered in workplaces (reported values in workplaces do not exceed 10 mg/m^3). This contrasts with inhalation experiments using crystalline silica which clearly demonstrated such effects. Although some collagen formation has been described in animals exposed to amorphous silica, this is at least partially reversible after discontinuation of exposure. However, some studies describe a minor persistent interstitial collagen deposition. As the available information in humans is not sufficient to definitely exclude a fibrogenic effect of amorphous silica in exposed workers, further epidemiological evidence should be obtained.

Bronchitis, airway obstruction and emphysema were considered by few studies as outcome variables. Such effects in workers exposed to amorphous silica have been described, but the importance of confounders cannot be quantified sufficiently in these studies. Inflammatory responses and emphysema have been described in a number of animal studies, especially in rats and monkeys. Thus, parameters assessing bronchitis, airways obstruction and emphysema have to be considered in further epidemiological studies as primary outcome variables.

Acknowledgements We thank Professor W. Mohrmann (Klinik für Berufskrankheiten der Berufsgenossenschaft der keramischen und Glas-Industrie, Bad Reichenhall), Dr. R. Schmoll, Dr. H. Ferch, and Dr. H.E. Toussaint (Degussa Corporation, Germany) for comments and help with technical questions.

References

American Conference of Governmental Industrial Hygienists (1987) Documentation of the threshold limit values and biological exposure indices. ACGIH, Cincinnati

American Thoracic Society (1997) Adverse effects of crystalline silica exposure. American Thoracic Society Committee of the scientific assembly on environmental and occupational health. Am J Respir Crit Care Med 155:761–765

Beskow R (1978) Silicosis in diatomaceous earth factory workers in Sweden. Scand J Respir Dis 59:216–221

Brambilla C, Brambilla E, Rigaud D, Perdrix B, Pramelle A, Fourcy A (1980) Pneumoconiosis due to amorphous silica fumes. Mineralogical and ultrastructural studies on 6 cases (in French). Rev Français Mal Resp 8:383–391

Bruce T (1937) The occurrence of silicosis in the manufacture of silicon alloys. J Ind Hygiene Toxicol 19:155–162

Caldwell DM (1958) The coalescent lesion of diatomaceous earth pneumoconiosis. Am Rev Tuberc 77:664–659

Checkoway H, Heyer HJ, Demers PA, Breslow NE (1993) Mortality among workers in the diatomaceous earth industry. Br J Ind Med 50:586–597

Choudat D, Frisch C, Barrat G, El Kholti A, Conso F (1990) Occupational exposure to amorphous silica dust and pulmonary function. Br J Ind Med 47:763–766

Cooper WC, Cralley LJ (1958) Pneumoconiosis in diatomite mining and processing. US Government Printing Office, Washington D.C.

Cooper WC, Jacobson G (1977) A 21-year follow-up of workers in the diatomite industry. J Occup Med 19:563–566

Cooper WC, Sargent EN (1984) A 26-year follow-up of workers in a diatomite mine and mill. J Occup Med 26:456–460

Corhay JL, Bury T, Delavignette JP, Baharloo F, Radermecker M, Hereng P, Fransolet AM, Weber G, Roelandts I (1995) Non-fibrous mineralogical analysis of bronchoalveolar lavage fluid from blast-furnace workers. Arch Environ Health 50:312–319

Deutsche Forschungsgemeinschaft (1989) Hazardous substances to health. MAK-value for amorphous silica. Wiley-VCH Verlagsgesellschaft mbH, Weinheim

Dutra FR(1965) Diatomaceous earth pneumoconiosis. Arch Environ Health 11:613–619

Ebina T, Takase Y, Inasawa Y, Horie K (1952) Silicosis in the diatomaceous earth factories. Sci Rep Res Inst Tohoku Univ 4:65–75

European Chemical Industry Council (CEFIC) (1996) Exposure to amorphous silica. CEFIC, Brussels

Ferch H, Toussaint HE (1996) Synthetic amorphous silicas in fine powder form: definitions, properties and manufacturing processes. Kautschuk Gummi Kunststoffe 49:589–596

Ferch H, Gerofke H, Itzel H, Klebe H (1987a) The question of silicogenic effects of amorphous silica (in German). Schriftenreihe Pigmente 76:3–31

Ferch H, Gerofke H, Itzel H, Klebe H (1987b) Examination of workers with long-term occupational exposure to Aerosil (in German). Arbeitsmed Sozialmed Präventivmed 22:33–37

Gärtner H (1952) Effects of small particle size dust of amorphous silica on the lungs of rabbits (in German). Arch Hyg Bakteriol 136:451–467

Groth DH, Moormann WJ, Lynch DW, Stettler LE, Wagner WD, Hornung RW (1981) Chronic effects of inhaled amorphous silicas in animals. In: Dunnom DD (ed) American Society for Testing and Materials, Special Technical Publication 732: 118–143

Harber P, Dahlgren J, Bunn W, Lockey J, Chase G (1998) Radiographic and spirometric findings in diatomaceous earth workers. J Occup Environ Med 40 [Suppl. 1]:22–28

Hughes JM, Weill H, Checkoway H, Jones RN, Henry MM, Heyer NJ, Seixas NS, Demers PA (1998) Radiographic evidence of silicosis risk in the diatomaceous earth industry. Am J Respir Crit Care Med 158:807–814

International Agency for Research on Cancer (IARC) (1997) Monograph on the evaluation of carcinogenic risks to humans. Silica, some silicates, coal dust and para-Aramid fibrils. Monograph 68, IARC Press, Geneva

Klosterkötter W (1953) Additional investigations about tissue effects of colloidal and dissolved silica (in German). Arch Hyg Bakteriol 137:307–316

Klosterkötter W (1965) Studies on hygiene and toxicology of amorphous silica. I. Aerosil-R 972 (in German). Arch Hyg Bakteriol 149:577–598

Klosterkötter W, Einbrodt HJ (1965) Quantitative animal experiments on the clearance of dust from the lungs to the lymph nodes (in German). Arch Hyg Bakteriol 149:367–384

Lee KP, Kelly DP (1993) Translocation of particle-laden alveolar macrophages and intra-alveolar granuloma formation in rats exposed to Ludox colloidal amorphous silica by inhalation. Toxicology 77:205–222

Legge RT, Rosencrantz E (1932) Observations and studies on silicosis by diatomaceous earth. Am J Publ Health 32:1055–1060

Legrand AP (1998) On the silica edge. In: Legrand AP (ed) The surface properties of silicas. Wiley-VCH Verlagsgesellschaft mbH, Weinheim

Lehnert BE, Valdez YE, Stewart CC (1986) Translocation of particles to the tracheobronchial lymph nodes after lung deposition: kinetics and particle-cell relationships. Exp Lung Res 10:245–266

Lewinson J, Mayr W, Wagner H (1994) Characterization and toxicological behavior of synthetic amorphous silica. Regul Toxicol Pharmacol 20:37–57

McLaughlin JK, Chow WH, Levy LS (1997) Amorphous silica: a review of health effects from inhalation exposure with particular reference to cancer. J Toxicol Environ Health 50:553–566

Mohrmann W, Kann J (1985) Amorphous silica can cause silicosis. In: Case reports (in German). Gentner Verlag, Stuttgart, p 587

Motley HL (1960) Pulmonary function studies in diatomaceous earth workers. A cross sectional survey of 98 workers on the job. Indust Med Surg 29: 370–378

Motley HL, Smart RH, Valero A (1956) Pulmonary function studies in diatomaceous earth workers. AMA Arch Indust Health 13:265–274

Omura T, Nagagawa H, Yamamoto S, Kato T, Honda R, Nogawa K. (1978) Respiratory function abnormalities in workers exposed to diatomaceous earth dust. Jap J Indust Health 20:
254–260

Philippou S, Teschler H, Morgenroth K (1992) Lung fibrosis after inhalation of amorphous silica (in German). Zentralbl Pathol 138:41–46

Plunkett ER, DeWitt BJ (1962) Occupational exposure to hi-sil and silene. Arch Environ Health 5:469–472

Pratt PC (1983) Lung dust content and response in guinea pigs inhaling three forms of silica. Arch Environ Health 38:197–204

Puntoni R, Goldsmith DF, Valerio F, Vercelli M, Bonassi S, Giogio FD, Ceppi M, Stagnaro E, Filiberti R, Santi L (1988) A cohort study of workers employed in a refractory brick plant (in Italian). Tumori 74:27–33

Rabovsky J (1995) Biogenic amorphous silica. Scand J Work Environ Health 21:108–110

Ratney R (1988) The threshold limit values for various forms of amorphous silica. Proceedings of the 17th National Pneumoconiosis Conference. NIOSH II, pp 1134–1135

Reuzel PG, Bruijntjes JP, Feron VJ, Woutersen RA (1991) Subchronic inhalation toxicity of amorphous silicas and quartz dust in rats. Food Chem Toxicol 5:341–354

Robalo-Cordeiro AJA, Baganha MF, Azevedo-Bernada R, Leite ACP, Almeida URG, Bairos VF, Gaspar E, Garcao MF, Lima MAM, Rosa MAS, Pega AF, Bastos JMP (1985) Biological effects of fume silica (amorphous type). In: Beck, EG, Bignon, J (eds) In vitro effects of mineral dusts. NATO ASI Series Vol G3. Springer-Verlag, Berlin, pp 489–496

Schepers GWH (1959) Hypertension due to inhaled submicron amorphous silica. Toxicol Appl Pharmacol 1:487–500

Schepers GWH (1962) Reaction of monkey lung to siliceous dusts. Arch Environ Health 5:8–29

Schepers GWH, Dunnom DD (1981) Biological action of precipitation-process submicron amorphous silica (hi-sil). American Society for Testing and Materials, Special Technical Publication 732. pp 144–173

Schepers GWH, Delahant AB, Schmidt JG, VonWecheln JC, Creedon FT, Clark RW (1957a) The biological action of Degussa submicron amorphous silica dust (Dow Corning Silica). Inhalation studies on rabbits. Arch Ind Health 16:280–301

Schepers GWH, Durkan TM, Delahant AB, Creedon FT, Redlin AJ (1957b) The biological action of Degussa submicron amorphous silica dust (Dow Corning Silica). The pulmonary reaction in uninfected guinea pigs. Arch Ind Health 16:27–48

Schepers GWH, Durkan TM, Delahant AB, Creedon FT, Redlin AJ (1957c) The biological action of Degussa submicron amorphous silica dust (Dow Corning Silica). Inhalation studies on rats. Arch Ind Health 16:125–146

Smart RH, Andersen WM (1952) Pneumoconiosis due to diatomaceous earth. Clinical and x-ray aspects. Indust Med Surg 21:509–518

Spain BA, Cummings O, Garcia JGN (1995) Bronchiolitis obliterans in an animal feed worker. Am J Ind Med 28:437–443

Swenson A, Kvarnstroem K, Bruce T, Edling NPG, Gloemme J. (1971) Pneumoconiosis in ferrosilicon workers – A follow-up study. J Occup Med 13:427–432

Vigliani EC, Mottura G (1948) Diatomaceous earth silicosis. Br J Ind Med 5:148–160

Vitums VC, Edwards MJ, Niles NR, Bormann JO, Lowdry RD (1977) Pulmonary fibrosis from amorphous silica dust, a product of silica vapor. Arch Environ Health 32:62–68

Volk H (1960) The health of workers in a plant making highly dispersed silica. Arch Environ Health 1:125–128

Warheit DB, McHugh TA, Hartsky MA (1995) Differential pulmonary responses in rats inhaling crystalline, colloidal or amorphous silica dusts. Scand J Work Environ Health 21:19–21

Wilson RK, Stevens PM, Lovejoy HB, Bell ZG, Richie RC (1979) Effects of chronic amorphous silica exposure on sequential pulmonary function. J Occup Med 21:399–402