Eur Respir J
1991, 4, 730–744

REVIEW

Silica and lung cancer: a controversial issue

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Silica and lung cancer: a controversial issue. J.C. Pairon, P. Brochard, M.C. Jaurand, J. Bignon.

ABSTRACT: The role of crystalline silica in lung cancer has long been the subject of controversy. In this article, we review the main experimental and epidemiological studies dealing with this problem.

Some evidence for a genotoxic potential of crystalline silica has been obtained in the rare *in vitro* studies published to date. *In vivo* studies have shown that crystalline silica is carcinogenic in the rat; the tumour types appear to vary according to the route of administration. In addition, an association between carcinogenic and fibrogenic potency has been observed in various animal species exposed to crystalline silica.

An excess of lung cancer related to occupational exposure to crystalline silica is reported in many epidemiological studies, regardless of the presence of silicosis. However, most of these studies are difficult to interpret because they do not correctly take into account associated carcinogens such as tobacco smoke and other occupational carcinogens. An excess of lung cancer is generally reported in studies based on silicosis registers.

Overall, experimental and human studies suggest an association between exposure to crystalline silica and an excess of pulmonary malignancies. Although the data available are not sufficient to establish a clear-cut causal relationship in humans, an association between the onset of pneumoconiosis and pulmonary malignancies is probable. In contrast, experimental observations have given rise to a pathophysiological mechanism that might account for a putative carcinogenic potency of crystalline silica.

Eur Respir J., 1991, 4, 730–744.

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Keywords: Epidemiology; lung cancer; silica; silicosis.

Received: January 12, 1990; accepted November 14, 1990.

Numerous authors have raised the possible carcinogenic potential of crystalline silica. In 1982, in a review of the literature, GOLDSMITH *et al.* [1] concluded that the available epidemiological and experimental evidence pointed to a carcinogenic effect of silica and forwarded several pathogenetic hypotheses. However, their conclusions have since been called into doubt by others including HEPPLESTON [2] who, in 1985, concluded that silica itself was not carcinogenic and that silicosis did not appear to give rise to bronchopulmonary cancer (BPC). Since that time other epidemiological studies have been published. In 1987 the International Agency for Research on Cancer (IARC) [3, 4] published monographs dealing with silica and some silicates; they classified crystalline silica in group 2A, *i.e.* limited evidence for carcinogenesis in man but sufficient evidence in animals. In contrast, no definite conclusion has been reached by the committee set up by the National Institute for Occupational Safety and Health [5] to investigate the possible relationship between silica exposure and BPC on the one hand, and BPC and silicosis on the other.

Following the 7th International Conference on Pneumoconiosis held in 1988, MCDONALD [6] concluded that it was probably too early to affirm that exposure to crystalline silica was carcinogenic in man. This view was based deliberately and exclusively on cohort and case-control epidemiological studies which are generally considered to be of greater scientific value than descriptive studies and case reports.

SAFFIOTTI and STINSON [7] recently reviewed possible pathogenetic hypotheses to explain the results of studies of carcinogenesis and stressed the probable importance of host factors.

Finally, in 1990 the IARC [8] published the results of a large number of studies investigating the possible carcinogenic role of crystalline silica. These studies, many of which were ongoing, had been co-ordinated by the IARC since 1983. The overall evaluation confirmed the conclusions reached in 1987 by the IARC [9].

We considered it of interest to review relevant studies published to date, in order to assess the BPC risk associated with silica exposure and to determine what preventive measures may be necessary.

Table 1. – Silica and carcinogenesis: *in vitro* tests

Authors	Year	Test	Cells	Type of silica	Doses of silica	Doses $\mu g \cdot cm^{-2}$	Results
Price Jones *et al.* [10]	1980	Sister chromatid exchanges	V 79-4 (Chinese hamster)	Quartz Min U Sil	1, 5, 15 $\mu g \cdot ml^{-1}$ Min U Sil	0.26, 1.33, 4	-
		Numerical chromosomal aberrations	*id*	*id*	*id*	*id*	-
Mortelmans and Griffin [11]	1981	Mutagenicity (Ames)	*Salmonella typhimurium* TA 1535 TA 1537 TA 1538 TA 98 TA 100 +/- S 9	Silicron G910	0.3 to 10^4 $\mu g \cdot dish^{-1}$	?	-
		Mutagenicity	*Escherichia coli* WP2-UVRA	*id*	*id*	?	-
Oshimura *et al.* [12]	1984	Chromosomal aberrations	Syrian hamster embryo cells	α-quartz	2 $\mu g \cdot cm^{-2}$	2	-
		Cell transformation	*id*	*id*	*id*	*id*	-
Hesterberg and Barrett [13]	1984	Cell transformation	Syrian hamster embryo cells	α-quartz	5, 10, 20, 40 80 $\mu g \cdot cm^{-2}$	5, 10, 20, 40, 80	+ (at dose >10 $\mu g \cdot cm^{-2}$)
		id	*id*	quartz Min U Sil	2, 5, 10, 20 40, 80 $\mu g \cdot cm^{-2}$	2, 5, 10, 20 40, 80	+ (at dose >2 $\mu g \cdot cm^{-2}$)
Hesterberg *et al.* [14]	1986	Cell transformation	Syrian hamster embryo cells	quartz Min U Sil	1, 20 $\mu g \cdot cm^{-2}$	1, 20	+ (at dose >2 $\mu g \cdot cm^{-2}$)
		Micronucleus	*id*	*id*	*id*	*id*	+ (at 20 $\mu g \cdot cm^{-2}$)
Pairon *et al.* [15]	1990	Sister chromatid exchanges	Human lymphocytes	Tridymite	1, 10, 100 $\mu g \cdot ml^{-1}$	0.5, 5, 50	+ (at 50 $\mu g \cdot cm^{-2}$)
				quartz Min U Sil	*id*	*id*	+/- (at 50 $\mu g \cdot cm^{-2}$)

-: no significant effect; +: significant enhancement compared to controls.

We first present an analysis of the data obtained from *in vitro, in vivo* and epidemiological studies and then discuss the question "does exposure to silica increase the risk of bronchopulmonary cancer?"

In vitro studies of genotoxicity and carcinogenicity

The results of the small number of *in vitro* studies published to date are summarized in table 1 [10–15]. In order to facilitate comparison, the amount of silica used is expressed, where possible, in $\mu g \cdot cm^{-2}$ of cell culture dish.

Three studies yielded positive results, two with micronuclei [14] and morphological cell transformation tests [13] in cultured Syrian hamster embryo cells and one with sister chromatid exchanges (SCE) in human lymphocytes [15]. There appears to be a threshold dose which varies according to the form of silica used. The negative results obtained by OSHIMURA *et al.* [12] may be due to the low doses used: studying the same doses, HESTERBERG and BARRETT [13] found that cell toxicity was low, but they observed a dose-effect relationship in the cell transformation test at higher doses. Nevertheless, this was far less marked than with chrysotile.

HESTERBERG *et al.* [14] observed the internalization of silica to a perinuclear localization, possibly explaining its action on the genome during mitosis after the disappearance of the nuclear membrane. These authors proposed the theory that silica had a direct genotoxic effect. For their part, PAIRON *et al.* [15] considered that the effect of silica might also be mediated by one or more clastogenic soluble factors released into the culture medium by monocytes in the presence of quartz. Finally, given the observed threshold doses in the positive tests, the negative results [10–12] might be explained by inadequate doses of silica.

Overall, the data obtained from the above studies are too few and insufficiently detailed to provide any definite conclusion on the genotoxic or carcinogenic effects of silica. This lack of *in vitro* studies is underlined in the conclusion of the IARC monograph [3].

In vivo studies

Among the numerous studies concerning the effect of silica *in vivo*, the results concerning the potential carcinogenic potency of crystalline silica are summarized in tables 2–5 and are classified according to the route of administration [16–35].

The following parameters are presented:
- the species of animal;
- the type of exposure, including the form of silica used and possible co-carcinogens. The control (saline-treated) group is also presented to indicate the histological type of spontaneous tumours;
- the dose used;
- negative (-) or positive (+) results for carcinogenesis as reported by the authors;
- the histological type of the tumours observed,
- the presence (+) or absence (-) of fibrosis, when reported.

Several important points emerge:
1) Various forms of crystalline silica were found to be carcinogenic in several studies using different routes of administration (intrapleural, intraperitoneal, intratracheal, inhalation) [16, 18–24, 26, 28–32]. However, species-related differences in susceptibility are observed: studies in the hamster are all negative, with the exception of those associating benzo(a)pyrene (BaP) and silica (significantly more tumours than with BaP alone) [26]. Studies in the rat are generally positive, while few have been conducted in the mouse.
2) Crystalline silica appears to be both carcinogenic and fibrogenic in animals [7, 36]. Pulmonary or peritoneal fibrosis is observed following both inhalation and intraperitoneal injection in the rat, but little or none in the hamster. Certain reports make no mention of fibrosis.
3) The type of induced tumour depends on the route of administration of the silica dust studied. Both inhalation and intratracheal administration gave rise to epithelial tumours in the rat (squamous cell carcinomas, adenocarcinomas, bronchiolo-alveolar carcinomas or mixed forms), while intrapleural and intraperitoneal injection produced lymphomas accompanied by fibrotic pleural or peritoneal lesions [29, 32].

On the basis of *in vivo* studies, the IARC concluded that "there is sufficient evidence for a carcinogenic effect of crystalline silica in animals" [3, 4].

Epidemiological studies

A summary of the results of epidemiological studies [35–89] is given in tables 6 and 7. We shall examine separately those which, according to their authors, gave positive results for a carcinogenic effect of silica and those which did not.

Studies considered positive

Cohort studies (populations exposed to silica). Several studies have examined the incidence of BPC (or deaths due to BPC) in populations exposed to silica, regardless of the presence of pulmonary fibrosis. A certain number of authors concluded that there was a significant excess of BPC in their cohorts.

However, some weaknesses should be pointed out: Firstly, the excess number of BPC is based on comparisons with general (regional or national) populations. Although certain reports took into account geographic variations in the rate of cancers, socio-economic factors (known to be related to the mortality rate in industrialized countries) were very rarely mentioned.

Secondly, when studied, smoking habits were not always assessed in the same way in the cohorts and the general population [37, 40–43, 51, 53, 54]. Worse, certain studies did not even take smoking into account [38, 44, 49, 50, 52, 55, 56, 58]. Only the work of

Table 2. – *In vivo* studies - route of administration: inhalation

Authors	Year	Animal species	Type of silica and co-carcinogens	Dose of silica*	Results	Histology													Fibrosis
						MLH	MLL	S + T	M Sch	H	P	A + Pap	PSCC	PAC	PMC	PBAC	PPC	M	
MARTIN *et al.* [16]	1977	Sprague Dawley Rat	Unexposed (control)	200 mg·m^{-3}															-
			Coal		?								x	x					±
			Coal + quartz 10%	200 mg·m^{-3}	+(a)								x	x					+
WILSON *et al.* [17]	1986	Balb C BYJ Mouse	Unexposed (control)									x							-
			quartz Min U Sil	1.47 to 1.9 mg·m^{-3}	-							x							-
			Olivine (containing 40% quartz and 49% MgO)	1.4 to 2 mg·m^{-3}	-							x							?
DAGLE *et al.* [18]	1986	344 SPF Fischer Rat	Unexposed (control)																-
			quartz Min U Sil	51.6 mg·m^{-3}	(a) +								x						+
HOLLAND *et al.* [19]	1986	Fischer Rat	Unexposed (control)									x							-
JOHNSON *et al.* [20]	1987		Quartz Min U Sil	12 mg·m^{-3}	(a) +							x	x	x					+
MUHLE *et al.* [21]	1989	344 SPF Fischer Rat	Unexposed (control)							?		x		x					-
			Quartz DQ 12	1 mg·m^{-3}	+					x		x	x	x	x				+
			Titanium dioxide	5 mg·m^{-3}	-					?		x		x					-

MLH: malignant lymphoma of histiocytic type; MLL: malignant lymphoma of lymphocytic type; S + T: sarcomas + thymomas; M Sch: malignant schwannomas; H: hyperplasia; P: polyps; A: papillary adenomas; PSCC: pulmonary squamous cell carcinoma; PAC: pulmonary adenocarcinoma; PMC: pulmonary mixed carcinoma; PBAC: pulmonary bronchiolo-alveolar carcinoma; PPC: pulmonary and pleural carcinoma; M: mesothelioma. *: all studies were performed with intermittent exposure (5 to 8 hours per day); (a): statistical significance not indicated by authors, or no statistical test mentioned.

Table 3. – *In vivo* studies - route of administration: intratracheal

Authors	Year	Animal species	Type of silica and co-carcinogens	Dose of silica	Results	Histology													Fibrosis
						MLH	MLL	S + T	M Sch	H	P	A + Pap	PSCC	PAC	PMC	PBAC	PPC	M	
HOLLAND *et al.* [22]	1983	Sprague Dawley Rat	Saline (control)																-
			Quartz Min U Sil	7 mg·W^{-1} × 10 W	+ (a)							x	x	x					+
		Syrian Golden Hamster	Saline (control)																-
			Quartz Min U Sil	7 mg·W^{-1} × 10 W	-														±
GROTH *et al.* [23]	1986	Fischer 344 Rat	Saline (control)											x					-
			Quartz Min U Sil	20 mg	+									x					+
			Quartz Novaculite	20 mg	+								x	x					+
PYLEV [24]	1980	White Rat	Untreated (control)																?
			BaP (5 mg)		-														?
			Quartz + BaP (5 mg)	50 mg	+(b)							x	x						?
RENNE *et al.* [25]	1985	Syrian Golden Hamster	Saline (control)																-
			Quartz Min U Sil	0.03 to 6 mg·W^{-1} × 15 W	-														±
			Quartz Min U Sil + Fe_2O_3	0.3–6 mg·W^{-1} × 15 W	-														±
NIEMEIER *et al.* [26]	1986	Syrian Golden Hamster	Saline (control)																-
																			-
			Quartz Min U Sil	0.75 mg·W^{-1} × 15 W	-										x				-
			Quartz Sil Co Sil	1.1 mg·W^{-1} × 15 W	-														-
			Fe_2O_3 (3 mg·W^{-1})		-							x							-
			Fe_2O_3 + Min U Sil		-														-
			BaP (3 mg·W^{-1})		+						x	x	x	x					-
			BaP + Min U Sil		+						x	x	x	x	x				-
			BaP + Sil Co Sil		+						x	x	x	x	x				-
			BaP + Fe_2O_3		+						x	x	x	x	x				-
			BaP + Fe_2O_3 + Min U Sil		+(c)						x	x	x	x	x				-

W: week; BaP: benzo(a)pyrene; (a): statistical significance not indicated by authors, or no statistical test mentioned; (b): no group treated with quartz alone; (c): respiratory tumours in animals receiving BaP + particles were significantly increased ($p<0.01$) compared to animals treated with BaP alone. For further abbreviation see legend to table 2.

Table 4. – *In vivo* studies - route of administration: intrapleural

Authors	Year	Animal species	Type of silica and co-carcinogens	Dose of silica	Results	Histology													Fibrosis
						MLH	MLL	S + T	M Sch	H	P	A + Pap	PSCC	PAC	PMC	PBAC	PPC	M	
WAGNER [27]	1962	Wistar Rat	"Silica"	20 mg	(a)	x													?
WAGNER and WAGNER [28]	1972	Standard Wistar Rat	Saline (control)				x	x											-
			Quartz	20 mg	+	x		x											+
		SPF Wistar Rat	Saline (control)				x	x											-
			Quartz	20 mg	+	x	x	x											+
WAGNER [29]	1976	Wistar Rat (Strain Alderley Park)	Saline (control)					x											-
			Cristobalite	20 mg	+	x		x		x									+
			Quartz Min U Sil	20 mg	+	x		x		x									+
			Coal dust	20 mg	-			x											?
WAGNER *et al.* [30]	1980	Wistar Rat (Strain Alderley Park)	Saline (control)																-
			Tridymite	20 mg	+	x													+
			Quartz Min U Sil	20 mg	+	x													+
			Quartz Dowson et Dobson	20 mg	+	x	x												+
			Quartz Snowit	20 mg	+	x													+
			Quartz DQ 12	20 mg	-	x													+
			Cristobalite	20 mg	-	x													+
		Agus Rat and PVG rat	Saline (Control)				x												?
			Quartz Min U Sil	20 mg	-	x	x												?
COLLIN and PALEKAR [31]	1986	344 SPF Fischer Rat	Saline (control)										x					x	?
			Grunerite (containing 12% quartz)	20 mg	+	x	x	x											?
JAURAND *et al.* [32]	1987	Sprague Dawley Rat	Saline (control)																-
			Quartz DQ 12	20 mg	+	x			x										+
WAGNER *et al.* [33]	1980	Wistar Rat (Strain Alderley Park)	Crocidolite (20 mg)															x	?
			Crocidolite (20 mg) + Quartz Min U Sil	20 mg	(b)	x												x	?
BIGNON *et al.* [34]	1983	Sprague Dawley Rat	Radon (6000 WLM) (control) (c)									x		x	x				?
			Radon (6000 WLM) + Quartz DQ 12	2 mg									x	x	x		x		?
			Radon (6000 WLM) + Quartz BRGM (d)	2 mg	(e)											x	x		?

(a): MLH observed in only 1 of 10 rats treated; (b): no statistical difference between the two groups with regard to the number of tumours but 3 rats in the group treated with crocidolite + quartz (26 animals) presented a lymphoma associated with a mesothelioma; (c): WLM=working level months; (d): BRGM=Bureau de Recherches Géologiques et Minières (France); (e): no group treated with quartz alone. Too few animals for statistical analysis. For further abbreviations see legend to table 2.

Table 5. – *In vivo* studies - other routes of administration

Authors	Year	Animal species	Type of silica and co-carcinogens	Dose of silica	Results	Histology													Fibrosis
						MLH	MLL	S + T	M Sch	H	P	A + Pap	PSCC	PAC	PMC	PBAC	PPC	M	
Intrathoracic																			
BRYSON *et al.* [35]	1974	Marsh Mice	Saline (control)											x					?
			Tridymite	10 mg	?	x	(a)			x				x					?
Intraperitoneal																			
WAGNER [29]	1976	Wistar Rat (Strain Alderley Park)	Saline (control)					x											-
			Quartz Min U Sil	20 mg	+	x		x		x									+
Intravenous																			
WAGNER [29]	1976	Wistar Rat (Strain Alderley Park)	Quartz Min U Sil	20 mg	? (b)			x		x									+
Deposition on thymus																			
WAGNER [29]	1976	Wistar Rat (Strain Alderley Park)	Quartz Min U Sil	20 mg	- (b)					x									?

Data include extrathoracic tumours. (a): intrapleural lymphomas, no additional information; (b): few animals. No control group. For abbreviations see legend to table 2.

Table 6. – Epidemiological studies classified according to type of exposure to silica

Type of exposure		Positive studies		BPC risk(a)	Negative studies	
Mines	Gold	Armstrong *et al.* [37]	1979	O/E=1.4**	McDonald *et al.* [60]	1978
		Katsnelson & Mokronosova [38]	1979	RR=3.1*	Armstrong *et al.* Ⓢ [37]	1979
					Brown *et al.* [61]	1986
					Hessel *et al.* [62]	1990
					Hessel *et al.* Ⓢ [62]	1990
	Coal	Vallyathan *et al.* Ⓢ [39]	1984	OR=?**	Cochrane *et al.* [63]	1979
					Ames *et al.* [64]	1983
					Miller & Jacobsen [65]	1985
	Iron	Pham *et al.* [40]	1983	SMR=350*	Radford *et al.* Ⓢ [41]	1984
		Radford *et al.* [41]	1984	O/E=3.42**		
		Chen *et al.* [42]	1990	SMR=3.7*		
		Chen *et al.* Ⓢ [42]	1990	SMR=5.3*		
	Others	Katsnelson & Mokronosova (talc) [38]	1979	RR=4.5*	Higgins *et al.* (taconite) [66]	1983
		Costello [43] (lead, zinc, mercury, chrome)	1982	SMR=126.6(a)**		
		Finkelstein and co-workers Ⓢ [44, 45]	1982–1987	SMR=230**		
		Westerholm and co-workers Ⓢ [46, 47]	1983–1986	RR=4.1*		
		Damber & Larsson [48]	1987	OR=2.7*		
Foundries		Fletcher [50] & Ades [49]	1984–1986	SMR=171***	Westerholm Ⓢ [46, 47]	
		Fletcher [50]	1986	SPMR=125*	*et al.*	1983–1986
		Silverstein *et al.* [51]	1986	SPMR=148*	Sherson & Iversen [67]	1986
					Thomas *et al.* [68]	1986
Granite and quarries		Steenland & Beaumont Ⓢ [52]	1986	OR=3.16***	Kurppa *et al.* [69]	1982
Stone works or slate quarries		Koskela and co-workers [53, 54]	1987–1990	SMR=156*	Davis *et al.* [70]	1983
					Steenland & Beaumont [52]	1986
		Guenel *et al.* [55]	1989	SIR=200*	Costello & Graham [71]	1988
					Mehnert *et al.* [72]	1990
					Mehnert *et al.* Ⓢ [72]	1990
Ceramics, pottery		Thomas [56]	1982	PMR=1.21**		
		Forastiere *et al.* [57]	1986	RR=2*(b)	Thomas & Stewart[73]	1987 (b,d)
		Forastiere *et al.* Ⓢ [57]	1986	RR=3.9*(b)		
		Tornling *et al.* Ⓢ [58]	1988	SMR=188NS(b,c)		
		Winter *et al.* [59]	1990	O/E=1.32*		
Refractory materials		Katsnelson & Mokronosova [38]	1979	RR=2*		

Ⓢ: studies concerning silicotic patients; SMR: standardized mortality ratio; SPMR: standardized proportional mortality rate; SIR: standardized incidence ratio; PMR: proportional mortality ratio; O/E: observed/expected; RR: relative risk; OR=odds ratio. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; NS: non-significant; (a): BPC risk given as expressed by authors; (b): results of this study have also been published in IARC publication N° 97 [8] without significant modifications; (c): after stratification according to time since diagnosis of silicosis, a significant O/E ratio is observed after a latency of 10 years; (d): the authors noted that the SMR for lung cancer was 1.37 (NS) among men exposed to high levels of silica dust with no talc exposure, while it was significantly elevated (SMR=1.81*) among all workers exposed to high levels of silica dust (including co-exposure to non-fibrous talc).

Neuberger *et al.* [75] involved a control population matched in terms of age, sex, housing, smoking, follow-up and socioeconomic status; unfortunately, exposure to pollutants other than silica was not taken into account.

Thirdly, associated occupational exposure to pollutants such as radon, asbestos and polycyclic aromatic hydrocarbons was poorly evaluated in most of these studies [37, 38, 43–45, 49–51, 56, 58, 59, 75].

Such isolated or cumulative design weaknesses undermine the relationship between silica exposure and BPC affirmed by the above authors, since the influence of these confounding factors is far from negligible, particularly when the excess of BPC is small. Among these positive studies, only that of Koskela and co-workers [53, 54] would appear valid, despite the use of a general population as reference, since confounding factors were taken into account. Moreover, in this cohort the incidence of BPC was between 1.2 and 3.8 fold higher than in the reference population, depending on the duration of follow-up. Such an excess does not support an exclusive confounding effect of smoking. Nonetheless, it is interesting to note that in the study of Koskela and co-workers [53, 54] the excess of BPC

Table 7. – Epidemiological studies - registers of silicosis or of professions exposed to silica of all origins

Reference (type of exposure)		BPC risk (a)
Lynge *et al.* [74] (foundries, mines, glass, stone)	1986	(b,c)
Neuberger *et al.* [75] (foundries, glass, pottery, ceramic, stone)	1986	SMR=148*** (b)
Kjuus *et al.* [76] (mines, quarries)	1986	RR=10.2*
Benhamou *et al.* [77] (mines, quarries)	1988	RR=2.14*
Siemiatycki *et al.* [78]	1990	OR=1.4* (d)
Westerholm Ⓢ [79] (mines, foundries)	1980	(e)
Gudbergsson *et al.* Ⓢ [80]	1983	O/E=3*
Kurppa *et al.* Ⓢ [81]	1986	SMR=312*
Schüler & Ruttner Ⓢ [82] (mines, stone foundries, ceramic)	1986	RR=2.2***
Zambon *et al.* Ⓢ [83]	1987	SMR=239*
Finkelstein *et al.* Ⓢ [45]	1987	SMR=302**
Mastrangelo *et al.* Ⓢ [84]	1988	RR=1.8* (f)
Forastiere *et al.* Ⓢ [85] (mines, pottery)	1989	OR=1.5* (g)
Infante-Rivard *et al.* Ⓢ [86] (mines, foundries, granite, pottery)	1990	SRM=3.47*
Chiyotani *et al.* Ⓢ [87]	1990	O/E=4.81*
Merlo *et al.* Ⓢ [88]	1990	SMR=5.03*
Ng *et al.* Ⓢ [89]	1990	SMR=2.03*

Ⓢ: studies concerning silicotic patients; SMR: standardized mortality ratio; PMR: proportional mortality ratio; O/E: observed/expected; RR: relative risk; OR=odds ratio; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; NS: non-significant; (a): BPC risk given as expressed by authors; (b): results of this study have also been published in IARC publication N° 97 [8] without significant modification; (c): RR given according to source of exposure and countries studied; (d): this OR was observed among workers with non-adenocarcinoma lung cancer with long-term, high-level exposure to silica; (e): O/E ratio calculated for silicotics, relative to two periods of diagnosis of silicosis (1931–1948 and 1949–1969). For the second period, the O/E ratio was significantly increased among mine (O/E=3.8**) and foundry workers (O/E=2.2**); (f): RR significantly increased only in silicotics. The authors suggest an additive carcinogenic role of tobacco smoke; (g): increased OR observed only in mine (OR=2.5*) and pottery workers (OR=2.1*).

was independent of the presence of silicosis, and was associated with an excess incidence of stomach cancers. However, a case-control study of the cancers in their cohort showed no clear relationship with exposure to silica, although an adjustment for regional variations in smoking habits seemed to confirm their hypothesis of a direct association between silica exposure and lung cancer [90]. The preliminary findings of Winter *et al.* [59], who conducted a follow-up study of pottery workers in the United Kingdom, suggest an excess of mortality from BPC among male workers, even after adjustment for smoking and regional mortality rates. However, exposure to other carcinogenic agents in these occupations cannot be ruled out.

Case-control studies (excluding those based on registers of silicosis or silica exposure). There are few published studies of exposure to silica (or employment in exposed situations) among patients with BPC compared to control populations.

Certain studies based on cancer and/or death registers found an excess risk of BPC in occupations involving exposure to silica, *e.g.* mines [48], mines and quarries [76, 77], mines, foundries and glassworks, as well as certain stoneworks [74]. However, studies based on cancer registers generally take into account the last occupation listed at the time of death and rarely consider smoking or other associated carcinogens.

Siemiatycki *et al.* [78], in a multicancer site, multifactor case-control study, reported an excess of non-adenocarcinoma lung cancer among male workers in Montreal who had been exposed to silica. It is noteworthy that a dose-response relationship was suggested when the duration and intensity of exposure were taken into account. It is also interesting to note the excess of stomach cancer which was observed and the synergistic effect of smoking and silica exposure: the odds ratio (OR) rose from 1.0 for nonsmoking, non-exposed subjects, to 2.6 for nonsmoking, "substantially" exposed subjects, and to 47.5 for "substantially" exposed smokers with more than 60 pack-years. However, these results did not take into account potential occupational carcinogens other than asbestos.

Vallyathan *et al.* [39], in an autopsy case-control study involving coal miners, observed an increased incidence of silicosis in the BPC group compared to a control group paired for smoking and the number of years spent working in the mine. However, no data concerning exposure to radon were presented.

Steenland and Beaumont [52], in a case-control study among stonemasons working with granite, also found an increased incidence of silicosis in the subjects with BPC. However, this was based only on death certificates, without radiological confirmation, and smoking was not taken into account.

In contrast, Forastiere *et al.* [57] published an interesting case-control study based on the death registry in an area where the ceramic industry was the main employer. The families of all the cases and controls

were interviewed to determine confounding factors such as smoking habits and types of occupation. The exposure to silica and the incidence of silicosis were both found to be higher in the BPC group. Furthermore, the relative risk of BPC in silicotic subjects was related to the duration of exposure.

MASTRANGELO *et al.* [84] performed a case-control study based on a hospital register in a region with industrial activity forming a source of exposure to silica. An increased incidence of silicosis was observed in the subjects admitted with BPC, although exposure to silica itself was not found to be related to BPC. The authors proposed an additive carcinogenic effect of smoking and silica exposure in the subjects with silicosis. However, the study design can be criticized, particularly with regard to recruitment, collection of data on smoking, and the diagnosis of BPC.

Studies based on registers of silicosis or silica-exposed workers. It should first be pointed out that the definition of silicosis varies enormously from country to country, with numerous authorities grouping silico-anthracosis, foundry-worker's pneumoconiosis, stone-mason's pneumoconiosis, *etc.* under the same term. However, these diseases would appear to be due not only to crystalline silica but also to non-fibrous silicates which have been incriminated in certain experimental studies [91, 92].

Apart from four papers which included incident cases of BPC [46, 47, 58, 80], such reports were based on all recorded cases of silicosis and related deaths during the period of the study. Once again, the major criticism is that smoking was not always taken into account [58, 79–82].

In the study by WESTERHOLM *et al.* [46, 47], an excess risk of BPC was observed among miners, quarry and tunnel workers with silicosis when compared to a silicosis-free population belonging to the same occupational groups. The ratio of deaths due to BPC between the former and the latter was 3.5:1. Although the authors considered that confounding factors were correctly controlled, their data are insufficient to confirm this.

In the study by FINKELSTEIN *et al.* [45], the role of smoking was estimated in a subgroup of the population studied. Expected values of BPC were calculated from the general population and adjusted according to the method of AXELSON and SUNDELL [93]. The excess risk of BPC was found to be greater than that due to smoking alone among workers in ceramic factories, brickworks and granite quarries. The value of the other conclusions of the study are dependent on the validity of the above methodology.

ZAMBON *et al.* [83], also using the Axelson adjustment, found a significant increase in the standardized mortality ratio (SMR) for BPC among a subgroup of quarry and tunnel workers compared to the general Italian population and the regional population of Venice (quarry SMR (BPC): 314; tunnel SMR (BPC): 187). This excess was statistically significant in subjects first exposed more than twenty years previously. In contrast, no relationship was found between the duration of exposure and the carcinogenic effect.

FORASTIERE *et al.* [85] reported an excess of mortality from BPC among financially compensated silicotics in the Latium region of Italy. This excess mainly concerned those who died before the age of 64 yrs and affected miners and pottery workers but not quarry workers, stone cutters or tunnelling workers. However, it should be noted that the authors took into account only the last occupation entailing exposure to silica dust. Smoking habits appeared to be similar in the cohort and in the reference population but the way in which smoking status was assessed was not the same in both groups.

INFANTE-RIVARD *et al.* [86] found a significant increase in the SMR for BPC among men financially compensated for silicosis in Quebec between 1938 and 1985. This excess mainly concerned miners, foundry workers and pottery workers (SMR (BPC): 3.78, 3.04 and 4.99, respectively), while the excess of BPC was not significant among granite workers. The confounding role of smoking was assessed according to the Axelson adjustment. The authors concluded that smoking alone could not account for such an excess risk of BPC, although no BPC was observed among the non-smokers.

CHIYOTANI *et al.* [87] reported the results of a study conducted in 11 Japanese hospitals. There was a significant excess of lung cancer among silicotics when compared to the general Japanese male population. The authors noted that the frequency of BPC among silicotics was twice that among anthraco-silicotics. However, the study design probably induced a selection bias.

MERLO *et al.* [88] conducted a mortality study among silicotics hospitalized in a department of occupational health in Genoa, Italy. They reported an excess of mortality from BPC when comparing silicotics to the national male population. The excess was also significant when a regional population was used as reference, as well as after adjustment for smoking. The study design may once again have induced a selection bias.

NG *et al.* [89] found a significant excess of mortality from BPC among silicotics in Hong Kong. The authors excluded patients with previous exposure to asbestos or polyaromatic hydrocarbons. Although a dose-response relationship was observed, the role of smoking seems important in the excess of BPC.

In summary, four of the above-mentioned studies of subjects with silicosis and little or no exposure to other occupational carcinogens can be considered positive [45, 83, 85, 86] if one considers valid the adjustments for smoking habits based on values in the general population.

Studies considered negative

More than 15 cohort or case-control studies have found no excess risk of BPC among subjects exposed to dust containing various proportions of crystalline silica (table 6). However, the difficulties encountered in interpreting the results are numerous, for the following reasons:

- an overestimation of the expected rate of BPC among the general population (high proportion of smokers or high incidence of BPC in the reference population);
- an underestimation of the number of cases of BPC in the study population (loss to follow-up, incorrect classification of exposure, recruitment bias by the use of volunteers, healthy worker effect, *etc.*);
- a lack of power when the risk is low (insufficiently large groups, short follow-up, low level of exposure, *etc.*).

For these reasons, silica can only, theoretically, be concluded to be non-carcinogenic if all the studies investigating a relationship between exposure and BPC are negative.

The specific role played by smoking must be taken into account before it is possible to make a valid assessment of the significance of the association between excess BPC and occupational factors. Theoretical studies have attempted to remedy the lack of information on smoking. A comparison of the SMR for BPC among American veterans, with and without adjustment for smoking, has shown a significant relationship, even for bronchial cancer (r=0.88). However, the population studied did not reflect the overall population in terms of socioprofessional status [94]. AXELSON and SUNDELL [93] suggested another approach using an equation to correct for the relative risk (RR) of BPC in a given population according to the percentage of nonsmokers. This problem was the subject of a recent general review [95]. However, the synergistic effect of carcinogens was not taken into account. HAMMOND *et al.* [96], studying a group of American insulation workers, showed a relative risk of BPC of 5 among nonsmokers, exposed to asbestos, 10 for non-exposed smokers, and 50 for exposed smokers. LIDDELL [97] has recently reviewed the fitness of this multiplicative model which some authors have called into doubt [98]. At all events, smoking must be correctly evaluated particularly when the observed RR is low (*i.e.* <3).

Discussion

Several points of interest emerge from this review of the literature. There exists clear experimental evidence for a carcinogenic effect of crystalline silica. While short-term tests are too few to draw a definite conclusion, it can be stated provisionally that the apparent carcinogenicity of silica might occur *via* its genotoxicity and transforming properties. However, the above phenomena are only observed under certain conditions which include adequate particle internalization [14], co-operation with phagocytes [15], and sufficiently high doses. These findings suggest that silica is carcinogenic in the long-term following high cumulative doses. In addition, there might be an indirect effect mediated by clastogenic factors released by macrophages. Several released factors have been implicated in the formation of pulmonary fibrosis following exposure to particles such as silica and asbestos [99, 100] and may include oxygen free radicals, fibroblast growth factors and chemotactic factors [100–106]. This similarity between the possible mechanisms of fibrosis and genotoxicity does not mean that tumours would necessarily arise from fibrotic lesions; however, the presence of fibrosis might increase the risk of genome damage in "transformable" cells, thus increasing the probability of cancer formation. It is thus clear that if these two distinct diseases can derive from a similar mechanism (release of mediators), an increase in one will be associated with an increase in the other. Crystalline silica shows greater potential to cause lung fibrosis than to give rise to lung cancer. These notions are schematized in figure 1. Several authors have reported positive results in studies *in vivo* which also appear to show a correlation between the development of fibrosis and malignant tumours. However, only the rat appears to be sensitive to silica. It is also noteworthy that, following intrapleural injection, the type of tumour observed is lymphomatous, not mesotheliomatous. This is in accord with the results of epidemiological studies, which found no cases of mesothelioma (in the absence of exposure to asbestos), and suggests that other tumour types should be looked at in subjects exposed to silica. However, to date no excess of lymphomas has been reported among silica-exposed workers.

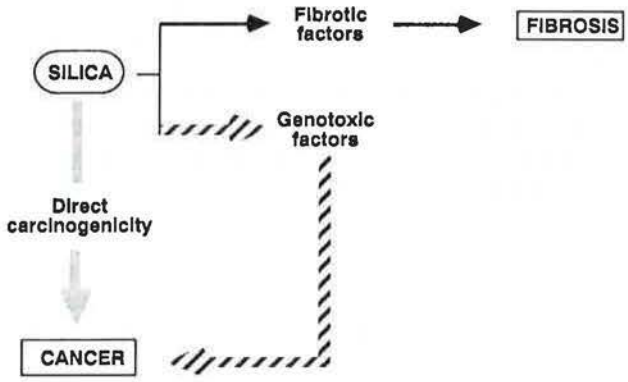

Fig. 1. – Schematic representation of the hypothesis on the mechanisms of action of silica. High activity (▬); potential not well-defined (zzzzz); low potential (▭).

In the absence of silicosis, human exposure to silica would not appear to result in cancer. After taking into account possible confounding factors (particularly smoking and other pulmonary carcinogens), few cohort or case-control studies remain positive. In addition, the relative risk of BPC is generally low when confounding factors are taken into account. No clear dose-response relationship exists; however, the highest relative risks were observed in cohorts with the longest follow-up, leading to the conclusion (in certain studies) that there is a time-effect relationship. These observations raise the question as to dust-control measures, which have significantly reduced the number of dust-exposed jobs and the number of non-malignant and malignant pulmonary diseases.

In contrast, studies concerning patients suffering from silicosis often show an excess of BPC. However, the term silicosis generally covers diverse forms of pneumoconiosis, and the patients were probably also exposed

to other pulmonary carcinogens. As a result, and given the difficulty in correctly interpreting the role of smoking, the possible causal relationship between silica and BPC must be viewed with caution. Nevertheless, some recent studies have shown an excess of BPC that cannot be explained only by smoking, if one accepts the mathematical adjustments that were generally employed. Another factor that could be involved in the excess of BPC among silicotics is unrecognized asbestos exposure before or associated with the silica exposure. This has already been raised by some authors [106] and could account for the mortality patterns reported in some studies. With this in mind, it is regrettable that no data concerning lung dust burden are available in published studies. Other occupational carcinogens have been incriminated by certain authors. One possible explanation is the so-called overload effect described in experimental models [107]. Indeed, patients with silicosis have a high pulmonary retention of particles and an impaired lung clearance. According to this hypothesis, silica would only be an indirect factor in the onset of BPC among silica-exposed workers, *via* an abnormal retention of other lung carcinogens.

In our opinion, studies published to date do not justify the classification of BPC as an occupational disease linked to silica exposure. On the other hand, patients suffering from pneumoconiosis are probably at an increased risk of BPC, even if exposure to silica is not the only aetiological factor. At all events, such subjects should be monitored closely, even after cessation of exposure, particularly if they are at a high risk for BPC, *i.e.* smokers with silicosis. Epidemiological and experimental research efforts must be pursued in order to resolve this important question of public health.

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Silice et cancer du poumon: un problème controversé. J.C. Pairon, P. Brochard, M.C. Jaurand, J. Bignon.
RÉSUMÉ: Le rôle de la silice cristalline dans le cancer du poumon a fiat l'objet de controverses prolongées. Dans cet article, nous revoyons les principales données expérimentales et épidémiologiques en rapport avec ce problème. Dans les rares études *in vitro* publiées à ce jour, l'on a pu relever quelques arguments en faveur d'un potentiel génotoxique de la silice cristalline. Les études *in vivo* ont montré que la silice cristalline est carcinogène chez le rat: les types tumoraux en cause varient selon la voie d'administration. En outre, une association entre le potentiel carcinogénique et fibrogénique a été observée dans différentes espèces animales exposées à silice cristalline.
Un excès de cancers du poumon en relation avec l'exposition professionnelle à la silice cristalline a été rapporté dans de nombreuses études épidémiologiques, indépendamment de la présence de silicose. Toutefois, la plupart de ces études sont difficiles à interpréter, parce qu'elles ne prennent pas correctement en compte les carcinogènes associés, comme la fumée de tabac ou d'autres carcinogènes professionnels. Une augmentation de fréquence du cancer est généralement rapportée dans les études qui se basent sur les registres de silicose.
Au total, les études expérimentales et humaines suggèrent une assoication entre l'exposition à la silice cristalline et un excès de cancers pulmonaires. Quoique les données disponibles soient insuffisantes pour établir une relation de cause à effet clairement démontrée chez l'homme, une association entre le développement de la pneumoconiose et des cancers pulmonaires et probable. En outre, des observations expérimentales ont permis de faire ressortir un mécanisme physiopathologique qui pourrait rendre compte du pouvoir carcinogénique supposé de la silice cristalline
Eur Respir J., 1991, 4, 730–744.