INITIAL TARGETED ASSESSMENT PROFILE (Human Health)

<table>
<tr><td>CAS No.</td><td colspan="2">Quartz: CAS RN 14808-60-7

Cristobalite: CAS RN 14464-46-1</td></tr>
<tr><td>Chemical Name</td><td colspan="2">Quartz and Cristobalite</td></tr>
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 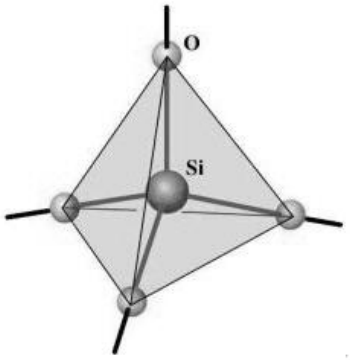
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 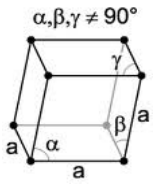

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 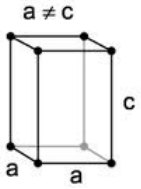

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SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following human health endpoints: repeated dose toxicity and carcinogenicity via the inhalation route of exposure, and genotoxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment included in the Canadian screening assessment but have not been presented to OECD member countries, and thus are not included in this profile.

The final screening assessment has been published under the responsibility of the Government of Canada. [http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=1EB4F4EF-1].

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Additional details may be found at http://www.chemicalsubstanceschimiques.gc.ca/about-apropos/categor/index-eng.php. Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological

endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release. Quartz and cristobalite were identified at that time, applying the categorization criteria, as high priorities for human health risk because they were considered to pose greatest potential for exposure and their respirable forms are classified by the International Agency for Research on Cancer as carcinogenic to humans (quartz and cristobalite) and by the National Toxicology Program as known human carcinogens (crystalline silica). These substances did not meet the ecological categorization criteria for bioaccumulation potential or inherent toxicity to aquatic organisms.

Under the Canadian legislation a determination of whether one or more of the criteria of the CANADIAN ENVIRONMENTAL PROTECTION ACT (CEPA) 1999, section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use.

Physical-chemical properties

The silicon dioxide group represents a polymorphic category containing a large number of forms identical in composition but with different atomic arrangements which afford different chemical properties. There are two sub-categories within this group: crystalline silica, to which the present substances quartz and cristobalite belong, and non-crystalline or amorphous silica. The key distinction between these sub-categories is that in crystalline substances, the building blocks are arranged in regular, repeating 3-dimensional pattern having long range order, whereas amorphous materials do not display long range order. In all forms of silica, (crystalline and non-crystalline), the silicon atom is tetrahedral and bound to four neighbouring oxygen atoms.

Quartz and cristobalite are solid at room temperature, existing normally as colourless or white crystals. The melting points for quartz and cristobalite are 1400-2000 ^{o}C and 1713-1728 ^{o}C, respectively and for both compounds, the boiling point is 2230^{o}C. Even though no experimental data were available, their vapour pressure and Henry's Law constant are likely negligible. Log K_{ow} (octanol-water partition coefficient) and log K_{oc} (organic carbon-water partition coefficient) are not applicable to these substances. The densities range from 2500-2700 kg/m^3 for quartz and 2300-2380 kg/m^3 for cristobalite.

The very similar physico-chemical properties of quartz and cristobalite reflect their closely related crystal forms. The solubility of crystalline silicates decreases as a function of silica tetrahedral packing density and long-range crystal order. For example, cristobalite has a more open framework structure than quartz and its density is lower, therefore, its solubility is higher. The water solubility of these minerals is also function of temperature, pH, particle size, and the presence of a disrupted surface layer. This may explain the variability of solubility values reported by many authors. The most probable solubility value for quartz is approximately 3.8 mg Si/L, or 6.4 mg/L expressed as the SiO_2 species, while the solubility of cristobalite is approximately 8.7 mg Si/L, or 18 mg SiO_2/L. The kinetics of dissolution of these substances is slow due to the high activation energy required to hydrolyse the Si-O-Si bond.

Human Health Targeted Endpoints

The majority of the studies described here have been reviewed by the International Agency for Research on Cancer (IARC 1997). However, additional data relevant to the screening assessment were identified up to August 2010.

Repeated dose toxicity/non-neoplastic effects (development of silicosis).

Studies on animals

Significant short-term and subchronic studies have demonstrated adverse effects in the lungs, while one of the 6 studies showed effects on the spleen in mice. Rats were exposed to 0, 10 or 100 mg/m^3 of cristobalite via inhalation for 6 hours/day during 3 days. Animals were observed 3 months after exposure. Elevated levels of granulocytes and elevated markers of cytotoxicity from the lung lavage fluid were noted in all exposed groups. Another study of similar duration (9 days) conducted in mice also identified a LOAEC of 10 mg/m^3. Effects observed included minimal interstitial thickening, accumulations of mononuclear cells and slight lymphoid tissue hypertrophy in the lungs.

In a 4-week inhalation study, female rats were exposed to 0, 0.1, 1 or 10 mg/m^3 of quartz 6 hours/day, 5

days/week. Bronchoalveolar lavage fluid was evaluated at 1, 8, and 24 weeks after exposure. Elevated levels of granulocytes and significant elevation of markers of cytotoxicity (Lactate dehydrogenase [LDH] and β-glucuronidase [β-glu]) were observed at 1 mg/m^3 and higher. The increased levels of LDH and β-glu were only significant at 24 weeks after exposure. A LOAEC of 1 mg/m^3 was identified at 24 weeks.

Male rats (4 animals per dose) were exposed to 0 or 3 mg/m^3 of cristobalite via inhalation for 6 hours/day, 5 days/week during 13 weeks. Pulmonary inflammation and fibrosis were observed in the exposed group at the end of treatment. When mice were similarly exposed to 5 mg/m^3 of quartz for 6 hours/day, 5 days/week for 15 or 27 weeks, the authors observed increased spleen weight and formation of plaque in the spleen.

In two separate studies, in which rats or hamsters were exposed to quartz via inhalation for at least 6 months, LOAECs of 2 and 3 mg/m^3 were identified, respectively. All the effects observed were related to inflammation and fibrosis of the lung tissue.

Several chronic studies investigated exposure of the respirable forms (i.e. accumulated via inhalation in the lung tissues) of quartz and cristobalite to rats, mice and hamsters. The following is a description of the study in which the lowest non-neoplastic LOAEC was determined. Groups of 50 rats/sex were exposed 6 hr/day, 5 days/week for 24 months to filtered air or 1 mg/m^3 of DQ-12 quartz, containing 74% of respirable quartz, through whole-body inhalation. An additional 50 rats/sex were exposed to 5 mg/m^3 of titanium dioxide as positive controls. The mean mass of particle at the end of the exposure period was 0.91 mg/lung. The LOAEC identified was 0.74 mg/m^3 (adjusted for 74% respirable quartz) based on lipoproteinosis, multifocal, inflammatory cell infiltrate and alveolar hyperplasia.

Human epidemiology data

In humans, the lowest observed adverse effect level was identified in a U.S. cohort study. The study was conducted on 3330 gold miners (all are males), who had an average of 9 years underground exposure during the period 1940 to 1965. The cohort was followed up through 1990. Silicosis[1] was identified through death certificates or chest X-rays. A job-exposure matrix together with work history was used to estimate individual exposure. The total silica content in the respirable dust in the mine was estimated at 13% and the median crystalline silica exposure was 0.05 mg/m^3. In this sub population of miners, 170 cases of silicosis were identified. The best predictor for risk of silicosis was cumulative exposure, which varied from less than 1% for a 0.5 mg/m^3-year exposure to 68-84% when exposed to more than 4 mg/m^3-year (based on the average daily dust exposure during the workday each year and summed over time for each miner). The main limitations identified

[1] Silicosis: Lung disease caused by inhalation of crystalline silica dust, and resulting in inflammation and scarring in forms of nodular lesions in the upper lobes of the lungs. By definition, clinically or pathologically diagnosed silicosis implies prior exposure to silica (Silicotics). It does not follow that a history of exposure to silica necessarily results in silicosis (Nonsilicotics). The typical "Silicotic" lung nodule is shown in Figure 1.

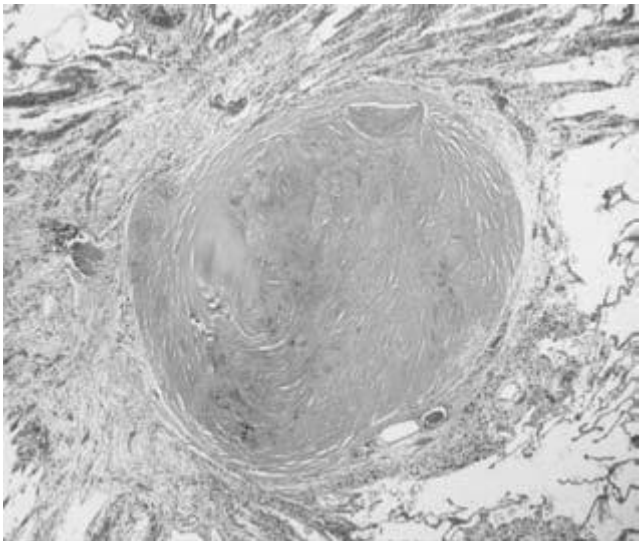

Figure 1. Silicotic nodule characterised by a central zone of hyalinised collagen with a whorled appearance and peripheral dust-containing macrophages (Rees and Murray, 2007).

by the authors include the limited number of radiographic surveys, the potential bias from death certificates (relying on death certificates instead of relying on repeated x-rays, which were lacking for each miner, may have underestimated the number of cases) and the fact that the conversion of dust counts to

gravimetric measurements may not be accurate based on the estimation of 13% silica content in the respirable dust (although based on a relatively large number of samples (n = 82) collected in two different surveys, there was broad range of content in these samples (1% to 48%, SD = 9), and the percentage of respirable quartz may have differed in earlier years, but data were lacking for these years).

Two other human studies have identified similar LOAECs based on the critical endpoint of radiographic confirmed silicosis. A LOAEC of 0.053 mg/m^3 (mean exposure) was identified in a cross sectional study of South African gold miners and a LOAEC of 0.064 mg/m^3 (mean exposure) was derived in a mining community population-based random sample survey in Colorado.

Carcinogenicity studies

Studies on animals

Experimental studies conducted in rats have shown clear and consistent increases in lung tumours after chronic inhalation exposure. In the nine rat studies identified, five were inhalation studies and four were intratracheal instillation studies. All studies except one inhalation study showed increased incidence of lung tumours. For the inhalation studies with treatment related tumours, concentrations ranged from 1 to 50 mg/m^3 (1, 6, and 30 mg/m^3 of DQ-12 quartz; 12 and 50 mg/m^3 of Min-U-Sil 5 quartz) and duration of exposure ranged from 29 days to 2 years. In the inhalation study with no treatment-related tumours, exposure was 60 mg/m^3 of Sikron F300 quartz for 13 weeks. The following is a description of the neoplastic results in the study also identified as the critical study for non-neoplastic results. Groups of 50 rats/sex were exposed 6 hr/day, 5 days/week for 24 months to filtered air or 1 mg/m^3 of DQ-12 quartz through whole-body inhalation. An additional 50 rats/sex were exposed to 5 mg/m^3 of titanium dioxide as positive controls. In the exposed group, 18 animals developed tumours (12 in females, 5 in males), as opposed to 3 and 2 for the control and positive control groups respectively. The majority (10/18) of the tumours observed were adenocarcinomas. The mean mass of particles in the lungs at the end of the exposure period was 0.91 mg/lung.

For the intratracheal instillation studies, doses ranged from 4 to 57 mg/kg-bw (based on 7, 12 or 20 mg/animal of Min-U-Sil (5) quartz or 20 mg/animal of novaculite quartz). Exposure regimes were diverse and included single instillation with observation for up to two years, to weekly instillation for 10 weeks. It is noteworthy that the single intratracheal administration of a 95% pure quartz particles (<5 μm) resulted in an increased incidence of silicotic granulomas after 3 weeks and lung tumours after 11 months. The most common tumours reported across the long term rat studies were adenocarcinomas, however other tumours such as squamous-cell carcinoma, alveolar carcinoma and bronchiole-alveolar adenoma were also reported, and all animals that developed tumours also showed some degree of fibrosis.

Of particular interest is the intratracheal instillation study, investigating the sequence of pathological events leading to lung tumors. An unspecified number of rats/sex/dose received a single intratracheal instillation of various crystalline silica dusts or ferric oxide, allowing direct administration into the bronchial tree. The doses were 12 or 20 mg of Min-U-Sil 5 quartz (MQZ), 12 mg of hydrofluoric-acid-etched Min-U-Sil 5 quartz (HFMQZ), 12 mg of cristobalite, 12 mg of tridymite and 12 mg of ferric oxide suspended in saline. All groups were observed until six months post exposure, except for both MQZ groups, the HFMQZ and the ferric oxide group which were observed up until 17 months post-exposure. Interim sacrifices were conducted at 6, 11 and 17 months. The rat lungs showed a clear progression of effects. The sequence of pathological events were, an initial inflammatory response leading to a marked hyperplasia and hypertrophy of alveolar cells after one month, and at six months hyperplasia was evident but no lung tumours were observed. In this study, lung tumours were observed starting at the 11 month sacrifice with a 17% and 42% incidence in males and females (based on 3/18 males and 8/19 females), respectively, and at 17 months incidences were 32% and 59% (based on 6/19 males and 10/17 females, respectively). No lung tumours were found in ferric oxide treated rats. Similar studies have also been conducted in hamsters and mice. Although treated mice and hamsters showed treatment related signs (inflammation or fibrosis), no tumours were observed in hamsters. No increase in the incidence of lung tumours was seen in mice treated with quartz; however silicotic granulomas and lymphoid cuffing around airways but no fibrosis were seen in the lungs of quartz-treated mice.

Human epidemiology data

There is an extensive dataset of human studies investigating the link between crystalline silica exposure and cancer. IARC (1997) identified over 50 epidemiological studies based on occupational exposure to dust containing respirable crystalline silica. Main industry sectors from which the human data is derived include gold mines, foundries, granite/stone industry, pottery workers and refractory brick workers. From the least

confounded studies, it was noted that lung cancer tended to increase with the following parameters: cumulative exposure; duration of exposure; peak intensity of exposure; presence of radiographically defined silicosis; and length of follow-up time from date of silicosis diagnostic. By definition, clinically or pathologically diagnosed silicosis implies prior exposure to silica (Silicotics).

Since the 1997 IARC report, a large number of epidemiological studies have been published, with the more recent studies being updates from supplementary follow-up of results from previously assessed case-control studies cohorts, new results based on refined exposure assessments or adjustment for confounders or meta-analyses of the pooled data from these epidemiology studies

In a meta-analysis of the data from 10 cohort studies of gold, tin and tungsten miners, granite workers, industrial sand, diatomaceous earth and pottery workers with quantitative exposure estimates for crystalline silica were pooled in order to analyse the risk related to lung cancer. The pooled cohort standardized mortality ratio (SMR, against national rates) [See Appendix 1 for definition] was 1.2 (Confidence Interval [CI] 1.1-1.3). The results from the case-control analyses show a statistically significant trend with duration of exposure (odds ratios (ORs) [See Appendix 1] by quintile of cumulative exposure increased from 1.0 to 1.6 [CIs of 0.85 to 2.1] and by quintile of average concentration increased from 1.0 to 1.7 [CIs of 1.1 to 2.3]), supporting the importance of the increasing lung burden of silica in the occurrence of cancer. Overall, the authors concluded that the results support the carcinogenicity conclusion presented by IARC (1997).

To investigate the link between crystalline silica, silicosis and lung cancer, epidemiological data published between 1966 and 2001 were gathered. Over 50 studies were selected and pooled according to type of study and the parameter being linked to lung cancer (i.e. silica exposure, presence of silicosis in subjects). The quality of study, adjustment for confounding factors, co-exposure to other carcinogens and availability of a more recent analysis of a same cohort were taken into consideration in the final selection of the studies. Analysis of the relationship between exposure to silica and lung cancer included 17 cohort and 13 case-control studies. For the analysis of lung cancer versus silicosis, 11 cohort and 5 case-control studies were selected. The third analysis included 6 cohort and 2 case-control studies to evaluate the risk of lung cancer in non-silicotics. A random effect model was used to conduct each meta-analysis. Pooled cancer risk ratios (RRs) were 1.32 (CI 1.23-1.41) for crystalline silica exposure, 2.37 (CI 1.98-2.84) for individuals exposed to silica with confirmed silicosis (Silicotics) and 0.96 (CI 0.81-1.15) for individuals with no evidence of silicosis (non-silicotics) with confirmed exposure to silica, supporting the general observation that silicosis has a stronger temporal relationship with crystalline silica exposure and furthermore support the view that a human silicotic response could be a preliminary stage in the development of cancer.

A more recent meta-analysis included 28 cohort, 15 case-control and two proportionate mortality ratio (PMR) [See Appendix 1] studies from a variety of occupational settings conducted between 1996 and 2005. Risk ratios (RRs) were calculated based on type of study and silicosis status using fixed and random effect models (results presented here are from the random model). RRs for all cohort studies was 1.34 (CI 1.25-1.45), and were 1.69 (CI 1.32-2.16) for silicotics, 1.25 (CI 1.18-1.33) for those with undefined silicosis status and 1.19 (CI 0.87-1.57) for non-silicotics. In the case-control studies, the general RR was 1.41 (CI1.18-1.67), and the same sub-groups as mentioned above resulted in RRs of 3.27 (CI 1.32-8.2), 1.41 (CI1.18-1.70) and 0.97 (CI 0.68-1.38), respectively. The proportionate mortality ratio for the last two studies was 1.24 (CI 1.05-1.47). The authors noted that the association between lung cancer and exposure to crystalline silica was more consistent for silicotics, i.e., those diagnosed with silicosis and RR values split into type of occupational settings in which participants worked.

Based upon the above three meta-analysis studies and the epidemiology studies discussed in IARC (1997), the following can be concluded. Lung cancer rates are higher in workers confirmed to have silicosis versus similarly exposed workers that do not have silicosis. Cancer risk is often more significant in workers exposed to crystalline silica over a 20 year period or to higher cumulative exposure levels; however a consistent finding is that the onset of silicosis, requires a smaller lag period than that for the appearance of tumours. Similarly, cancer risk is often more significantly associated at higher quintiles of exposure compared to the lower quintiles.

There have been reports of tumours outside of the lungs in persons with high silica exposure; however, these reports are sparse and the data inconsistent and have not been unequivocally linked to exposure to either one of the crystalline forms (quartz or cristobalite). Some of the reported locations are: oesophagus, stomach, liver, skin and bone. Sufficient epidemiological or toxicological data do not currently exist for quantitative assessment of the exposure-response relationship on these other tissues or organs.

Genotoxicity

Potential genotoxicity has been assessed in multiple *in vitro* and *in vivo* assays. Table 1 below gives a brief summary of the positive results observed in each type of assay.

Table 1. Summary of positive results over total number of results for each assay and each category (all studies conducted with crystalline silica: quartz, except where indicated).

Assay	Animal data		Human data		Positives/Total	
	In vitro	In vivo	In vitro	In vivo[d]	In vitro	In vivo
Rec Assay	0/1				0/1	
DNA strand break	1/1	2/2	5/5[b]	1/1	6/6	3/3
Sister chromatid exchange	0/1		0/1[c]	1/1	0/2	1/1
Micronucleus	2/3	0/1	2/2[b]	1/1	4/5	1/2
Chromosome aberration	0/1			1/1	0/1	1/1
Aneuploidy/polyploidy	0/3				0/3	
Cell transformation	4/4				4/4	
Hprt mutation	1/2	2/2[a]	1/1[b]		2/3	2/2
Oxidative DNA damage		4/5	2/2		2/2	4/5
DNA binding		1/1				1/1
p53 activation		0/1				0/1

a. one assay conducted with crystalline silica: cristobalite
b. one assay conducted with "ultrafine crystalline silicon dioxide".
c. crystalline silica: tridymite
d. crystalline silica dust (subtypes not provided).

All the *in vivo* human genotoxicity studies are based on three independent studies that used blood samples from workers from diverse occupational settings with confirmed exposures to crystalline silica dust; however, quantification of exposure was not provided. After stratification by smoking status, sister chromatid exchange remained statistically significant in both smokers and non-smokers although the frequency was higher in smokers. For the chromosome aberration assay conducted as part of the same study (blood samples from workers in the stone crusher industry), the increased frequency was no longer significant after stratification. In the DNA damage study of foundry and pottery workers and the micronucleus assay of workers involved in sandblasting and related jobs, results were positive when compared to controls. However, in both studies, smoking status influenced the results, contributing to the increased DNA damage observed since results were greater in smokers versus non-smokers, and the frequency of micronuclei in nasal epithelial cells was higher in smokers ($p=0.002$) but when using peripheral blood lymphocytes did not differ statistically between smokers and non-smokers who were similarly exposed to silica dust,

The role of *in situ* generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) has been well established in the following types of DNA damage: small scale insertions, DNA base pair deletion, base modification, chromosomal change/loss, microsatellite instability, DNA strand break, 8-hydroxydeoxyguanosine (8-OHdG) mutation and point mutations. ROS and RNS generation is postulated to be (a part of) the DNA damage mechanism for crystalline silica. Studies are described below to support this hypothesis.

DNA was exposed *in vitro* to various crystalline silica dusts, to H_2O_2, or to both. Results show that DNA damage was limited when dust or H_2O_2 were administered alone but increased with the co-exposure. When the reactive oxygen scavenger, dimethylsulfoxide, was added to the test system, DNA strand break was inhibited, data supporting the viewpoint that it is the presence of radicals generated in response to quartz and cristobalite that causes the DNA damage and not quartz or cristobalite themselves.

Hprt mutation assays in rat alveolar epithelial cells, both *in vitro* and *in vivo*, were positive in response to quartz. The positive results *in vivo* were seen only in the presence of significant inflammatory responses in the treated animals. Also, in a parallel *in vitro* experiment, rat alveolar epithelial cells were incubated with the bronchoalveolar lavage fluid from the rats exposed to quartz. Both macrophage and neutrophil enriched lavage cells induced mutation in the exposed alveolar epithelial cells. Addition of catalase (an enzyme which inactivates H_2O_2) before incubation inhibited the increase in *hprt* mutation.

Rats were exposed to either crystalline or amorphous silica in a manner to induce the same level of inflammation in the lungs. The inflammatory response was assessed by measuring the proportion of neutrophils in the bronchiolar lavage fluid. The actual concentrations were 3 and 50 mg/m^3 for crystalline and amorphous silica respectively. The animals were exposed for 13 weeks. *Hprt* mutation frequency was measured in the alveolar epithelial cells at the end of the exposure period. Mutation frequency was greatly increased only in the crystalline silica treated rats; no treatment related increase was found in the rats treated with the amorphous form.

In an 8-OHdG assay conducted to monitor DNA damage by reactive oxygen species, female rats were exposed to 0, 0.3, 1.5 and 7.5 mg/animal of quartz via intratracheal instillation. Effects were observed 90 days post-exposure. A clear dose-response relationship was identified between quartz exposure and various inflammation markers (differential cell count, protein, lung surfactant lipids and tumour necrosis factor alpha). Inflammation was present starting at the lowest dose. However, 8-OHdG showed a statistically significant increase starting at 1.5 mg/animal only. Similarly, in another study, 8-OHdG and DNA strand breaks were observed at concentrations of or above 10 ug/m^3 in rat lung epithelial cells.

In the aim of investigating the role of ROS in lung carcinogenesis, rat lung epithelial cells were incubated with polymorphonuclear (PMN) leukocytes (involved in the inflammatory process and responsible for the release of certain ROS) or hydrogen peroxide. Statistically significant increases in 8-OHdG were observed in the presence of PMN or hydrogen peroxide in a dose-response manner.

In a series of experiments which used *in vitro* stimulation of macrophages with crystalline silica and *in vivo* intranasal instillation of crystalline silica in mice, it was demonstrated that that the chronic fibrosis seen in a murine model of silicosis *in vivo* is dependent on the presence of adaptor molecule ASC and Nalp3 inflammazome. These data support a potential mode of action whereby silica triggers cellular responses that in turn activate alveolar macrophages, resulting in an inflammatory response and silicosis. In mice deficient in Nalp3 inflammazome, the development of inflammation and collagen deposition was significantly reduced compared with normal mice 3 months after the initial intranasal instillation of silica.

Analysis of Lung Tumour Data

The weight of evidence for both rats and humans indicates that fibrotic and silicotic lesions in the lung result from inhalation exposure to crystalline silica and that lung cancer is secondary to those lesions in the lung. Although the mechanism of induction for the lung tumours has not been fully elucidated, there is sufficient supportive mode of action evidence from the data presented to demonstrate that a threshold approach to risk assessment is appropriate based on an understanding of the key events in the pathogenesis of crystalline silica induced lung tumours. The body of evidence include the following:

- In experimental studies, all rats that developed tumours also showed fibrosis.
- Adenocarcinomas, the most common type of tumour identified in rats, are commonly associated with fibrosis and deeply scarred lung tissue.
- Experimental rat studies showed a clear progression of the effects from initially mild inflammation, followed by fibrosis over-time, leading eventually to lung tumours.
- Tumours are not present in all treated species dosed in the same way.
- The tumours, both in rats and humans, are concentrated in the lungs only, although other organs are indirectly exposed.
- In human studies, cancer risk is often more significant in workers exposed over a 20 year period or to higher cumulative exposure levels; however a consistent finding is that the onset of silicosis, requires a smaller lag period than that for the appearance of tumours.
- Similarly, cancer risk is often more significantly associated at higher quintiles of exposure compared to the lower quintiles
- Lung cancer rates are higher in workers confirmed to have silicosis versus similarly exposed workers that do not have silicosis.
- For genotoxicity, in vitro results were mostly mixed and in vivo results were mostly positive. However, the vast majority of the positive genotoxicity assay results can be explained by the generation of reactive oxygen species, as demonstrated experimentally, where ROS scavenging prevents the genotoxicity.
- *In vivo*, macrophage deficient mice (macrophages produce ROS in response to crystalline silica) do not develop silicosis nor do they develop tumours and the Nalp3 inflammazome, a key player in the

macrophage initiated inflammatory response, is required for the development of pulmonary fibrosis after inhalation of silica.

- Though inhalation exposure to crystalline silica in multiple occupational settings is clear, the increase in risk, based on the several recent meta-analyses of the multiple human epidemiological studies, remains low.

It is worth noting that where aggressive engineering controls have been made to reduce silica dust levels in the workplace (Sweden), silicosis has been eliminated. By corollary, existing exposures outside of the workplace in such areas do not pose a risk for silicosis to the general population.

The respirable forms of quartz and cristobalite possess properties indicating a hazard for human health (repeated dose toxicity, carcinogenicity and genotoxicity). The mode of action in the lungs involves irritation, inflammation and reactive species formation, leading to silicosis, and eventually to tumour formation.

Exposure

Uses

Consistent with oxygen and silicon being the two most abundant elements in the Earth's crust, silicon-oxide minerals, including quartz are ubiquitous in the natural environment. In particular, as a component of sand, quartz may find use in a diverse array of applications. Several high volume uses include, but are not limited to, the use of sand as a filling material for the construction of roads and in general building activities, the use of sand and gravel aggregates as abrasives on roads in winter and the use of fly-ash, which may contain 4-14% quartz and 0.5-1% cristobalite, as a cement additive. These abrasives when used on winter roads are usually mixed with road salts and may be sand only, stone dust, sand and gravel aggregates, or pre-treated sand. They are used mainly by rural municipalities or in areas where cold temperatures diminish the efficiency of salts for de-icing. Quantities of abrasives used in Canada were 5.73×10^9 kg, 4.59×10^9 kg, and 4.93×10^9 kg for 2007, 2008 and 2009, respectively.

Industrial sand, high purity silica sand products with closely controlled sizing are expected to contain quartz and cristobalite, include lump silica (2-3mm up to 15 cm or more), silica sand (75µm to 2-3mm) and silica flour (less than 75µm). Lump silica may be used in the production of silicon alloys, silica bricks, and the linings of certain types of pulverizers (eg. ball mills and tube mills).

Silica sand may be used in the manufacture of glass and glass fibres, silicate chemicals and silicon carbide, the hydraulic fracturing of wells, foundry moulding, and for sandblasting. Silica flour may find use in the ceramics and cement industries, as a filler and extender in rubber and coatings, and as an abrasive in soaps.

Natural clays, such as bentonite and fuller's earth, are used in cat litters for their high water absorbance capacities. Quartz is a natural component of these clays, and consequently, it may be present in cat litter products. High purity α-quartz is a piezoelectric material, which means that application of a voltage induces a distortion in the crystal shape and vice versa. This ability to interconvert electrical and mechanical energy has led to the use of quartz crystals in electronic devices requiring precise timing control, for example telephones, radios, watches and computers.

According to a survey conducted in Canada, quartz and cristobalite are also used in abrasives, adsorbents, filter products (diatomaceous earth), grout and cement. These substances reportedly also find use as fillers, which add bulk and improve wear resistance, in paints and coatings, adhesives, sealants, polymer films, caulking, epoxy resins and silicones. Also, quartz is listed as an ingredient in 60 cosmetic products in Canada. The types of products include anti-wrinkle preparation, eye and face makeup, lipstick, hair dyes, shampoos and grooming products, as well as skin cleansers, moisturizers and tanning preparations.

Natural Sources

In Canada, quartz naturally occurs in many types of rock formations. Those with high silicon dioxide content (95% SiO_2 or more) include vein and massive intrusion bodies, quartz pebbles, silica sand, sandstone and quartzite. Sandstone is a sedimentary rock mostly composed of quartz grains cemented by a bonding material such as clay, calcite or iron oxide. Quartzite is a hard, compact, metamorphosed sandstone made of grains of quartz firmly bonded with a siliceous cement. Mineral aggregates (e.g., sand and gravel) have variable silicon dioxide content. Quartz is also found as crystals, aggregates or discrete particles in certain igneous rocks (e.g., granites and pegmatites), soils, sediments, air and surface water. This omnipresence is consistent with the fact

that silicon is the second most abundant chemical element on Earth.

Cristobalite is naturally produced in the ashes of volcanic eruptions, and by combustion metamorphism which is a local phenomenon of spontaneous combustion of naturally occurring substances such as bituminous rocks, coal or oil. It may be found in cavities in volcanic rocks and in thermally metamorphosed sandstones and may also be a transient stage in the diagenesis of diatomaceous shale with the result that soils made of these geologic formations may be rich in cristobalite. Unlike quartz, the natural occurrence of cristobalite is limited to specific geographic regions and mineral types.

Anthropogenic Sources

Natural quartz is isolated from ore via beneficiation, which involves milling or grinding the material into particles that are separated into desired mineral and waste. The materials obtained are either used directly or further purified. In Canada, in 2006, 2.146×10^{9} kg of pure quartz were mined, and 2.385×10^{11} kg of sand and gravel aggregates were produced. The proportion of quartz in silica sand deposits and gravel aggregates will vary from one site to another.

Cristobalite can form from silica melts during the preparation of silica glass; quartz is not obtained from melts but is manufactured at elevated temperature and pressure via a hydrothermal process. Cristobalite also forms during the calcination[2] of diatomaceous earth.

Human Exposure Estimate

Ambient air

The exposure assessment is focussed on respirable quartz and cristobalite, which in ambient air comprises a component of total particulate matter (PM). In Canada, data on the concentrations of silicon in PM was available and used as a surrogate for quartz and cristobalite. This approach is conservative because the measured silicon includes all silicon-containing substances and therefore represents the upper limit for quartz and cristobalite in ambient air.

The National Air Pollution Surveillance (NAPS) Program measured concentrations in $\mu g/m^3$ of silicon in PM with aerodynamic radii less than 2.5 μm ($PM_{2.5}$ (dichot)), and from 2.5 to 10 μm (PM_{10} (dichot)) (the total particulate matter with aerodynamic radii less than 10 μm (PM_{10}) is obtained by adding these values) in Canada. In 2009, as part of the NAPS Program, silicon concentrations were determined on over 1600 samples of $PM_{2.5}$(dichot) and over 1500 samples of PM_{10}(dichot) at 24 urban locations across Canada. An estimate of exposure to quartz and cristobalite can be obtained by assuming that all the silicon in the PM is represented stoichiometrically as SiO_2, and multiplying the reported concentration of silicon by 2.14 to obtain a value for silica.

The intake of respirable quartz and cristobalite by the general population of Canada is estimated using a range covering the lowest 50^{th} percentile SiO_2 concentration in PM_{10}, measured in Pt. Petre, ON, (0.12 $\mu g/m^3$) to the highest 50^{th} percentile concentration in PM_{10} measured in Calgary, AB (2.1 $\mu g/m^3$). The 50^{th} percentile SiO_2 concentrations ranged from 0.1 to 2.1 $\mu g/m^3$ across the survey sites; the top of this range is quite close to the average of the maximum values for the 24 sites (3.7 $\mu g/m^3$). The outdoor data were used to represent the indoor levels, because information on indoor silicon concentrations was not available, and the range of PM_{10} measured indoors is generally lower than the outdoor range. Thus, this approach conservatively overestimates indoor exposure in homes.

The highest exposure group based on these calculations is children ages 0.5 to 4 years with an estimated daily intake ranging from 0.07 to 5.26 μg/kg-bw per day; the estimated daily intake decreases with age due to changes in the ratio of inhalation rates to body weights; the daily intake of adults, 20-59 years old, is estimated to range from 0.03 to 2.00 μg/kg-bw per day.

Consumer Products

Exposure to respirable quartz from the use of cosmetic products, which contained quartz as an ingredient, was considered low because they are not formulated for spray application, the loose powders were reported to contain less than 0.1% quartz, and in these products the substance is not expected to be associated with other components of the formulation and not available in a free form.

For consumer Do It Yourself (DIY) activities around the home, the highest mean breathing zone concentration

[2] Calcinations: Heat treating a substance, but without fusion, to bring about change in its physical or chemical constitution.

of particles from sanding dry wall (median cut-point of 10μm) of 6.31 mg/m^3, was used to derive an upper-bound exposure estimate ranging from 2 to10 μg/kg-bw per event.

Quartz is used to formulate a large number of paints and coatings. To estimate potential inhalation exposure to quartz from these products, the spray painting of wall paints with an airless spray gun was considered appropriate as a conservative scenario. Exposure to respirable paint particles was estimated using data from controlled a laboratory study in which walls of poorly ventilated test rooms were painted by professional painters using an airless sprayer to apply interior latex paint. The maximum concentration of 13% quartz in paint in Canada was used to estimate exposure. The upper-bound estimate of exposure to quartz, based on the maximum concentration of 13% quartz in paint in the Canadian market and the maximum concentration of respirable paint particles measured in these controlled studies when recommended personal protective equipment is used, is 0.954 μg/kg-bw per event.

Inhalation of ambient air containing quartz and cristobalite is the dominant pathway of chronic exposure (excluding that from DIY activities) for the general population. Because SiO_2 makes up only approximately 5% of PM_{10}, silicon concentrations (expressed as SiO_2) measured in the Canadian NAPS survey of 24 urban locations were considered most relevant to the estimation of exposure by the general population. Quartz and cristobalite comprise only a portion of the total SiO_2 in PM_{10}, therefore, the use of the total silicon concentration to represent the upper bound crystalline silica concentrations results in an overestimation of exposure.

Appendix 1: Definitions of Epidemiological Terms in the ITAP

SMR (Standardized Mortality Ratio): The ratio (x 100) of observed to expected deaths in a study population. Expected deaths are calculated by applying a set of standard age-specific mortality rates to the age distribution of the study population. Standardized ratios are only useful for comparisons. They have no intrinsic meaning.

OR (Odds Ratio): In epidemiological case-control studies, a relative measure of disease occurrence. The odds in favour of a particular disease occurring in an exposed group are divided by the odds in favour of its occurring in an unexposed group. If the condition being studied is rare, the odds ratio is a close approximation to the relative risk.

RR (Risk Ratio): The probability of the occurrence of a disease in a group that has been exposed to some environmental, medicinal, microbial, or toxic influence, relative to its probability in a randomly selected population.

PMR (Proportionate Mortality Ratio): Proportionate mortality is the proportion of deaths in a specified population over a period of time attributable to different causes. Each cause is expressed as a percentage of all deaths, and the sum of the causes must add to 100%. These proportions are not mortality rates, since the denominator is all deaths, not the population in which the deaths occurred. Thus, proportionate mortality ratio is a measure of the frequency of occurrence of the proportionate mortality in a defined population during a specified interval of time.