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RESEARCH ARTICLE

Ceramics manufacturing contributes to ambient silica air pollution and burden of lung disease

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Abstract Inhalation of silica (SiO_2) in occupational exposures can cause pulmonary fibrosis (silicosis), lung function deficits, pulmonary inflammation, and lung cancer. Current risk assessment models, however, cannot fully explain the magnitude of silica-induced pulmonary disease risk. The purpose of this study was to assess human health risk exposed to airborne silica dust in Taiwan ceramics manufacturing. We conducted measurements to characterize workplace-specific airborne silica dust in tile and commodity ceramic factories and used physiologically based alveolar exposure model to estimate exposure dose. We constructed dose–response models for describing relationships between exposure dose and inflammatory responses, by which health risks among workers can be assessed. We found that silica contents were 0.22–33.04 % with mean concentration ranges of 0.11–5.48 and 0.46–1763.30 μg m^{-3}, respectively, in commodity and tile ceramic factories. We showed that granulation workers in tile ceramic factory had the highest total SiO_2 lung burden (~1000 mg) with cumulative SiO_2 lung burden of ~4×10^4 mg-year. The threshold estimates with an effect on human lung inflammation and fibrosis are 407.31±277.10 (mean± sd) and 505.91±231.69 mg, respectively. For granulation workers, long-term exposure to airborne silica dust for 30–45 years was likely to pose severe adverse health risks of inflammation and fibrosis. We provide integrated assessment algorithms required to implement the analyses and maintain resulting concentration of silica dust at safety threshold level in the hope that they will stimulate further analyses and interpretation. We suggest that decision-makers take action to implement platforms for effective risk management to prevent the related long-term occupational disease in ceramics manufacturing.

Keywords Silica · Ceramics manufacturing · Lung · Silicosis · Air pollution · Risk assessment

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Introduction

Adverse health effects from exposure to silica are some of the most important concerns of public health because workers in a variety of industries and occupational settings are excessively exposed to respiratory crystalline silica. It is estimated that at least two to three million workers worldwide are occupationally exposed to silica annually (Jutzi and Schubert 2003; Sellamuthu et al. 2013). Inhalation of silica in occupational exposures can cause pulmonary fibrosis (silicosis), lung function deficits, pulmonary inflammation, and lung cancer and has been associated with glomerulonephritis and disorders of the liver, spleen, and immune systems (Başaran et al. 2002; Brown and Rushton 2005; Calvert et al. 2003; Chen et al. 2005; 2012; Meijers et al. 1996; Möhner et al. 2013; Sellamuthu et al. 2013).

Rong et al. (2013) and Sellamuthu et al. (2013) indicated that the biological effects of silica included direct ones on several pathways such as inflammatory responses, cell-to-cell signaling and interaction, cellular movement that lead to inflammatory and respiratory diseases, and finally cancer. Porter et al. (2006) and Shen et al. (2001) indicated that silica could produce reactive oxygen species (ROS) and lipid peroxidation to disrupt lipid rafts and active protein tyrosine kinase, resulting in the subsequent translocation of transcription factors. Several studies (Dostert et al. 2008; Kuroda et al. 2011; Premasekharan et al. 2011) also implicated that link to pathogenic silica-related pulmonary inflammatory diseases could ultimately lead to fibrosis and lung cancer. Taken together, based on the observations in animal models and in human lungs with silica-related lung diseases, inflammatory responses are hallmarks of exposure to silica.

A previous study indicated that 32 % of the material samples contain crystalline free silica in ceramics manufacturing environment across Taiwan region in that glazing worker had the highest average dust exposure of 1.37 mg m^{-3} (Lin et al. 2003). They also found that dust with crystalline free silica in all process zones were within the respirable range. In China, a significant exposure–response relationship was also found between cumulative silica dust exposure and mortality from all causes, respiratory diseases, respiratory tuberculosis, and cardiovascular diseases (Chen et al. 2012). Chen et al. (2012) implicating that the long-term silica dust exposure was strongly associated with substantially increased mortality among Chinese workers.

Numerous well-established physiologically based mathematical models have been developed in a decade for describing respirable crystalline silica dynamics, inflammatory reaction, and fibrosis development (Kuempel et al. 2001a; 2001b; Tran et al. 2001; 2002). Cox (2011) used a statistical analysis to investigate the exposure–response relations between crystalline silica and risk of lung pathologies. Morfeld et al. (2013) reported that the best threshold estimate was 0.25 (95 % confidence interval (CI) 0.15–0.30)mg m^{-3} for the respirable quartz dust concentration and silicosis incidence among workers in German porcelain industry.

Currently, however, no information is available on the potential silicosis risk related to occupational exposures in Taiwan. Furthermore, setting scientifically based limit values is complicated, owing to the difficulties in interpreting heterogeneous experimental and epidemiological findings (Chen et al. 2001a; OEHHA 2005; Zhuang et al. 2001). Despite much recent progress in our understanding of source attribution, emission factors, and regulation of silica (Chen et al. 2012; Rong et al. 2013; Sellamuthu et al. 2013), current risk assessment models based on parameterization of laboratory experiments cannot fully explain the magnitude of silica-induced pulmonary disease risk. Furthermore, the silicosis is rated the most prevalent occupational disease among all industries in Taiwan (Shih et al. 2008).

The objective of this study was fourfold: (i) to characterize the workplace-specific airborne silica dust including particle size distribution, exposure profile, and silica content, (ii) to estimate the internal exposure dose by using a physiologically based alveolar exposure model to construct dose–response models for describing the relationships between exposure dose and inflammatory responses, (iii) to integrate a probabilistic risk assessment framework and derived dose–response profiles to estimate silica dust exposure risks among workers, and (iv) to employ a statistical threshold concept to derive point and interval concentration threshold estimates for airborne silica dust exposure.

Materials and methods

Study population

In Taiwan region, Yingge district is where local industries are majorly (~80 %) dominated by ceramics manufacturing (Fig. 1a). Yingge district, situated in New Taipei City, Taiwan, has a population of nearly 90,000 peoples. Epidemiological report indicated that all-cause mortality of Yingge (~16 per 100,000 populations) was ranked the tenth in New Taipei City in that the majority was strongly associated with pneumoconiosis (~5 per 100,000 populations) (Ministry of Health and Welfare (MOHW and Taiwan) 2011). Here we selected two representative ceramics manufacturing of commodity (~20 workers) and tile ceramic factories (~75 workers) as our study cases (Fig. 1b). The supplementary Figs. S1 and S2 detail the layouts of commodity and tile ceramic factories.

Measurements

Respirable particle dust samplings were conducted in 12 working areas during working hours (8 h) in 12 days dispersed in June and July (Supplementary Figs. S1 and S2). Five working areas were selected in commodity ceramic factory including molding (grouting), molding (extrusion), repairing, glazing, and burning (Fig. S1). On the other hand, in tile ceramic factory, seven working areas included soil mixing, glaze mixing, granulation, molding, drying and glazing, burning (at entrance), and burning (at middle) (Fig. S2).

An aerosol spectrometer (Grimm 1.109) (PAS 1.109, Grimm Technologies, Germany) was used to measure the mass concentration of airborne dust particles and particle size distributions from 0.22 to 32 μm with a flow rate of 1.2 l min^{-1}. A 37-mm aluminum cyclone (Cat. No. 225-01-02, SKC Inc., USA) with a flow rate of 2.5 l min^{-1} was used to measure airborne dust particle deposition dose that represents the inhaled dust particle burden in the alveolar–interstitial (AI)

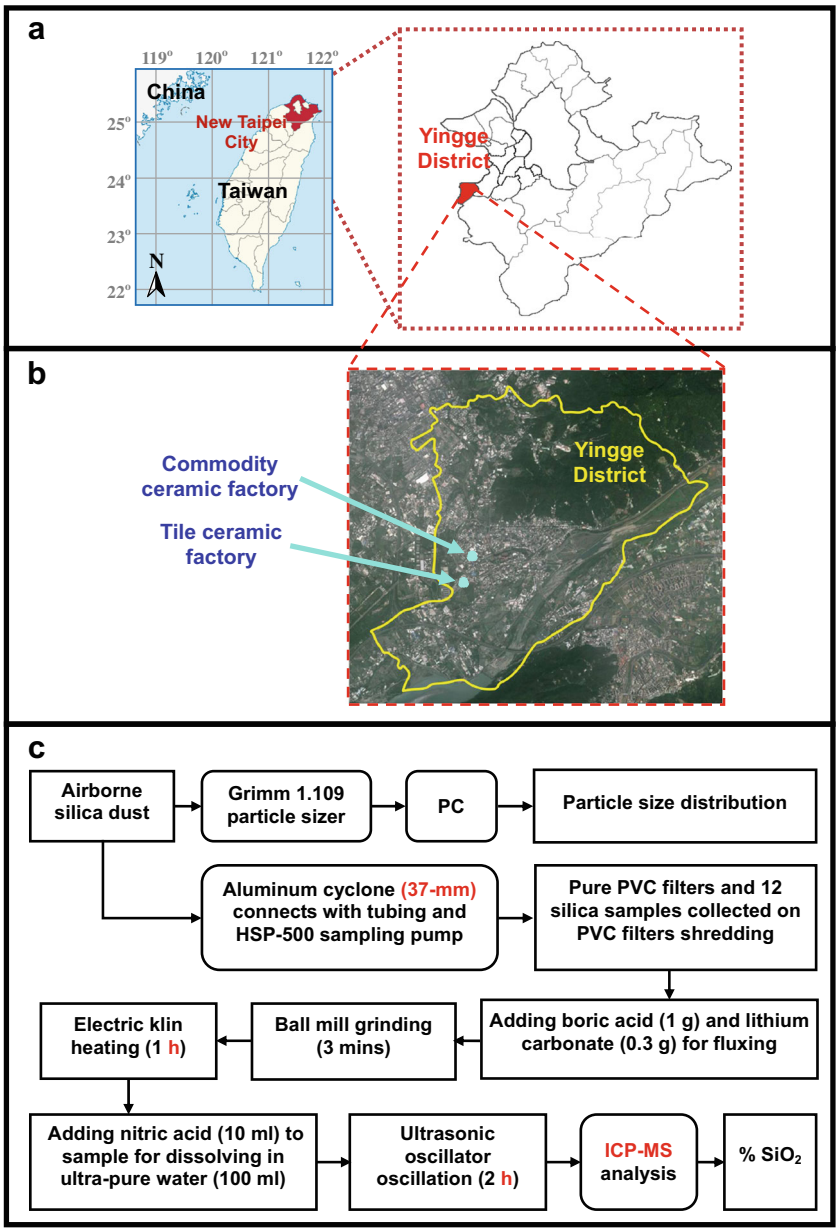

Fig. 1 **a** Study area, **b** sampling locations, and **c** schematic showing the processes of measurement and quantification of silica

region. Instruments were racked at a height of 165–170 cm (average height of adults) to sample respirable silica dust in the breathing zone.

The sampled filters that were collected from 12 sampling points were mixed with 1 g H_3BO_3 and 0.3 g Li_2CO_3 to enhance filter melting. The treated filters were then placed in an electric kiln and calcined at a temperature of 1000 °C for 1 h. Waiting for cooling down, 10 ml HNO_3 was added to the molten samples for dissolving in 100 ml ultra-pure water and then agitated by an ultrasonic oscillator for 2 h. An inductively coupled plasma–mass spectrometer (ICP-MS) (Ultima 2000, Jobin Yvon, France) was used to determine the silica content in the samples. Figure 1c illustrates the overall measuring processes.

Alveolar deposition model

We used a compartmentalized physiologically based alveolar deposition (PBAD) model developed by Kuempel et al. (2001a; 2001b) and Tran et al. (2001; 2002) to estimate SiO_2 lung burden. The PBAD model is capable of describing the long-term total silica burden and the alveolar macrophage-mediated clearance processes in the pulmonary region associated with the particle redistribution and the overload phenomena.

The PBAD model mainly divides the lung into three regions of alveolar surface, interstitium, and lymph nodes (Supplementary Fig. S3). The alveolar surface region contains two compartments: one for incoming daily inhaled SiO_2 dose (D) in alveolar region (A) and the other represents alveolar

macrophages (M). On the other hand, there is one compartment assigned for interstitium region (I). From the interstitium region, some free particles inside interstitial macrophages can be removed to the lymph node region that is represented by compartment L.

Tran et al. (2001; 2002) have comprehensively described the PBAD model framework and the essential model parameters characterizing the model structure and function. Briefly, the inhaled silica dust in the alveolar region (X_1) would be transferred into the alveolar macrophage (X_2) by phagocytosis at a rate k_p (day^{-1}) and in turn results in X_2 in M compartment being released into the alveolar region after apoptosis of macrophage at a certain rate k_d (day^{-1}). The silica dose in alveolar surface can be also transferred into the interstitial region (X_3) and lymph nodes (X_4) by rates of k_i and k_l (day^{-1}), respectively. Moreover, alveolar macrophages can consume inhaled silica dust by a physical clearance rate of k_c (day^{-1}) (Supplementary Fig. S3).

A set of ordinary differential equations (Eqs. (1)–(5a and 5b)) can be reformulated based on Tran et al. (2001) with new parameter groupings to describe the dynamic behavior of PBAD model (Table 1). The lung physiological parameters and rate constants along with their likely values employed in the PBAD model are also given in Table 1.

To determine the daily inhaled SiO_2 dose (D) into AI region, a mass-basis dosimetric exposure model was used as

$$D = C \times \mathrm{DF} \times \mathrm{ED} \times \mathrm{BR}, \tag{1}$$

where C is the mass concentration of airborne silica dust ($\mu g\ m^{-3}$), BR is the breathing rate ($0.38 \pm 0.07\ m^3\ h^{-1}$) based on the investigation for Taiwanese (Ministry of Health and Welfare (MOHW and Taiwan) 2007), ED is the exposure duration (8 h), and DF is the silica deposition fraction in AI region and can be calculated as a function of particle diameter d_p (μm),

$$\mathrm{DF} = \left(\frac{0.0155}{d_p}\right)\left[\exp\left(-0.416\left(\ln d_p + 2.84\right)^2\right) + 19.11\exp\left(-0.482\left(\ln d_p - 1.362\right)^2\right)\right]. \tag{2}$$

Eq. (2) is obtained by fitting to the empirical model for monodisperse spheres with standard density and conditions, based on the deposition model of International Commission on Radiological Protection (ICRP) (Hinds 1999; ICRP 1994). Eq. (2) is suited for males and females at different exercise levels. In the size range of 0.001–100 μm, the errors of deposition fractions predicted by Eq. (2) agreed with the ICRP model within ±3 % (Hinds 1999).

Table 1 Equations for physiologically based alveolar deposition (PBAD) model along with point/range and used values of rate parameter used in this study

Interpretation	Equations[a]
Silica dose (mg) in alveolar region A: X_1	$\frac{dX_1}{dt} = D - k_p X_1 - k_i X_1 + k_d X_2$ (T1)
Silica dose in alveolar macrophage M: X_2	$\frac{dX_2}{dt} = k_p X_1 - k_c X_2 - k_d X_2$ (T2)
Silica dose in interstitial region I: X_3	$\frac{dX_3}{dt} = k_i X_1 - k_l X_3$ (T3)
Total silica dose in alveolar–interstitial region AI: X	$X(t) = X_1(t) + X_2(t) + X_3(t)$ (T4)
Silica dose in lymph nodes L: X_4	$\frac{dX_4}{dt} = k_l X_3$ (T5)
Rate parameter	Range value (day^{-1})
k_p	9.66×10^{-1} (0–9.66×10^{-1})[b, c]
k_c	1.10×10^{-4} (1.10×10^{-4}–4.4×10^{-3})[d]
k_d	3.30×10^{-2} [c]
k_i	1.15 (0–1.15)[c]
k_l	2.80×10^{-6} (2.8×10^{-6}–4×10^{-5})[d]

[a] See text for symbol meanings

[b] (Min–Max)

[c] Adopted from Tran et al. (2001)

[d] Adopted from Kuempel et al. (2001b)

Dose–response model

Here we used a three-parameter Hill model that is commonly used in pharmacodynamic modeling to optimally fit the experimental data to construct dose–response profiles taking into account the silica dust exposure effects on human lung inflammation and fibrosis. The well-analyzed data points from Porter et al. (2001; 2002) were appropriately and carefully selected (Supplementary Table S1). They used the number of polymorphonuclear leukocytes (PMN) isolated from bronchoalveolar lavage (BAL) of silica-exposed rats as the marker of inflammation (Porter et al. 2002). On the other hand, Porter et al. (2001) used a biochemically based hydroxyproline (HYP) as the marker of pulmonary fibrosis.

Hill model captures the relation between SiO_2 lung burden and effect (E) as

$$E = \frac{E_{max}}{1 + \left(\frac{EC50}{X}\right)^n}, \tag{3}$$

where X is the SiO_2 lung burden (mg), E_{max} is the maximum dose effect, EC50 is the concentration that causes an effect equal to half of the E_{max} (mg), and n is a slope factor referred

to as the Hill coefficient determining the overall shape of the curve. Hill coefficient is a measure of cooperativity. A value of $n>1$ indicates positive cooperativity.

Predictive risk threshold

To protect the ceramics manufacturing workers from pulmonary diseases when exposed to airborne silica dust, the conservative EC1 values representing 1 % adverse effects when exposed to airborne contaminants were considered (Gaylor 1989). A three-parameter Weibull threshold model was employed to best fit with the EC1 cumulative distribution functions (cdfs) of toxicity data for estimating the threshold concentrations causing adverse pulmonary effects that can be used as guidelines. The estimated EC1 cdfs can be derived from the Hill-based dose–response models in Eq. (3) by fitting with the toxicity data and treated probabilistically.

The Weibull threshold model can be written as

$$F(X) = 1-\exp\left[-\left(\frac{X-\gamma}{\alpha}\right)^{\beta}\right],\ X>\gamma>0,\ \alpha>0,\ \beta>0, \tag{4}$$

where $F(X)$ represents the EC1 cdf data corresponding to the specific SiO_2 lung burdens, α is the scale parameter, β is the shape parameter, and γ is the fitted threshold (mg).

Probabilistic risk model

Applying the Hill-based dose–response model in Eq. (3), the cdf of predicted adverse effects for a given SiO_2 lung burden can be expressed mathematically as the conditional cdf of $P(\text{PMN}|X)$ and $P(\text{HYP}|X)$ for pulmonary inflammation and fibrosis, respectively. Thus, followed by the Bayesian inference, the exposure risk posed by airborne silica dust (the posterior probability) can be calculated as the product of $P(X)$ (the prior probability) and the conditional probability of $P(\text{PMN}|X)$ or $P(\text{HYP}|X)$ (the likelihood) where $P(X)$ represents the probability density of SiO_2 lung burden. It results in a joint probability function or exceedance profile, which describes the probability of exceeding the concentration associated with a particular degree of effect.

This can be expressed mathematically as a probabilistic risk model as

$$R(E_I) = P(X)\times P(\text{PMN}|X), \tag{5a}$$

$$R(E_F) = P(X)\times P(\text{HYP}|X), \tag{5b}$$

where $R(E_I)$ and $R(E_F)$ are the cdfs describing the exposure probabilistic risks of human pulmonary inflammation and fibrosis, respectively. Graphic display of Eq. (5a and 5b) provides a means of assessment on the occupational exposure of ceramics manufacturing workers to airborne silica dust based on pulmonary responses of silica-induced inflammation and fibrosis. The exceedance risk profile can be obtained by $1-R(E)$.

Uncertainty and data analysis

To quantify the uncertainty and its impact on the estimation of expected risk, a Monte Carlo (MC) simulation was implemented that included input distributions for the parameters of the derived dose–response function as well as for estimated exposure parameters. Largely because of limitations in the data used to derive model parameters, inputs were assumed to be independent. A total of 10,000 iterations were made in the MC simulation to ensure the stability of results.

Moreover, a MC simulation with 10,000 iterations was also performed to generate 2.5 and 97.5 percentiles as the 95 % confidence interval (CI) for the PBAD and the fitted dose–response model. Crystal Ball® software (Version 2000.2, Decisioneering, Denver, Colorado, USA) was used to implement the MC simulation. Table Curve 2D (Version 5.01, AISN Software Inc., Mapleton, OR, USA) was used to perform the model fittings including size distribution profiles with lognormal model, dose–response relationships by Hill model, and threshold estimates through Weibull model. The PBAD model simulation was performed by Berkeley Madonna: Modeling and Analysis of Dynamic Systems (Version 8.3.9, http://www.berkeleymadonna.com). The overall framework and computational algorithm of this study is illustrated in Supplementary Fig. S4.

Results

Quantitative analysis of data

The working area-specific size distributions of airborne dust particle measured from commodity and tile ceramic factories were demonstrated in Fig. 2. Our results indicated that the lognormal (LN) distribution model was successfully fitted to the size distribution measurements (r^2=0.70–0.93 and 0.91–0.96 with $p<0.001$ for commodity and tile ceramic factories, respectively) (Fig. 2, Supplementary Table S2). We found that commodity ceramic factory had mass median aerodynamic diameter (MMAD) estimates ranging from 5.64 μm in burning area to 10.86 μm in repairing area, whereas the MMADs ranged from 7.26 μm in glaze-mixing area to 20.90 μm at burning entrance area in tile ceramic factory (Table 2).

On average, 70 % of the particles from commodity and tile ceramic factories were larger than 8 and 12 μm in diameter,

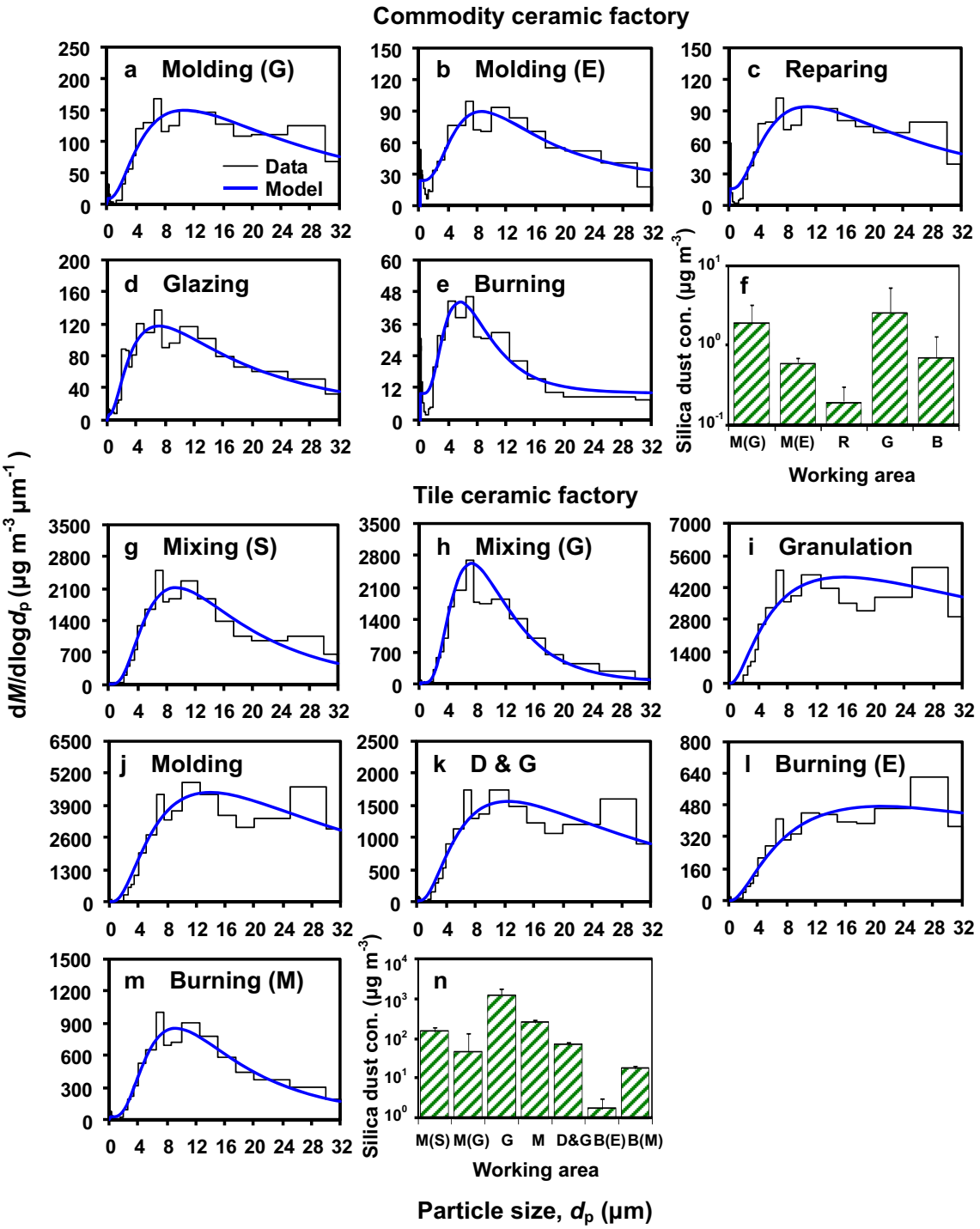

Fig. 2 **a**–**e**, **g**–**m** Working area-specific size distributions of airborne dust particle and **f**, **n** concentrations of silica dust measured from two selected factories

respectively. Notably, the particle size distributions in granulation, molding, drying/glazing, and burning areas experienced likely bimodal fashions compared to the other working areas at tile ceramic factory (Fig. 2i–l).

The measured silica contents ranged from 0.22 % in repairing area to 2.18 % in glazing area at commodity ceramic factory, whereas 0.46 % in burning entrance to 33.04 % in granulation area at tile ceramic factory (Table 2). The concentrations of airborne silica dust inside working areas during operating were very high in tile ceramic factory (1246.32±516.98 (mean±sd), 250.08±43.85, and 148.72±39.30 μg m^{-3} in granulation, molding, and soil-mixing areas, respectively), compared with those from commodity ceramic factory (ranging from 0.21±0.10–2.64±2.84 μg m^{-3}) (Fig. 2f, n and Table 2).

Table 2 Working area-specific particle size distribution and concentration at commodity and tile ceramic factories

Working area	MMAD (μm)[a]	GSD[a]	Silica content (%)	Silica dust concentration (μg m^{-3})
Commodity ceramic factory				
Molding (grouting)	10.76	2.44	1.37	1.93±1.40[b]
Molding (extrusion)	8.69	1.95	0.56	0.55±0.13
Repairing	10.86	2.28	0.22	0.21±0.10
Glazing	7.13	2.50	2.18	2.64±2.84
Burning	5.64	1.74	1.77	0.71±0.57
Tile ceramic factory				
Soil mixing	9.46	2.00	9.48	148.72±39.30
Glaze mixing	7.26	1.73	3.13	46.68±90.57
Granulation	15.72	3.03	33.04	1246.32±516.98
Molding	13.92	2.47	7.33	250.08±43.85
Drying and Glazing	12.48	2.44	5.27	69.55±11.87
Burning (at entrance)	20.90	3.08	0.46	1.74±1.28
Burning (at middle)	9.26	1.94	2.72	17.39±3.65

[a] MMAD and GSD stand for mass median aerodynamic diameter and geometric standard deviation, respectively. Fitted by $\mathrm{LN}(a,b,c,d) = a + b\exp\left[-0.5\left(\frac{\ln(x/c)}{d}\right)^2\right]$ where c and e^d represent MMAD and GSD, respectively

[b] Mean±sd

Lung deposition analysis

Our results indicated that glazing workers in commodity ceramic factory were exposed to higher airborne silica dust with a total SiO_2 lung burden of nearly 1–10 mg during 10–45-year exposure period (Fig. 3a). From a 45-year long-term exposure point of view, the cumulative SiO_2 lung burden for glazing workers were ~150 mg-yr (Fig. 3b). On the other hand, we found that granulation workers in tile ceramic factory appeared to be having the highest total silica SiO_2 lung burden (~1000 mg) with a 45-year cumulative SiO_2 lung burden of ~4×10^4 mg-yr (Fig. 3c, d).

Dose–response analysis

The Hill model provided an adequate fit to the human SiO_2 lung burden data converted from the published rat-model data (Supplementary Table S1) and associated responses in PMN (r^2=0.68, p<0.05) (Fig. 4a) and HYP (r^2=0.88, p<0.05) (Fig. 4b). Our results showed that the 50 % effective SiO_2 lung burden estimate (EC50) for PMN and HYP were 1585.50±618.15 mg (mean±sd) and 1603.30±401.32 mg, respectively. The fitted Hill coefficients (n) were estimated to be 9.99 for both PMN and HYP. Moreover, the estimated average maximum effects for PMN and HYP were 210.10±216.23 and 4.79±3.36 folds of normalized adverse effect elevation, respectively.

Threshold estimation

Our results showed that the Weibull threshold model could best fit to the relationship between SiO_2 lung burden and EC1 data representing probability of causing 1 % adverse effect elevation on inflammation and fibrosis (r^2=0.99, p<0.001) (Fig. 5). The fitted threshold estimates (γ) were 407.31±277.10 (mean±sd) and 505.91±231.69 mg for inflammation and fibrosis, respectively, indicating that there is no significant difference between the two thresholds.

Risk estimates

Our results showed that airborne silica dust in commodity ceramic factory was unlikely to pose substantial risk on lung inflammatory and fibrotic responses for workers in the worst glazing area under the short- and long-term exposure scenarios (Fig. 6a, b). However, there were on average 10^2 and 10^1 folds of adverse effect elevation, respectively, for granulation workers in tile ceramic factory having 50 % probability rendered lung inflammation and fibrosis (Fig. 6c, d).

To complement the risk analysis and to characterize incremental long-term exposure adverse effects, we linked Figs. 4 and 5 for determining the marginal values to designate the mild, moderate, and severe responses from inflammation and fibrosis. We used the threshold estimates γ+sd and γ−sd from Fig. 5 to determine normalized adverse effect elevations by using Fig. 4, resulting in the marginal values in the mild–moderate–server schemes for inflammation and fibrosis (Fig. 7a, b).

Based on risk profiles in Fig. 6, the incremental adverse effects for workers in the worst working areas in commodity and tile ceramic factories during incremental short- and long-term exposures can then be determined (Fig. 7c, d, e, f,

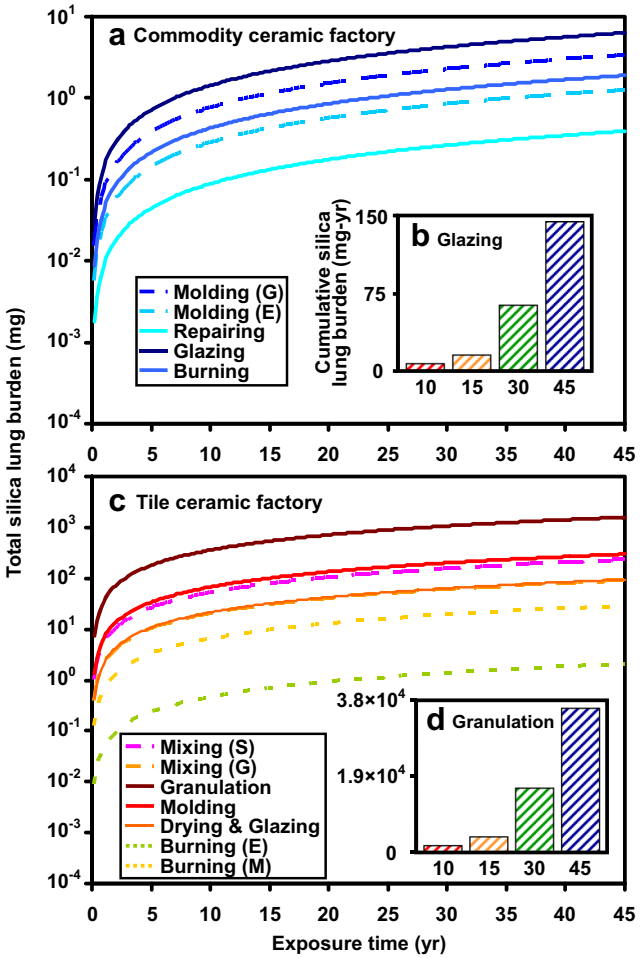

Fig. 3 **a**, **c** Time-dependent total SiO_2 lung burden and **b**, **d** cumulative SiO_2 lung burden at most influenced working areas in two selected factories

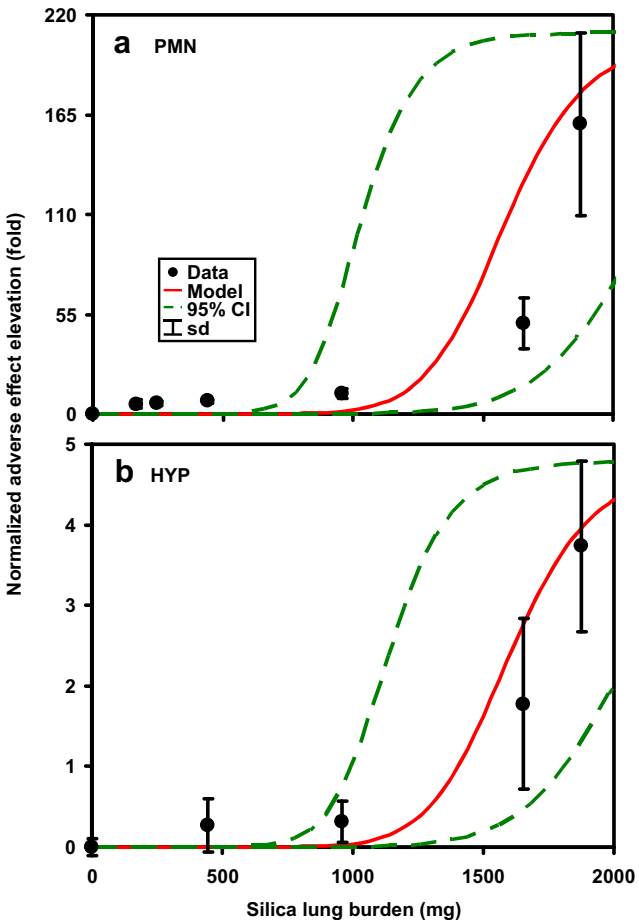

Fig. 4 Dose-response profiles fitted by the Hill model with 95 % confidence interval on **a** polymorphonuclear leukocytes (PMN) and **b** hydroxyproline (HYP)

Supplementary Table S3). Our results indicated that glazing workers in commodity ceramic factory experienced mild incremental adverse effects from inflammation and fibrosis for incremental 10–15-, 15–30-, and 30–45-year exposures (Fig. 7c, d). However, for granulation workers in tile ceramic factory, severe incremental adverse effects from inflammation and fibrosis were likely to set off a health alarm during an incremental 30–45-year exposure (Fig. 7e, f).

Discussion

Occupational hazard with long-term exposure

Our study revealed that measured daily 8-h concentrations of airborne silica dust in working areas were much higher in tile than those in commodity ceramic factory ranging from 0.46 to 1763.30 and from 0.11 to 5.48 μg m^{-3}, respectively, with silica contents of 0.22–33.04 %. Cherry et al. (1998) indicated that daily 8-h time-weighted concentration of respirable silica dust ranged from 2 to 800 μg m^{-3} with mostly between 50 and 200 μg m^{-3} in UK pottery factories. Chen et al. (2012) found that mean concentrations of respirable silica dust ranged from 120 to 300 μg m^{-3} in China pottery factories (Chen et al. 2012). Chen (2002) indicated that a maximum concentration of 5750 μg m^{-3} with silica content <10 % was found in Taiwan ceramics manufacturing. Our measured data were within the ranges of previous studies.

We also found that there was a potentially higher health risk of inflammation to workers exposed to silica dust associated with a longer duration of employment. This finding implicates that the development of pneumoconiosis, fibrosis, and pulmonary diseases are most likely to occur in the future with the persistence of exposure. In Taiwan, statistical data showed that the majority in labors' insurance benefit payment for occupational disease was pneumoconiosis of 34.2±28.8 % in the period 2003–2012 (Ministry of Labor and Executive Yuan 2012). Long-term occupational silica exposure can also lead to deterioration of lung function, even in the chronic low-level silica dust exposure (Mwaiselage et al. 2004). Ehrlich et al. (2011) have correlated respirable silica dust exposure with

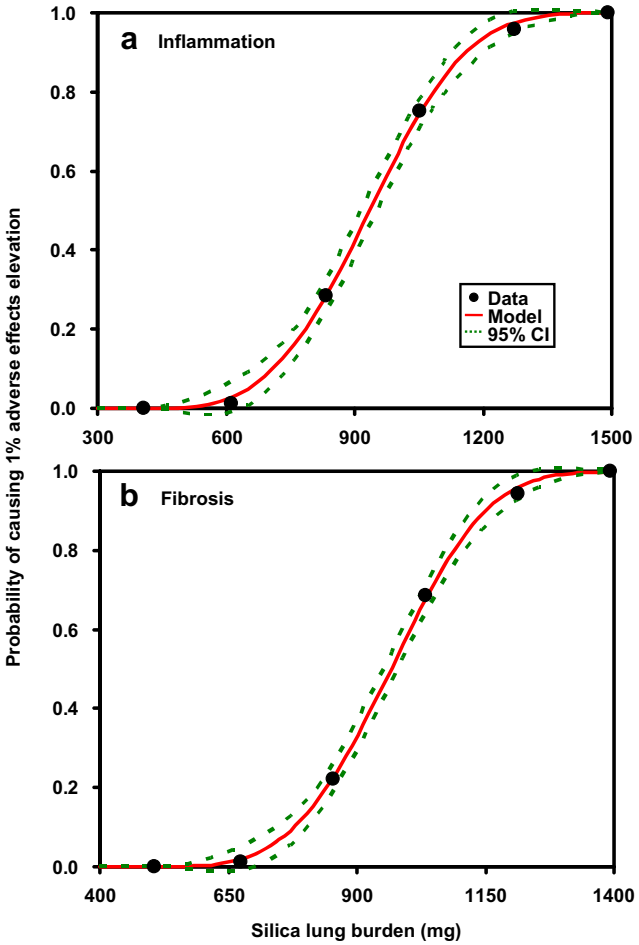

Fig. 5 Threshold curves fitted by the Weibull threshold model to the relationship between probability of causing 1 % adverse effect elevation and SiO_2 lung burden on **a** inflammation and **b** fibrosis

lung function loss for gold miners with average service duration of 21.8 years. They found an estimated mean loss of 3.0 ml in forced expiratory volume in the first second (FEV_1) for each year of service in the absence of other diseases, implicating that for a 45-year working period, an additional 135 ml of FEV_1 could be deprived.

Chen (2002) reported that the prevalence of abnormal lung function were 79 and 81 % for male and female ceramic workers, respectively. Chen et al. (2001b) found that the decline of ratio of FEV_1 to forced vital capacity was significantly higher in the exposed group than in the controlled group after adjustment for smoking. Whether exposure to silica dust is associated with lung cancer for workers has been debated for a long time. Kachuri et al. (2014) indicated that an increasing duration of employment at any concentrations of silica dust exposure was associated with a significantly higher lung cancer risk in Canadian males with odds ratio of 1.76 (95 % CI 1.34–2.31) for ≥30 exposure years adjusted for age, residence, cigarette smoking, and passive smoking. Moreover, excessive and prolonged exposure to silica dust could lead to inflammation in the lung, resulting in pneumoconiosis and progression of pulmonary fibrosis and related lung diseases (Castranova and Vallyathan 2000; Dostert et al. 2008; Fubini and Hubbard 2003; Kuroda et al. 2011).

Epidemiological perspectives

In a UK study, risks of cause-specific mortality from respiratory diseases including chronic bronchitis and emphysema showed an increase with increased exposure to silica dust in the 15-year follow-up (Miller and MacCalman 2010). Meijers et al. (1996) showed that an extremely high standardized mortality ratio (SMR) for all causes among ceramic workers was 65.3. Chen et al. (2012) have conducted a retro-prospective cohort study of 74,040 Chinese workers from 1960 to 2003, indicating a SMR for all causes was 1.21 (95 % CI 1.19–1.23).

Workers exposed to silica dust posed a greater risk of cardiopulmonary mortality from all causes (hazard ratio (HR)= 1.026, 95 % CI 1.023–1.029), respiratory diseases (HR= 1.069, 95 % CI 1.064–1.074), and pneumoconiosis (HR= 1.060, 95 % CI 1.053–1.067) than non-exposed workers (Chen et al. 2012). Moreover, silicosis among workers was observed with significant SMRs of 20.6 (95 % CI 15.39–26.87) for exposure of 32 years (Graham et al. 2004) and of 30.5 (18.4–50.5) in the period 1982–1995 (Calvert et al. 2012). Steenland (2005) found that workers exposed to 0.1 mg m^{-3} respirable silica particle for 45 years were likely to pose a mortality risk of silicosis ranged from 47 to 77 %. The SMR for larynx cancer of 3.26 (1.30–8.22) was also reported in the ceramics manufacturing (Scarselli et al. 2011). Many studies have provided strong evidence for linking chronic inflammation resulting in fibrosis and lung damage to increased excess mortality from lung cancer risk in silicosis (Amabile et al. 2009; Le Jeune et al. 2007; Soutar et al. 2000). Spigno et al. (2007) reported that lung cancer risk was elevated among patients with silicosis, especially for those who smoke.

Toxicity of SiO_2 or nano-SiO_2

Numerous studies have confirmed the toxicological effects of natural crystalline silica particles of 0.5–10 μm on the respiratory system by examining the association between occupational inhalation and severe health effects (Calvert et al. 2003; Napierska et al. 2010; Parks et al. 2002). Occupational exposure to a mixed form of crystalline and amorphous silica continued to be a primary health issue. A number of epidemiological studies have evidenced that even after ending of exposure, silicosis might develop or progress provided certain particle lung burdens existed (Hnizdo and Murray 1998; Porter et al. 2004).

Our study estimated that nearly all silica dust particles were distributed within the coarse regime with estimated MMAD of 2.5–10 μm in that there were small fractions of silica particle

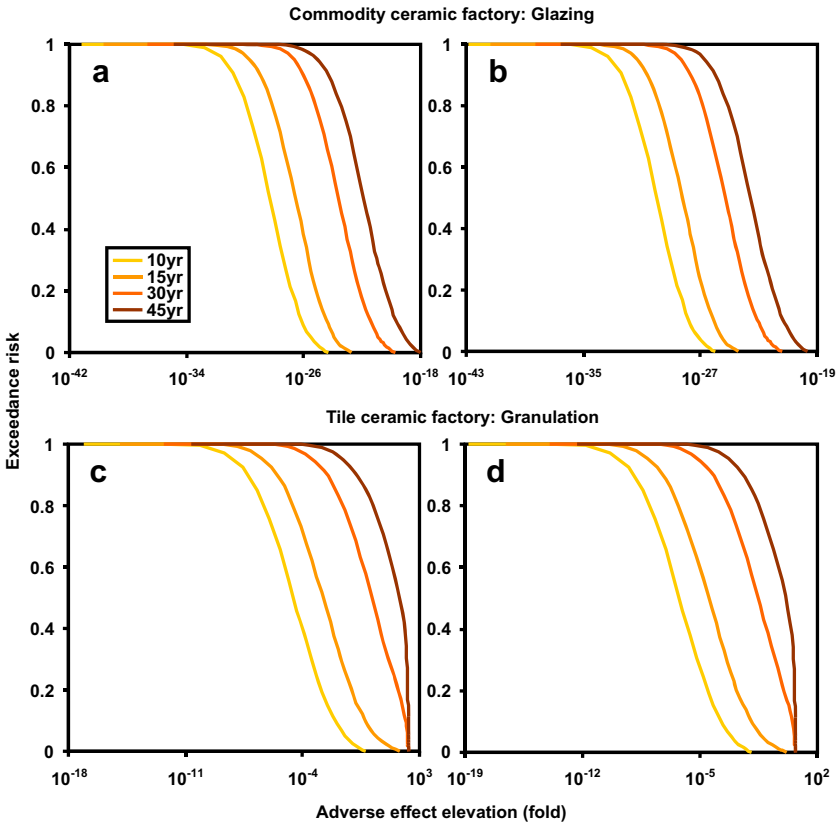

Fig. 6 Estimated exceedance risk curves for **a**, **c** inflammation and **b**, **d** fibrosis at the worst working areas in two selected factories

falling within the fine size range with MMAD <2.5 μm. In brief, fine and coarse SiO_2 particles would be exclusively located in the cytoplasm and accumulated around the nucleus, forming nuclear indentations (Nabeshi et al. 2010). On the other hand, there was higher toxicity of ultrafine particles (UFPs) compared to that of fine particles (FPs), due to the larger surface area (SA) per given mass of UFPs (Napierska et al. 2009).

Generally, increase in dose, decrease in particle size, and increase in SA would result in increment in toxicity of silica nanoparticles (SNPs) to cells or organisms (Lu et al. 2009; Nabeshi et al. 2010; Napierska et al. 2009; Rabolli et al. 2010; Yang et al. 2010; Yu and Luo 2009). Napierska et al. (2009) indicated that the concentration of SNPs leading to 50 % reduction in cell viability increased as the size of SNPs increased from 14 to 19 nm (with correspondent SAs reducing from 196 to 145 $m^2\ g^{-1}$). On the other hand, Lin et al. (2006) compared the toxicity effects between amorphous SNPs (15 and 46 nm) and crystalline silica (0.6 μm) on human bronchoalveolar epithelial cells, indicating that SNPs had significantly higher toxicity to cells than crystalline silica.

Limitation and implications

We selected 12 main working areas in two representative ceramics manufacturing as our study cases. Respirable particle dust samplings were conducted in 12 working areas during working hours (8 h). Thus, our observed data is representative to support the probabilistic risk assessment. In view of crystalline free silica, it is the form that is most likely to cause adverse effects, considering exposure measurements of crystalline free silica and total silica dust can improve the adequacy of data to reflect important exposure consequences. However, there were certain limitations in our study. First, a 37-mm aluminum cyclone was fixed at a certain height and location to measure workers' respirable silica dust in the working areas. In practice, the breathing zone is varying because workers are always changing their positions. Moreover, airborne silica dusts at positions where workers are exposed to often have different particle size distributions. Therefore, we suggest that the cyclone should be racked on workers' shoulder to take into account time-varying height and location of exposure in the future study.

Second, we preformed a one-way sensitivity analysis by varying each parameter individually used in the PBAD model based on its 95 % CI estimate to examine the influence of each parameter on the total lung burden. We found that the most important physiological parameter was the rate for transferring silica dose in alveolar region into interstitial region, implicating that if we control appropriately the daily inhaled SiO_2 dose, the total lung burden could be reduced. Therefore, we suggest that applications of personal protection (e.g., face mask) and mechanic exhaust are necessary for reducing exposure concentration of SiO_2 dust.

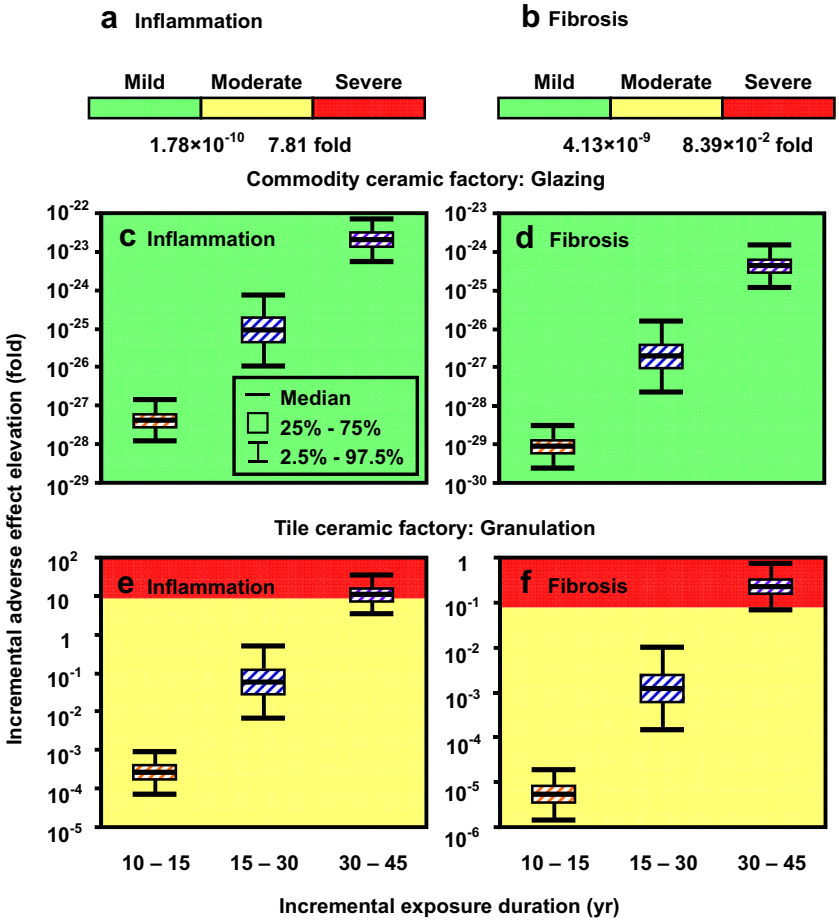

Fig. 7 Estimated marginal values in the mild–moderate–severe schemes for **a** inflammation and **b** fibrosis. *Box and whisker plots* represent incremental adverse effects with incremental exposure durations for inflammation and fibrosis at **c**, **d** glazing and **e**, **f** granulation working areas in the commodity and tile ceramic factories, respectively

Third, the factors such as race and smoking habit could influence the prediction of total SiO_2 lung burden. In fact, these factors could reduce elimination rate of lung and accelerate accumulation of SiO_2 dust (Kuempel et al. 2001a; 2001b), resulting in an elevating risk of SiO_2 exposure-related diseases. Hence, we suggest that race and smoking habit can also be incorporated into the PBAD model to improve the predictability in the future research.

Conclusions

We have developed a robust and reproducible risk assessment that is pivotal for well-informed and iterative decision-making towards an effective health management of the ceramics manufacturing workers. Our analysis is based on a well-documented probabilistic risk assessment approach appraised with field measurements and well-analyzed published data. We have also provided an integrated assessment algorithm required to implement the analyses and maintain the resulting concentration of silica dust below the safety threshold level, hoping they will stimulate further analyses and interpretations. Here we have quantitatively shown the considerable potential risks at stake. It is important that decision-makers and other stakeholders take action to implement platforms for effective risk management to prevent the related long-term occupational disease in ceramics manufacturing and use these to reduce airborne SiO_2 lung burden.

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Conflict of interest The authors declare that they have no competing interests.

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