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RESEARCH ARTICLE

Estimates of lung burden risk associated with long-term exposure to TiO_2 nanoparticles as a UV-filter in sprays

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Abstract

Titanium dioxide (TiO_2) nanoparticles (NPs) are employed as an ultraviolet filter in sunscreen products because of their high ultraviolet absorptivity. However, sunscreen sprays may pose health risks due to the toxicity of inhaled TiO_2 NPs. Therefore, we estimated the potential human health risk posed by inhaled TiO_2 NPs emitted from sunscreen sprays. The physiology-based lung model was employed to predict the lung TiO_2 NPs burden caused by long-term exposure. A Hill-based dose–response model described the relationship between lung inflammation and TiO_2 NP accumulation. The Weibull threshold model was used to estimate the threshold amount of accumulation inducing 0.5% of the maximum increase in neutrophils. The potential health risk was assessed using a hazard quotient–based probabilistic risk model. All data obtained to date indicate that application of sunscreen sprays poses no significant health risk. However, using data simulations based on the threshold criterion, we discovered that in terms of practical strategies for preventing the risks posed by inhaled TiO_2 NPs emitted from spray products, the suggested daily use amount and pressing number are 40 g (95% confidence interval: 11–146 g) and 66 (18–245), respectively. In this study, we successfully translated the potential health risk of long-term exposure to NP-containing sunscreen sprays and recommendations for daily application into mechanistic insights.

Keywords Titanium dioxide nanoparticles · Ultraviolet filter · Sprays · Lung burden · Risk assessment · Nanotoxicity

Introduction

Titanium dioxide (TiO_2) nanoparticles (NPs) are applicable in various fields, including the pharmaceutical (medical) and food industries, agriculture, and environmental protection. Of all types of NPs, TiO_2 NPs are the most widely used and account for 70% of the total volume of all pigments produced worldwide because of their high refractive index, brightness, and strong ultraviolet (UV) absorption (Baan et al. 2006; Rossi et al. 2010a). TiO_2 NPs mostly occur in rutile, anatase, and brookite forms, among which the anatase form has the most industrial applications because of its relatively high photocatalytic activity (Baranowska-Wójcik et al. 2020; Bourikas et al. 2014).

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Although application to skin through sunscreen is the route through which TiO_2 NPs most commonly come into contact with humans, most studies performed on humans or animals have demonstrated that TiO_2 NPs do not penetrate the outer layers of the stratum corneum to reach viable cells or reach the circulatory system (Dréno et al. 2019; Escobar-Chavez et al. 2008; Filipe et al. 2009; Furukawa et al. 2011; Monteiro-Riviere et al. 2011; Sadrieh et al. 2010; Sagawa et al. 2012; Wu et al. 2009; Xu et al. 2011). Ingestion of TiO_2 NPs most often occurs through food products, water, liquid beverages, and drug carriers (Hagens et al. 2007; Lomer et al. 2002). Thus, the potential risks associated with the dermal and oral routes are less considered than that associated with inhalation. The toxicities of NPs that are inhaled are more likely to be a cause of concern than the toxicities of NPs entering the body through other routes because NPs have sizes comparable to those of viruses and biological molecules (e.g., proteins), which can enable them to easily penetrate into the pulmonary epithelium and subsequently reach other organs (Lynch and Dawson 2008; Miller et al. 2017; Oberdörster et al. 2002; Wiemann et al. 2017). A growing body of evidence indicates that inhalation of TiO_2 NPs induces airway inflammation,

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increasing the risks of pulmonary diseases, especially in individuals susceptible to immune-mediated airway diseases (Gustafsson et al. 2011; Jonasson et al. 2013). Furthermore, Medina-Reyes et al. (2019) suggested that TiO_2 nanofibers enhance the aggressive tumor phenotype in lung epithelial cells; accordingly, assessing the inhalation risks to human lungs posed by acute or chronic exposure to TiO_2 NPs from all sources is imperative. The probability of TiO_2 NP ingestion during the application of a spray product should be low.

Apart from occupational exposure, spray products constitute the primary means of exposure to TiO_2 NPs through the airborne route in consumers. In bulk form, TiO_2 is usually used as a white pigment, but the nanoform is primarily applied in sunscreens and leave-on products purported to provide UV protection (SCCS 2018). The SCCS (2018) suggested that TiO_2 NPs pose no risks to the human body when applied to healthy, intact, or sunburnt skin. However, they cannot be considered safe when used in spray products.

Information regarding the use of a comprehensive risk assessment framework for determining the potential risks of TiO_2 NP inhalation from spray products is lacking. Accordingly, the aim of this study was to characterize the long-term risks of TiO_2 NPs in pulmonary systems of the human body by employing a mechanistic approach linked with a human health risk assessment framework.

The objectives of this study were fivefold: (i) to collect information regarding the exposure concentration of TiO_2 NPs resulting from sunscreen sprays, (ii) to develop a mechanistic tool for predicting the long-term accumulation of TiO_2 NPs in the lungs, (iii) to construct a dose–response relationship describing the pulmonary effects of various TiO_2 NP doses, (iv) to obtain suitable threshold values of daily use amount and number of presses for each spray product, and (v) to assess the long-term risks of TiO_2 NPs to obtain implications for the safety considerations of using NPs in pharmaceuticals and personal care products.

Materials and methods

Quantitative data analysis

Empirical data on exposure concentrations and measurements of TiO_2 NPs in human lungs are limited. The SCCS has provided valuable data on the daily inhaled doses of airborne TiO_2 NPs contained in eight commercial sunscreen spray products (SCCS 2018). Briefly, eight TiO_2 NP–containing spray products, named P1−P8, with the same nozzle type (pump) were covered, and these spray products had four sunscreen formulations (recipe 22, recipe 35, E42026503-00, and E47028018-00-4; Supplementary Table S1). The emitted volume of each product ranged from 0.19 to 0.90 mL per action, and the viscosity and water content ranged from 1080 to 5000 mPa·s and 25−75% (oil-in-water emulsion), respectively (Supplementary Table S2).

The mass released from a spray dispenser, ranging from 4.36 to 4.84 g per gram of spray formulation was measured by spraying each product (~9 g) into a chamber with a defined control volume of 75 L, and time-resolved measurements of aerosol concentration (remaining nonvolatile part) were made (SCCS 2018). Particle measurements were implemented using two parallel RESPICONs, which are commercial instruments used to monitor inhalable, thoracic, and respirable fractions of aerosols during occupational inhalation (SCCS 2018). Continuous photometric and gravimetric measurements were performed on the filter stages of three fractions in the RESPICONs, with masses of Ti on filters analyzed using inductively coupled plasma mass spectrometry (ICP-MS; SCCS 2018).

Physicochemical characterization of TiO_2 NPs

The TiO_2 NP content of the spray products ranged from 2.54 to 5.5% (PARSOL® TXr, Supplementary Table S2). The crystalline structure of TiO_2 NPs was mainly the rutile form, as determined using X-ray diffraction (Albers et al. 2015; SCCS 2018). In terms of physical appearance, the TiO_2 NPs were spherical clusters and coated with amorphous silica (0.1–1%) and dimethicone ($((C_2H_6OSi)_xC_4H_{12}Si$; 0−0.1%) as the second and first layers, respectively (Albers et al. 2015). The median particle size of the TiO_2 NPs was approximately 102 nm in P1−P6 and ≥30 nm in P7 and P8, in compliance with the Draft Commission Regulation (EU) amendment Annex VI to Regulation (EC) No. 1223/2009 of the European Parliament and SCCS (2018). Each spray product also complied with the regulation requiring a volume-specific surface area of ≤460 m^2 cm^{-3} (SCCS 2018).

Physiology-based lung model

A compartmentalized physiologically based (PB) lung model was developed on the basis of previous studies to mechanistically estimate the burden of TiO_2 NPs in human lung tissue (Stöber et al. 1990; Tran et al. 1999, 2000, 2003). The PB lung model can predict long-term TiO_2 NP lung burden and describe clearance processes mediated by alveolar macrophages (AMs) in pulmonary regions. In the PB model, three regions—the alveolar surface, interstitium, and lymph nodes—were defined to describe the distribution of TiO_2 NPs in the human lungs (Fig. 1). The alveolar surface region had four compartments describing the distributions of incoming TiO_2 NPs (X_1), mobile AMs (X_2), decayed and inactive AMs (X_3), and alveolar sequestration (X_4; Fig. 1a, b). The interstitium region also had four compartments describing the distributions of (i) free TiO_2 NPs (X_5), (ii) mobile interstitial macrophages (IMs) (X_6), (iii) decayed and inactive IMs

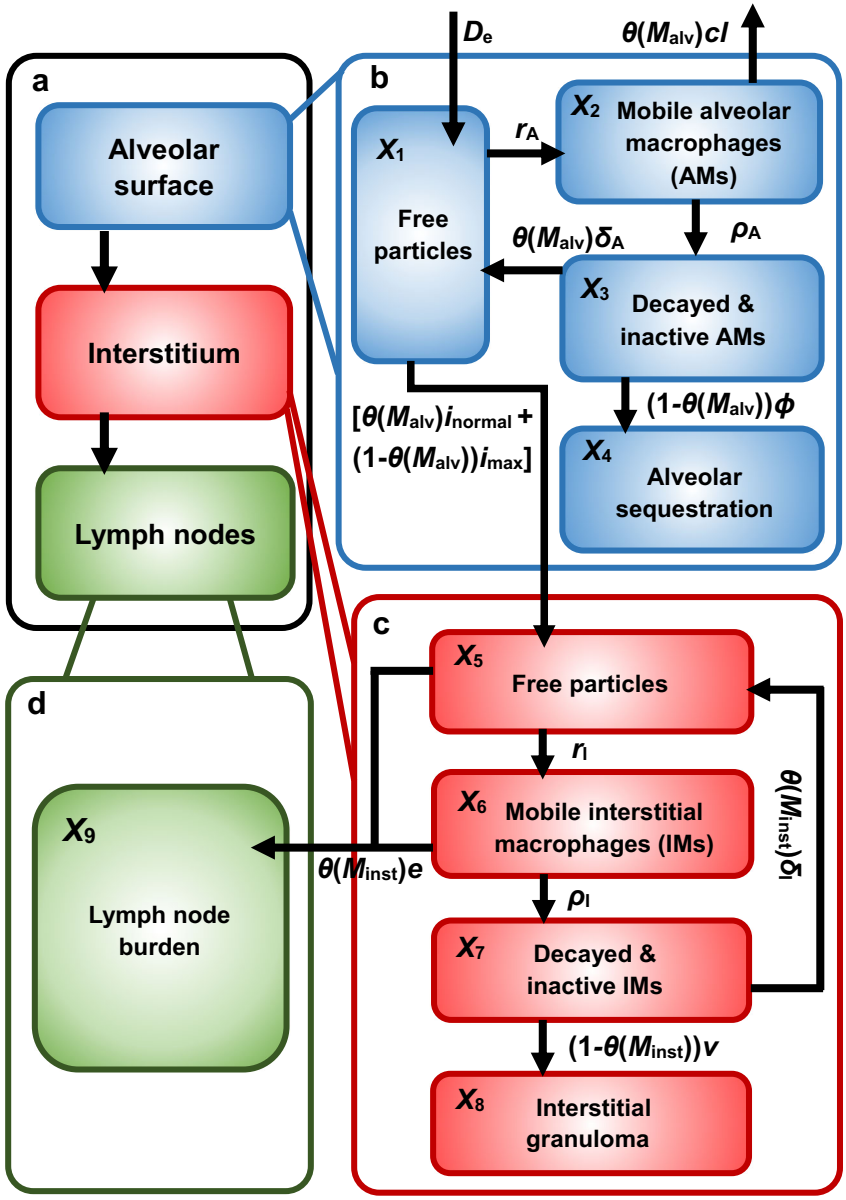

Fig. 1 Schematic of the compartmentalized physiologically based (PB) lung model

(X_7), and (iv) interstitial granuloma (X_8; Fig. 1a, c). Some free TiO_2 NPs or those from mobile IMs can be removed to the lymph node region (X_9; Fig. 1a, d).

The PB lung model framework and model parameters were fully constructed and estimated by Tran et al. (2003). A set of first-order ordinary differential equations with re-estimated parameters were used to simulate the dynamic distribution of TiO_2 NPs in different regions of the human lungs, enabling mechanistic description of the biodynamic interactions of TiO_2 NPs among compartments (Table 1).

When TiO_2 NP–containing aerosols are inhaled (i.e., respiratory fraction in the RESPICONS; Figs. S1 and S2), the TiO_2 NPs are deposited on the alveolar surface, which has four designated compartments ($X_1(t)$–$X_4(t)$; Eqs. (1)–(4); Table 1). D_e represents the rate of TiO_2 NP deposition (mg·day^{-1}), which is based on datasets from SCCS (2018); t is the duration of exposure (days); r_A is the phagocytosis rate by AM (day^{-1}), i_{normal} is the normal interstitialization rate of TiO_2 NPs (day^{-1}); $\theta(M_{alv})$ is the function of the alveolar surface burden that describes the retardation of the clearance of insoluble dust; δ_A is the rate of particles back to alveolar surface for rephagocytosis (day^{-1}); ρ_A is the transfer rate of particles from active to inactive AMs (day^{-1}); cl is the AM-mediated clearance of particles (day^{-1}); and ϕ is the alveolar sequestration (day^{-1}). The transfer of TiO_2 NPs from the alveolar surface to the interstitium region, which has the four compartments $X_5(t)$–$X_8(t)$, can be expressed by Eqs. (5)–(8) (Table 1), where e refers to the removal rate of particles to lymph nodes, $\theta(M_{inst})$ is the function of the interstitium burden that describes the retardation of the clearance of insoluble

Table 1 Equations and input parameters used in the present PB lung model[a]

PB lung model

Alveolar surface

$$\frac{dX_1}{dt} = D_e - r_A X_1 - [i_{normal}\theta(M_{alv}) + (1-\theta(M_{alv}))i_{max}]X_1 + \theta(M_{alv})\delta_A X_3, \quad (1)$$

$$\frac{dX_2}{dt} = r_A X_1 - \theta(M_{alv})clX_2 - \rho_A X_2, \quad (2)$$

$$\frac{dX_3}{dt} = \rho_A X_2 - \theta(M_{alv})\delta_A X_3 - (1-\theta(M_{alv}))\,\varphi X_3, \quad (3)$$

$$\frac{dX_4}{dt} = (1-\theta(M_{alv}))\,\varphi X_3, \quad (4)$$

Interstitium

$$\frac{dX_5}{dt} = [i_{normal}\theta(M_{alv}) + (1-\theta(M_{alv}))i_{max}]X_1 - \theta(M_{inst})eX_5 - r_I X_5 + \theta(M_{inst})\delta_I X_7, \quad (5)$$

$$\frac{dX_6}{dt} = r_I X_5 - \rho_I X_6 - \theta(M_{inst})eX_6, \quad (6)$$

$$\frac{dX_7}{dt} = \rho_I X_6 - \theta(M_{inst})\delta_I X_7 - (1-\theta(M_{inst}))\,\nu X_7, \quad (7)$$

$$\frac{dX_8}{dt} = (1-\theta(M_{inst}))\,\nu X_7, \quad (8)$$

Lymph node

$$\frac{dX_9}{dt} = \theta(M_{inst})e(X_5 + X_6), \quad (9)$$

Parameter values

r_A (day^{-1}) = 0.966 (0.690 – 3.450)[b,c]

i_{normal} (day^{-1}) = 0.007[d]

i_{max} (day^{-1}) = 0.435[d]

δ_A (day^{-1}) = 0.140[d]

ρ_A (day^{-1}) = 0.036 (0.029 – 0.200)[b,c]

cl (day^{-1}) = 0.004 (0.002 – 0.007)[c,d]

ϕ (day^{-1}) = 0.140[d]

$\theta(M_{alv})$ (—) = 0 – 1

r_I (day^{-1}) = 0.966 (0.6900 – 3.4502)[b,c]

δ_I (day^{-1}) = 0.140[d]

ρ_I (day^{-1}) = 0.036 (0.0286 – 0.2000)[b,c]

ν (day^{-1}) = 0.140[d]

$\theta(M_{inst})$ (—) = 0 – 1

e (day^{-1}) = 0.024 (0.001 –0.319)[c,d]

[a] See text for meanings of abbreviations and parameter symbols

[b] Adopted from Stöber et al. (1990)

[c] (Min–Max)

[d] Adopted from Tran et al. (2003)

dust, r_I is the phagocytosis rate by IMs (day^{-1}), δ_I is the rate of particles back to interstitium for re-phagocytosis (day^{-1}), ρ_I is the transfer rate of particles from active to inactive IMs (day^{-1}), and ν is the rate of formation of interstitial granuloma (day^{-1}). Movement of TiO_2 NPs from mobile IMs in the interstitium region to lymph nodes can be expressed by Eq. (9), where $X_9(t)$ is the time-dependent dose of TiO_2 NPs in the lymph node region (mg; Table 1).

Animal-based dose–response model

We designed the dose–response profiles of TiO_2 NPs and adverse effects in a murine model by adopting experimental conditions aligned with the physiochemical characteristics of TiO_2 NPs. The TiO_2 NPs were in rutile form and coated with amorphous silica; they had a particle size and specific surface area of 10×40 nm^2 and 132 m^2 g^{-1}, respectively (Rossi et al. 2010a). A three-parameter Hill model was used to fit the dataset describing neutrophil infiltration to bronchoalveolar lavage (BAL) (%) posed by TiO_2 NPs lung burdens in 7-week-old female BALB/c/Sca mice (Scanbur AB, Sollentuna, Sweden) (Rossi et al. 2010a). Briefly, the mice were exposed to 10 mg m^{-3} airborne TiO_2 NPs for either 2 h, 2 h a day on 4 consecutive days, or 2 h a day on 4 consecutive days for 4 weeks.

Before modeling the dose–response relationship, we must transform the dose data derived from the exposure test to ensure that they corresponded to the human lung TiO_2 NP burden dose (total mass of TiO_2 NPs in the human lungs) that was forecast using the PB lung model. Accordingly, the data on the TiO_2 NP burden in the mouse lungs were multiplied by the ratio of human and mice lung weight to obtain the equivalent burden in the human lungs.

The dose–response model describing the relationships between TiO_2 NPs lung burden and neutrophils in BAL cells

(%) is expressed as Eq. (10) (Table 2), where D is the TiO_2 NP lung burden (mg); E_{max} is the maximum response of neutrophils increment in BAL cells (%); $EC50$ is the TiO_2 NP lung burden corresponding to an effect equal to 50% of E_{max} (mg); and n is the fitted Hill coefficient, for which $n = 1$ would represent a linear response (Michaelis–Menten mode) and $n > 1$ would imply that the biomarker was ultrasensitive to TiO_2 NP toxicity. $EC0.5$, corresponding to 0.5% of E_{max}, was employed to explore the toxic effects of TiO_2 NPs in different extents of sensitivity. One reason for employing this more conservative criterion was that direct application of sunscreen to the body leads to a higher probability of exposure to TiO_2 NPs, especially near the nose and mouth. Another reason was that considering the intrapopulation variation in sensitivity to toxicants, the use of the $EC0.5$ criterion could ensure the protection of the potentially sensitive population.

Predictive risk threshold

To prevent human lung from toxicities of TiO_2 NP–containing aerosols, the thresholds of TiO_2 NP lung burdens were estimated using a three-parameter Weibull threshold model to achieve the best fit for the 2.5th, 5th, 50th, 95th, and 97.5th percentiles of the $EC0.5$ cumulative distribution function (CDF). The CDF was probabilistically estimated from the Hill-based dose–response model expressed in Eq. (10) on the basis of the experimental datasets (Rossi et al. 2010a).

The Weibull threshold model can be described by Eq. (11) (Table 2), where $F(D)$ represents the $EC0.5$ CDF data corresponding to a specific TiO_2 NP lung burden in the human body, α is the scale parameter influencing the distribution of $F(D)$ as a change in the abscissa scale, β is the shape parameter representing the slope of the line in the CDF data, and γ is the fitted threshold dose of TiO_2 NPs (mg). The threshold value estimated based on $EC0.5$ CDF is denoted as $\gamma_{0.5}$.

Probabilistic risk model

To meet the objective of protecting the human lungs from the potential toxicities of and pulmonary diseases caused by airborne TiO_2 NPs from spray products, $\gamma_{0.5}$ was selected as a conservative criterion. A probabilistic risk assessment (PRA) model integrated with the PB lung model was developed to characterize neutrophils in BAL cells (%) following exposure to TiO_2 NP–containing aerosols.

The PRA model was implemented on the basis of the theory of Bayesian inference, which holds that the cumulative risk of neutrophil increments in BAL cells under a given TiO_2 NP lung burden ($R(E)$) (i.e., posterior probability) is the product of a prior probability $P(D)$ and a conditional probability function $P(E|D)$, which can be expressed as Eqs. (12) and (13) (Table 2). To characterize the cumulative risk posed by TiO_2 NPs, the exceedance risk (ER) could be derived with the exceedance profiles as $1 - R(E)$.

The potential risks of TiO_2 NP lung burdens could also be evaluated with the criterion of the threshold TiO_2 NP dose by using the hazard quotient (HQ) model, expressed in Eq. (14) (Table 2), where D and $\gamma_{0.5}$ were probabilistically estimated. Specifically, $HQ > 1$ would indicate that the TiO_2 NP–induced lung burden poses a risk to human health based on increments of neutrophils in BAL cells, whereas $HQ < 1$ would indicate that the TiO_2 NP–induced lung burden poses no risk to human health.

Table 2 Equations used in the overall probabilistic risk assessment model[a]

Animal-based dose–response model

$$E(D) = \frac{E_{max}}{1+\left(\frac{EC50}{D}\right)^n}, \quad (10)$$

Weibull threshold model

$$F(D) = 1-\exp\left[-\left(\frac{D-\gamma}{\alpha}\right)^{\beta}\right], \quad D > \gamma > 0, \quad \alpha > 0, \quad \beta > 0, \quad (11)$$

Probabilistic risk assessment model

$$R(E)=P(D)\times P(E|D), \quad (12)$$

$$P(E|D) = \Phi\left(\frac{E_{max}}{1+\left(\frac{EC50}{D}\right)^n}\right), \quad (13)$$

Hazard quotient model

$$HQ = \frac{D}{\gamma_{0.5}}, \quad (14)$$

[a] See text for meanings of abbreviations and parameter symbols

Uncertainty and data analysis

The PB lung model was implemented using Berkeley Madonna 8.0.1 (developed by Robert Macey and George Oster at the University of California, Berkeley). Mathematical models were fit using TableCurve 2D (Version 5.01, AISN Software, Mapleton, OR, USA). Uncertainty analyses of the parameters in the PB lung model were implemented through 10,000 Monte Carlo (MC) simulations to obtain 2.5th and 97.5th percentiles as 95% confidence intervals (CIs) by using the Crystal Ball software (version 2000.2, Decisioneering, Denver, CO, USA). Sensitivity analyses were performed for each parameter in the PB lung model to determine the most influential parameter on TiO_2 NPs lung burdens in the human system. The overall study framework is displayed in Supplementary Fig. S3.

Results

Lung deposition analysis

The simulated total TiO_2 NP lung burden ranged from 0.06 to 0.21 mg (Fig. 2a). Specifically, inhalable TiO_2 NPs contributed 80% to the total lung burden, with 79% on the alveolar surface and approximately 1% in the interstitium; 20% of the TiO_2 NPs were eliminated from the lungs in lymph nodes (Fig. 2b). Furthermore, in the alveolar surface region, the mobile AM compartments had the highest distribution of TiO_2

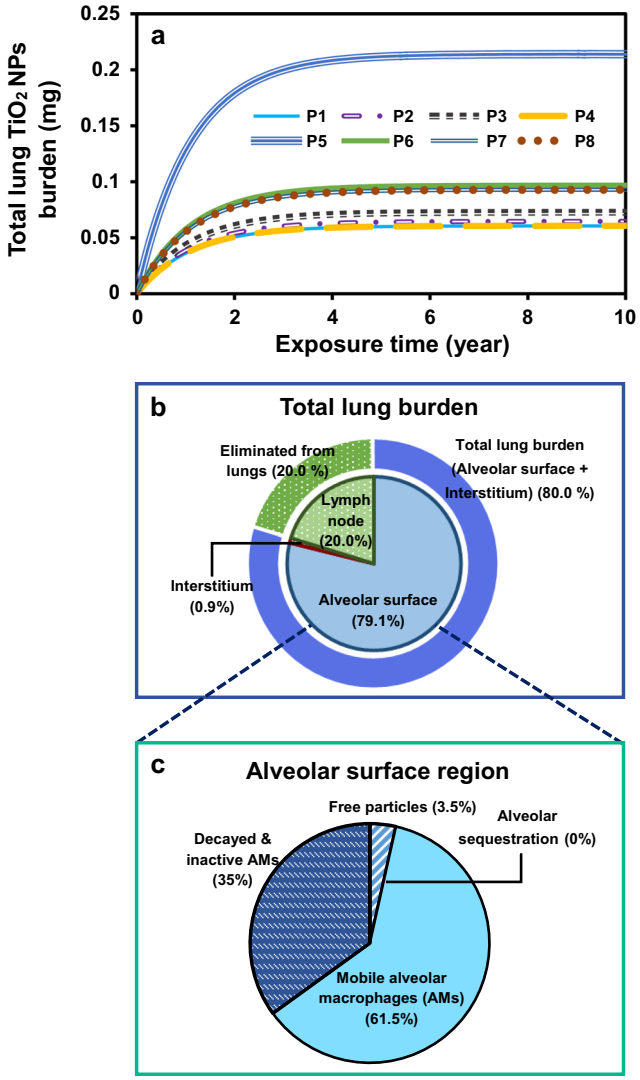

Fig. 2 (a) Time-dependent total lung TiO_2 NPs burdens in human lungs posed by long-term exposure of aerosolized TiO_2 NPs emitted from sunscreen spray products P1–P8 and (b, c) proportions of TiO_2 NPs accumulations in each compartment of the PB lung model

NPs (62%), followed by the decayed and inactive AM compartments and free particles (35% and 3%, respectively; Fig. 2c). Because the total TiO_2 NP lung burden caused by exposure to each product was saturated after 4 years of exposure, the 4th year within the exposure duration was employed as the time point at which to characterize the risk (Fig. 2a).

Sprays P7 and P8 were discovered to have the highest TiO_2 NP concentrations (4.3% and 5.5%, respectively; Supplementary Table S2). However, the exposure assessment results demonstrated that the estimated total TiO_2 NP lung burdens posed by P7 and P8 were lower than those posed by P5 and P6 (2.54% TiO_2 NP concentration; Fig. 2; Supplementary Table S2). This may have been because of the smaller emitted volumes (0.19 ml per action) of P7 and P8. Compared with P1–P3 and P4–P6 (recipes 22 and 35, respectively), P7 and P8 contained sunscreen with higher viscosity (3020 and 5000 mPa·s, respectively). This reduced the likelihood of the formation of small aerosol liquid droplets with relatively high deposition fractions in pulmonary (Supplementary Table S2).

Products made from recipe 22 (P1–P3) had lower total TiO_2 NP lung burdens than did products made from recipe 35 (P4–P6; Fig. 2). This may be attributed to the higher viscosity in recipe 22 (2100 mPa·s) than in recipe 35 (1080 mPa·s; Supplementary Table S2). A possible reason for the lower TiO_2 NP lung burdens posed by P1 and P2 is that these sprays emitted the least volume per action (0.19 mL) and TiO_2 NP containment. Because aerosol particle size distribution and concentration data are not provided by the SCCS, we could not adequately explain the estimated total TiO_2 NP lung burdens.

Dose–response analysis

We obtained the Hill-based dose–response profile of TiO_2 NP burdens in the human lungs by converting experimental mouse data by using weight ratios and corresponding neutrophil increments in BAL cells (Fig. 3). The results revealed that the Hill model fit the dose–response datasets favorably (r^2 = 0.95, $p < 0.001$), with a fit coefficient n of 3.40 ($p < 0.01$; Fig. 3; Supplementary Table S3). The mean estimated TiO_2 NP lung burdens that caused 0.5% and 50% of the maximum increments of neutrophils in BAL cells were 4.31 and 20.50 mg, respectively (Fig. 3; Supplementary Table S3).

Threshold estimation

The Weibull threshold model could best fit to CDFs of *EC*0.5 extracted from the dose–response profile (Supplementary Fig. S4; Table S4). The threshold estimate of $\gamma_{0.5}$, which was selected as the most conservative criterion for preventing the

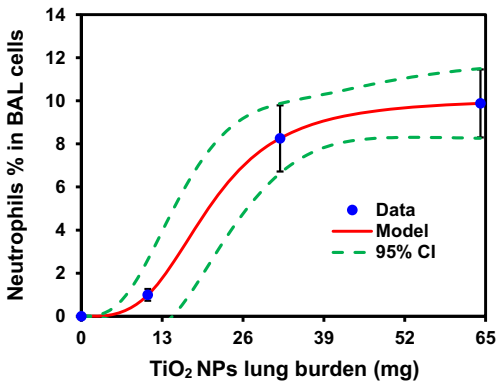

Fig. 3 Dose–response relationship between lung burdens of TiO_2 NPs and percentage of neutrophils in bronchoalveolar lavage (BAL) cells based on the Hill model

risks of TiO_2 NP inhalation in the human body, was 1.09 ± 0.76 (mean ± SE) mg (Supplementary Fig. S4; Table S4).

Risk estimates

The risks posed by inhaling each of the TiO_2 NP–containing spray products were assessed using $\gamma_{0.5}$ as a conservative criterion to indicate the potential long-term toxicity of the products (Fig. 4a). Overall, the *HQ*s of P1–P8 were all lower than 1 in different percentiles. Among the products, P5 had the highest *HQ* estimates of 0.23 (0.07−0.82) (median (95% CI); Fig. 4a; Supplementary Table S5). To more clearly compare the relative risks posed by the various spray products, the risk ratio (RR) of each product was estimated relative to the lowest *HQ*, which was that posed by P1. P5 was discovered to also have the highest RR estimate of 3.53 (3.47−3.60) among products (Fig. 4b; Supplementary Table S6).

Moreover, the ERs corresponding to specific *HQs* in different risk probabilities were determined for each product (Fig. 4c; Supplementary Table S7). Consistent with the *HQ* and RR results, P5 had the highest *HQ*s (~0.2) in the 20%, 50%, and 80% risk probabilities (Fig. 4c; Supplementary Table S7), followed by P6–P8, for which the *HQs* under the 50% risk probability (ER = 0.5) were all approximately 0.08 (Fig. 4c; Supplementary Table S7).

Suggested daily using amounts and pressing numbers

To provide practical strategies for preventing the pulmonary risks posed by TiO_2 NPs inhaled from spray products, we derived suggested daily use amounts and numbers of presses on the basis of the estimated $\gamma_{0.5}$ (Fig. 5; Supplementary Table S8). Consistent in the results of risk estimates, spray P5 had the lowest median of suggested daily using amount of ~40 g with a pressing number of 66. On the contrary, results showed that spray P1 had the highest median of suggested daily using amount of 142 g with a pressing number of 750 (Fig. 5; Supplementary Table S8).

The wide ranges in the suggested daily using amounts and pressing numbers (e.g., the daily using amount for P1 ranged from 39 to 528 g; Fig. 5; Supplementary Table S8) mainly originated from the large uncertainty in the threshold criterion $\gamma_{0.5}$ (1.09 ± 0.76; Supplementary Table S4).

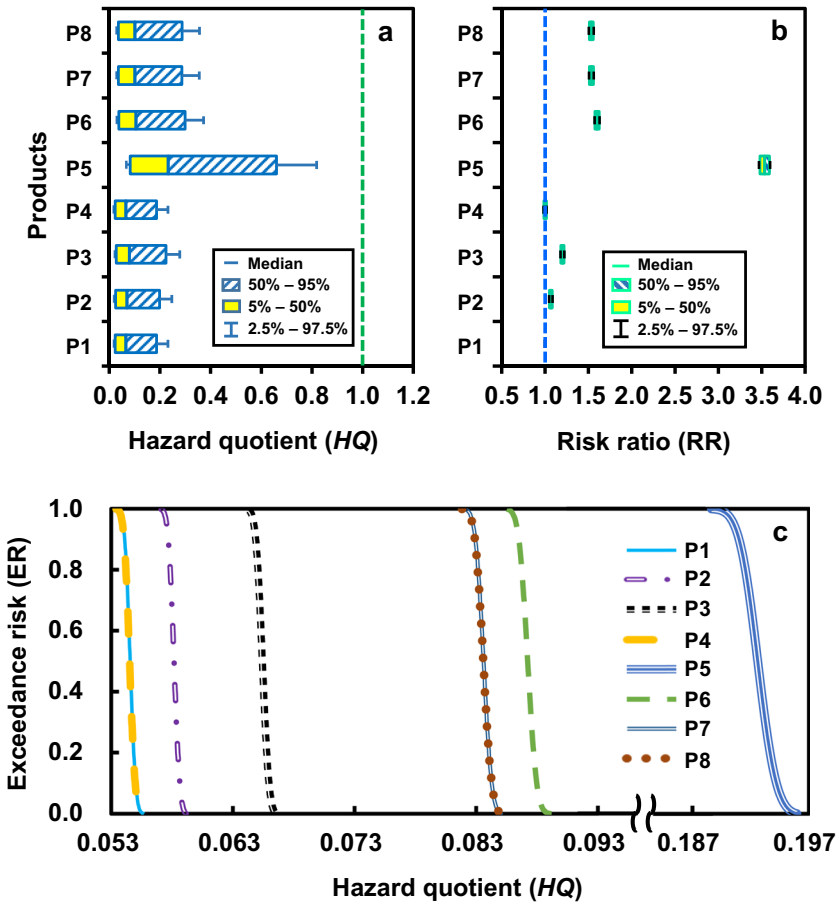

Fig. 4 Box and whisker plots of (a) hazard quotients (*HQ*s) for 4-year exposure to aerosolized TiO_2 NPs, emitted from sunscreen spray products P1–P8, (b) the estimated relative risks (RRs) for application of sunscreen sprays (P1–P8) based on the *HQ* value of sunscreen P1, and (c) exceedance risks (ERs) for *HQ* of exposure to aerosolized TiO_2 NPs from P1–P8

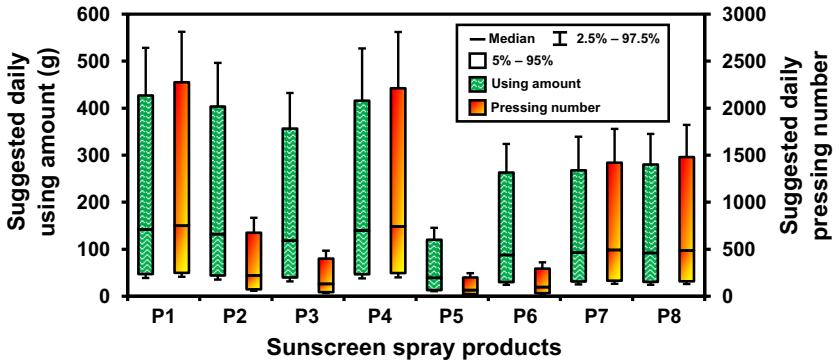

Fig. 5 Suggested daily using amounts and pressing number of TiO_2 NP–containing sunscreen spray products P1–P8

Sensitivity analysis

On the basis of the results regarding the total TiO_2 NP lung burdens caused by 10 years of exposure to P5, local sensitivity analysis was performed to determine the physiological parameter with the most influential effect on the total TiO_2 NP lung burdens in the PB lung model (Fig. 6). The results revealed that the AM-mediated clearance of TiO_2 NPs (*cl*) had the strongest effect on the total TiO_2 NP lung burdens; the estimated burdens were 0.91 and 0.02 mg when the parameter was 0.1- and 10-fold, respectively (Fig. 6). Moreover, the rate at which particles were returned to the alveolar surface for rephagocytosis (δ_A) had the second strongest effect, followed by the parameters of transfer rate of particles from active to inactive AMs (ρ_A) and normal interstitialization rate of particle (i_{normal}) (Fig. 6).

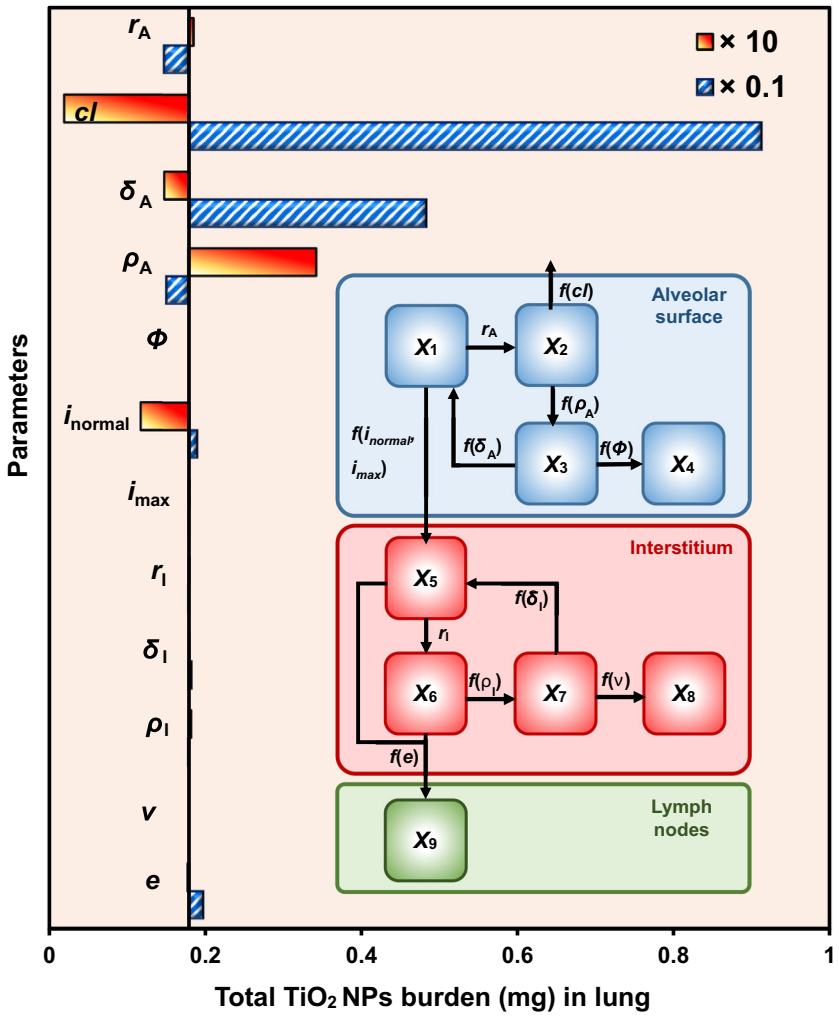

Fig. 6 Sensitivity analysis for physiological parameters used in the PB lung model against total TiO_2 NPs accumulation in human lung (mg) posed by application of sunscreen spray P5

Discussion

Realistic exposure scenarios of TiO_2 spray products

Regarding the use of TiO_2 spray products, a mass of approximately 9 g corresponds to the SCCS (2015)-recommended amount of 18 g day^{-1} for each adult under the consideration of two applications. To explore whether the experimental settings of the eight spray products could be applied to realistic conditions, we compared the exposure scenario with those in previous studies. Wu and Hicks (2019) indicated that more than 70% of individuals were exposed to 0–10 mg day^{-1} of TiO_2 NPs through the use of personal care products, revealing that the employed exposure concentrations (0.46–1 mg per spray product) were within the scope of the present study.

Studies have reported that 0.5 to 2.0 mg cm^{-2} of sunscreen products are applied to 75% of the body's surface area (Autier et al. 2001, 2007; Bech-Thomsen and Wulf 1993; Diffey 1996; Gottlieb et al. 1997; Matta et al. 2019; Stenberg and Larkö 1985). The mean body surface areas of men and women are 2.03 and 1.73 m^2, respectively (Tikuisis et al. 2001), implying that the daily sunscreen use amount is approximately 6.5–30.5 g.

However, frequency of use and peak exposure should be particularly considered in specific scenarios because most studies have averaged the concentration over a reference period of time (Kuhlbusch et al. 2018).

Other crucial factors such as humidity, cause of other products, and the behavior of aerosols used in large volumes could be considered to design more rigorous exposure scenarios and model exposure to nanosized aerosols during the spraying of commercial products (Lorenz et al. 2011). Because the efficiency of airborne nanomaterial deposition in the respiratory system is governed by the material's aerodynamic diameter, which is typically larger than that of the primary nanomaterial (Vance and Marr 2015), influencing factors such as the spray mechanism and intensity should be explored in exposure assessments. Experimental setups for simulating realistic application of spray products near the human breathing zone should also be designed in future exposure assays (Nazarenko et al. 2011).

Estimation of TiO_2 NPs burdens in human lung

Studies have assessed the accumulated lung burden posed by exposure to airborne TiO_2 NPs. Ling et al. (2011) applied the multiple-path particle dosimetry model and exposure model to determine the lung surface area exposed to TiO_2 NPs; the dose was estimated to be 0.21 m^2. The PB lung model was employed to estimate the TiO_2 NP lung burden, in terms of the total surface area (m^2), for factory workers exposed over a 1-year period (Liao et al. 2008, 2009). Liao et al. (2008, 2009) have evaluated the retardation of the clearance of insoluble dust in the alveolar surface and interstitium ($\theta(M_{alv})$ and $\theta(M_{inst})$) to be 0.6, which is much higher than that (~0) predicted in the 10-year exposure experiment of the present study. This contrast suggests that factories have a relatively high level of exposure, which could lead to the retardation of clearance by the immune system in the lungs.

In the study by Rossi et al. (2010b), mice were exposed to three types of airborne TiO_2 particle (silica-coated rutile TiO_2 NPs of size 10 × 40 nm, coarse rutile TiO_2 of size <5 μm, and TiO_2 NPs of size 30–40 nm with a rutile-to-anatase ratio of 9:1) under the same exposure conditions (concentration of 10 ± 2 mg m^{-3}, after 2 h of exposure on four consecutive days for 4 weeks). ICP-MS analysis of the mouse lung tissue revealed no significant differences in accumulation rate between the three TiO_2 particle types. This finding indicates that the PB lung model can be employed to estimate the lung burdens induced by different TiO_2 NP types.

In the lung deposition model, several factors can influence lung burden forecasts. Breathing rate affects the inhaled amount per unit time. Lung weight determines the magnitude of the NP burden. Clearance is related to immune ability and health condition. Men generally have a higher breathing rate and larger lung weight than do women (Thamrong et al. 2006). Studies have also reported a difference in breathing rate between Korean and Taiwanese people (MHW 2007; Park et al. 2017). Immunity and health condition are known to vary among age groups. Children and order adults are usually more sensitive to airborne pollutants (Zhang et al. 2016).

Inhalation toxicity of TiO_2-containing aerosols

Consistent with the biomarker employed in the present study, evidence is increasingly showing that lung inflammation is associated with dose-dependent increments of total cells and neutrophil count in BAL fluid (Kobayashi et al. 2009; MaHock et al. 2009; Nemmar et al. 2011; Roursgaard et al. 2011). Airborne TiO_2 NP–induced airway hyperreactivity in mice indicated that TiO_2 NPs may induce asthma in individuals with reactive airway disease (Hussain et al. 2011). Moreover, several studies have discovered significant migration of TiO_2 NPs from the alveolar surface to the interstitium after inhalation or intratracheal instillation (Sager et al. 2008; Shi et al. 2013). Studies examining rats after intratracheal instillation of TiO_2 NPs have observed expanded lung gaps; hyperemia; alveolar thickness; and increased lactate dehydrogenase activity, malodialdehyde, total protein, leukocytes, and pulmonary inflammation (Tang et al. 2010; Zhang et al. 2009). Furthermore, increments of lung indices, severe inflammatory response, pulmonary edema, pneumocyte apoptosis, and lung bleeding were observed after 90 days in mice with high susceptibility to TiO_2 NP exposure (Sun et al. 2012).

The tumorigenicity of TiO_2 NPs was demonstrated in an exposure test, indicating that the squamous cell carcinoma and lung adenocarcinoma rates were significantly increased in mice and rats after 2 years of exposure to 10 mg m^{-3} TiO_2 NPs (Heinrich et al. 1995). However, the increased tumorigenicity risk is correlated with chronic inflammation or induced by the possible formation of precancerous lesions such as granuloma (Saffiotti and Stinson 1988; Multhoff et al. 2012). Because there is no inflammation risk, sequestration, or granuloma formation in this study, the tumor formation risk posed by sprays emitting TiO_2 NPs is considerably low.

Studies have discovered that TiO_2 NPs were localized within epithelial and endothelial cells, connective tissue, blood capillaries, and even red blood cells in rats exposed to 0.11 mg m^{-3} TiO_2 NP aerosols (Geiser et al. 2005; Mühlfeld et al. 2007). Li et al. (2010) also revealed that after 28 days of intratracheal instillation, a small fraction of TiO_2 NPs may have entered the blood circulation and reached other organs, including the liver and kidneys. Several inhalation studies have also shown that TiO_2 NPs can act as an airway irritant and affect the expression of certain genes in both the heart and lungs, exerting genotoxic effects (Kan et al. 2012; Li et al. 2010; Shi et al. 2013; Yazdi et al. 2010).

Aggregation of TiO_2 NPs in rat lung tissue was observed in an intratracheal instillation test by Gustafsson et al. (2011). On day 30 after the exposure, the number of TiO_2 NP aggregates in AMs was clearly increased. Cell-shaped areas of aggregates were also observed, possibly resulting from disrupted cells that were "overloaded" with the particles. On day 90, the aggregates were mainly found in the interstitium. Although the aggregation of inhaled NPs is normal, the influence of NP aggregates on toxicity and NP transportation remains unknown. In the present study, the dose–response relationship and total lung TiO_2 NP burden were comprehensively described and forecast without consideration of NP aggregations.

The characteristics of NPs (e.g., shape, size, and surface coating) play a major role in the NP's toxicity. Several studies have explored the respiratory system toxicity posed by TiO_2 NPs of different sizes. Liu et al. (2009) reported that after 1 week of intratracheal instillation exposure, TiO_2 NPs of size 5 nm led to more severe inflammation than did particles of size 21 or 50 nm. In an experiment involving 6-h acute exposure of rats of various sizes to 20 mg m^{-3} aerosol TiO_2 NPs, Noël et al. (2013) found the following: (i) larger TiO_2 NPs (>100 nm) had an acute inflammation effect, with significant neutrophil increment found in BAL fluid; (ii) smaller TiO_2 NPs (5, 10–30, or 50 nm) induced only significant oxidative stress and cytotoxicity; and (iii) larger TiO_2 NPs had a more severe toxic effect than did smaller TiO_2 NPs.

Compared with fine particles, TiO_2 NPs have stronger pulmonary effects because of their larger specific surface area, easier interstitial access, and longer deposition time (Geiser et al. 2008; Noël et al. 2012; Oberdörster et al. 1994). The surface characteristics of NPs also play a major role in inhalation toxicity. Rossi et al. (2010a, 2010b) have indicated that (i) TiO_2 microparticles (<5 μm) induced more severe respiratory tract irritation than did silica-coated TiO_2 NPs; (ii) rutile- and anatase-form TiO_2 NPs did not induce significant inflammation effects; and (iii) silica-coated TiO_2 NPs caused increments in TNF-α and neutrophils.

The mechanism through which TiO_2 NPs induce a toxic effect may be related to the particles' high specific surface area and electrostatic force. After they are ingested by cells, TiO_2 NPs attach to the cell membrane, organelles, and biomolecules, leading to lipid peroxidation and membrane damage. The catalysis of TiO_2 NPs induces unpaired electrons on organic molecules, leading to reactive oxygen species (Hou et al. 2019). Under moderate oxidative stress, inflammatory responses could be induced by NPs due to activation of NF-κB cascades (Cao 2018). Under high oxidative stress, NPs resulted in oxidative damage and eventually apoptosis and necrosis (Cao 2018).

Administrative strategies

The International Agency for Research on Cancer has classified TiO_2 NPs as a possible carcinogen to human beings (i.e., group 2B; Baan et al. 2006). The National Institute for Occupational Safety and Health (NIOSH) has also recommended that TiO_2 be classified as a "potential occupational carcinogen" on the basis of observations made in a chronic inhalation study that rats exposed to 250 mg m^{-3} fine TiO_2 particles developed lung tumors (NIOSH 2011).

The SCCS has established a standard stating that a maximum concentration of 25% TiO_2 NPs should be used in UV filters within cosmetic products because of concerns regarding the particles' potential inhalation toxicity (SCCS 2018). The committee has also suggested that TiO_2 NPs within sunscreen could be coated with inorganic material to prevent harmful radicals being generated by UV excitation (EWG (Environmental Working Group) 2018; Fang et al. 2017). Recommended limitations on the exposure concentrations of TiO_2 have varied in studies, ranging from 0.3 to 15 mg m^{-3} depending on the particle size or standard employed (ACGIH 2007; SCCS 2018). The NIOSH recommends airborne exposure limits of 2.4 mg m^{-3} for fine TiO_2 particles (<2.5 μm) and 0.3 mg m^{-3} for ultrafine TiO_2 particles (e.g., engineered NPs), which were based on a time-weighted average concentration of up to 10 h day^{-1} during a 40-h work week (SCCS 2018).

Regarding the threshold dose of TiO_2 NPs, Thompson et al. (2016) estimated a no significant risk level (NSRL) of 300 μg day^{-1} for various biomarkers (e.g., particle overload, chronic inflammation, and cell proliferation) on the basis of empirical evidence obtained for human systems and through mechanistic approaches. Compared with the threshold value

identified in the present study (1.09 ± 0.76 mg), which was derived on the basis of a more conservative criterion ($\gamma_{0.5}$), this NSRL is lower, possibly because of differences in the sensitivity of the adopted biomarkers (Thompson et al. 2016). Moreover, the human-equivalent lung-deposited surface area concentration was estimated to be 30.3 $\mu m^2\ cm^{-3}$, corresponding to the human-equivalent internal dose of $4.3 \times 10^{-3}\ cm^2\ g^{-1}$ after 8 h of exposure (Thompson et al. 2016).

Furthermore, for occupational groups, small quantities of TiO_2 NPs involved in activities such as weighing, mixing, transferring, sonication, and solution creation should be handled under laboratory fume hoods (Lee et al. 2010; Mazzuckelli et al. 2007; Methner et al. 2010). The protective measures employed during spray manufacture vary and depend on the fabrication procedure because small particles are mostly released during high-energy processes such as synthesis, spraying, and machining (Ding et al. 2017). In addition to factories having local exhaust ventilation together with a central ventilation system, occupational workers are recommended to wear typical process-specific enclosures including a full-body protection suit, laboratory clothes, glasses, gloves, and masks to prevent exposure (Ding et al. 2017).

In 2009, the European Commission established a regulation stating that anatase-crystalline TiO_2 NPs, which are highly irritating, cannot be present in concentrations higher than 5% within sunscreen products on sale to the public. The TiO_2 NPs employed in sunscreen products should be coated to prevent the generation of harmful radicals (EWG (Environmental Working Group) 2017). To reduce inhalation, sunscreen sprays should be kept away from the nose and mouth during sunscreen application (Kessler 2011; EWG (Environmental Working Group) 2017). The risk estimates derived in the present study suggest that sprays emitting a relatively large volume per action, sprays with relatively high TiO_2 NP concentrations, and lotions with relatively low viscosity have the highest *HQ*. Therefore, we suggest that products be designed that emit small volumes per action, have low TiO_2 NP concentration, and have low viscosity to help reduce the level of exposure.

Limitations and implications

Regarding the PB lung model implemented in this study, because of limited knowledge of the behaviors of TiO_2 NPs, the model may not have been fully predictive because it did not consider the transport and fate of TiO_2 NPs in the human body after their inhalation. Few studies have validated the TiO_2 NP lung burden estimations obtained using the PB lung model. Geiser et al. (2005) showed a deposition of 4–5 μg of TiO_2 NPs per rat through 1 h of exposure, which is much higher than the simulated human lung burden (3.4×10^{-5} to 0.42 μg) in our constructed PB lung model. This discrepancy can be attributed to uncertainties in parameter estimations, differences in chamber volume, or physiological differences between the target animals (e.g., respiratory rate). Because the input parameters of the model constructed in the present study were obtained from previous studies, the uncertainties could be reflected in the risk estimates. However, studies on the application of the PB lung model sufficiently concur that difficulties are encountered when exploring the long-term accumulation of TiO_2 NPs in animal models.

Regarding the application frequency, duration, and scenarios for the eight sunscreen spray products investigated in the present study, the experimental settings and assumptions were relatively simple; approximately 9 g day^{-1} of the product was sprayed into a release chamber (SCCS 2018). Clearly, the datasets employed in human health risk assessments are not applicable to every consumer and lack consideration of realistic exposure scenarios (SCCS 2018). Although consumer exposure assessments usually rely on modeling and assumptions, risk estimates and lung burden estimates can be more accurate if reasonable exposure scenarios are rigorously considered (Kuhlbusch et al. 2018).

We conducted a comprehensive risk assessment of eight TiO_2 NP–containing spray products. In the exposure assessment, sprays were only pressed twice within a certain period; frequency of application is likely to be higher in reality if the user follows the consumer guidelines as stated on the product labels (Matta et al. 2019). Therefore, although the eight spray products did not pose significant pulmonary risks, the *HQ*s and ERs may have been underestimated because of insufficient exposure dose and frequency (SCCS 2018). Additionally, the pulmonary risks of TiO_2 NPs should be a matter of concern for populations with weakened pulmonary defense systems because ineffective macrophage clearance of inhaled TiO_2 NPs from the periphery of the lung has been demonstrated to lead to biopersistence of NPs and to favor their translocation into the lung interstitium and then the vasculature, having deleterious effects (Geiser et al. 2008).

Conclusions

We employed a mechanistic approach to evaluate the long-term risks associated with TiO_2 NP inhalation from different sunscreen spray products. Given the investigated exposure scenarios (e.g., frequency and duration), the eight spray products are unlikely to pose significant inhalation risks even after 10 years of exposure. Nonetheless, the risk estimates could be higher if the products were applied more frequently or for longer durations, including as directed on product labels. In other cases, the inhalation risks of TiO_2 NP–containing aerosols are potentially higher when the products are used by individuals with allergic airway diseases. We conclude that the human health risk assessment framework integrated with the PB lung model facilitated estimations of the risk of long-

term use of nanotechnology-based spray products. Mechanistic models and extrapolation tools can bridge knowledge gaps and solve difficulties in chronic exposure assessments within rodent or even human systems. Given the importance of the issue of NP inhalation to the management of nanomaterials, the present study suggests that the amount of product of number of spray presses could be employed as pragmatic tools for evaluating appropriate standards for other NP-containing spray products. However, public acceptance of sunscreen products may depend on updated approval from the SCCS and convincing safety data.

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Author contribution Wei-Ming Wang: performed data collection, analyzed the data, implemented simulations, and drafted original manuscript. Chi-Yun Chen: analyzed the data and performed the research. Tien-Hsuan Lu: analyzed the data and performed the research. Ying-Fei Yang: planned the research, performed results analysis, and did supervision. Chung-Min Liao: designed the research, did supervision, and wrote the paper. All authors helped to interpret the results and provided feedback on the manuscript.

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Declarations

Research involving human participants and animal rights The article does not contain any studies with human participants or animals performed by any of the authors.

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