Heliyon 5 (2019) e02165

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.heliyon.com

A risk assessment framework for self-management of poorly soluble low toxic nanomaterials

Satomi Kawai *, Masanori Niwano, Masayuki Sato

Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., 3-1-98, Kasugadenaka, Konohana-ku, Osaka, 554-8558, Japan

ARTICLE INFO

Keywords:
Nanotechnology
Analytical chemistry
Theoretical chemistry
Environmental science
Atmospheric science
Risk assessment
Poorly soluble low toxic
Particle surface area
OEL
Optical particle counter

ABSTRACT

The safety of nanomaterials is still being debated and the risk should be assessed using the latest available information. As for poorly soluble low toxic (PSLT) nanomaterials, the US National Institute for Occupational Safety and Health estimated the occupational exposure limit (OEL) for titanium dioxide (TiO_2) based on a particle surface area (SA) metric. The Organisation for Economic Co-operation and Development (OECD) suggested a tiered exposure assessment approach. This article proposes a risk assessment framework for self-management of PSLT particles. Lung burden (described in SA units), which had positive correlation with low observed adverse effect levels for PSLT particles, is chosen as the dose metric. In-house OEL is determined for individual workplaces. For materials with limited data, we suggest evaluating in-house OEL by utilizing the no observed adverse effect level (NOAEL) for TiO_2, as a representative PSLT nanomaterial. As for the exposure assessment, workplace concentration is first measured with simple equipment (ex. optical particle counter, OPC), and respirator performance is taken into account if it is unavoidable as a last resort. This framework enables efficient risk assessment for PSLT particles by assuming worst cases for each step, and considering the particle characteristics and operational conditions in each workplace.

1. Introduction

The safety of nanomaterials is still under discussion. In such a situation, titanium dioxide (TiO_2) is recognized as one of the representative nanomaterials for risk assessment for poorly soluble low toxic (PSLT) particles, and agencies have suggested several occupational exposure limits (OELs) for TiO_2 as assessed by a variety of methods. The US National Institute for Occupational Health (NIOSH) recommended 0.3 mg/m^3 as the permissible exposure limit (PEL), based on a tumor-response curve of TiO_2 using particle surface area (SA) as a dose metric, utilizing a particle deposition model (NIOSH, 2011). In accordance with the EU Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) guidance document (ECHA, 2008), "The EU engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES)" (ENRHES, 2009), evaluated 0.017 mg/m^3 as the derived no effect level (DNEL) for workers, using a no observed adverse effect level (NOAEL) obtained in a subchronic inhalation study of TiO_2 in rats (Bermudez et al., 2004). The Japan Advanced Industry Science and Technology (AIST) suggested the time limited exposure limit as 0.6 mg/m^3 (Gamo, 2011), using the particle deposition rate to the lung (mg/kg/day) observed in the same rats study as the ENRHES had used for its assessment. In this way, various organizations have proposed OELs for management of their own based on different endpoints, targets for their assessment and evaluation methods.

As for exposure assessment, several agencies have suggested tiered approaches. For example, the Organisation for Economic Co-operation and Development (OECD) suggested a three-tiered approach consisting of 1) gathering as much information as possible on workplace conditions and characteristics of the materials handled there; 2) conducting a basic exposure or release assessment using easy-to-use portable equipment; 3) obtaining as much information as possible on airborne nanomaterials in the workplace (OECD, 2015b).

Generally, Occupational exposure limit (OEL) has been derived assuming the basic exposure scenario, such as 8 hours per working day. Numerous mathematical models have also been proposed to adjust OEL for unusual work schedules (ACGIH, 2017). With respect to particulate matters, the Multiple Path Particle Deposition Model (MPPD model, Applied Research Associates, Inc., available at https://www.ara.com/capabilities/inhalation-and-respiratory-mechanics) is widely used for the risk assessment, utilizing particle characteristics and physiological parameters of animals and humans to analyze particle deposition and retention in the respiratory tracts to each exposure scenario.

* Corresponding author.
E-mail address: kawais2@sc.sumitomo-chem.co.jp (S. Kawai).

https://doi.org/10.1016/j.heliyon.2019.e02165
Received 4 March 2019; Received in revised form 18 July 2019; Accepted 24 July 2019

OELs suggested by agencies are compared with the workplace concentration (Gamo, 2011; NIOSH, 2011). As for worker-DNELs, applying appropriate personal protective equipment is also considered when calculating the exposure concentration if it is used as the last resort and utilized to assess adequate control of the risk at the workplace (ECHA, 2016).

Considering the above information, this article suggests a risk assessment framework for self-management of particles defined as PSLT, utilizing limited data, worst case assumptions, and operational conditions at each workplace.

2. Methodology

2.1. Hazard assessment

2.1.1. Particle surface area (SA) lung burden as the dose metric

Dose-responses obtained in toxicity studies are usually discussed based on the mass dose (mg/kg or mg/m^3). However, lung toxicity due to nanomaterials exposure has been well described by the SA of the particles retained in the lung, hereafter referred to as the "particle SA lung burden" (m^2/lung or m^2/g lung), which is calculated by multiplying the mass of the particle retained in the lungs (mg/lung or mg/g lung) by the Brunauer-Emmett-Teller (BET) SA (m^2/g) of the particle (NIOSH, 2011; Oberdörster and Yu, 1990; Tran et al., 2000; Nakanishi, 2011; Keller et al., 2014). When the dose was expressed as particle SA lung burden, TiO_2 and other PSLT particles with nano and bulk sizes showed a consistent dose-response relationship to persistent pulmonary inflammation or lung tumors in rats, while different dose-response relationships were observed between particles when the dose was expressed as particle mass (NIOSH, 2011).

Table 1 provides a comparison of particle SA lung burdens at lowest observed adverse effect levels (LOAELs) of PSLT particles obtained in the repeated inhalation studies in rats, according to various exposure durations and various chemical characteristics of nano and bulk sized materials. As expected, the LOAELs (expressed in particle concentration [mg/m^3]) varied a lot (0.8–50 mg/m^3). However, the particle SA lung burdens at LOAELs (m^2/lung) were not so different and largely around 0.1 m^2/lung.

Therefore, particle SA lung burden is suggested as the dose metric for hazard assessment in this framework.

2.1.2. Calculation of an in-house occupational exposure limit (OEL) based on the particle SA lung burden

Fig. 1 shows the schematic diagram for determination of in-house OEL using PSLT particle SA lung burden. The details of each assessment step are described in sections 2.1.2.1, 2.1.2.2 and 2.1.2.3.

2.1.2.1. Evaluation of particle SA lung burden at a no observed adverse effect level (NOAEL) in rats. First, the mass lung burden was determined at a repeated inhalation NOAEL for rats and then converted into the particle SA lung burden using the BET SA of the PSLT particle (Fig. 1, left side).

If the mass lung burden at the NOAEL could not be obtained in this manner, it would be calculated using a particle deposition model, such as the MPPD model. The deposition rate of particles depends on size distribution, density, and also on the respiratory conditions in rats. The mass lung burden was calculated using these respiratory conditions and the physico-chemical properties as parameters in the MPPD model (Anjilvel and Asgharian, 1995; EPA, 2004; Winter-Sorkina and Cassee, 2002; Oller and Oberdörster, 2016).

The benchmark dose (BMD) approach could also be used in parallel for derivation of a NOAEL (ECHA, 2012). In this case, we suggest using particle SA lung burden as the dose as suggested in section 2.1.1.

When evaluating the in-house OEL of a material for which no repeated inhalation data are available, we propose to use the NOAEL of TiO_2 instead, as explained in the last part of section 2.1.2.3.

2.1.2.2. Extrapolation of rat data to the human lung burden, considering species differences. When extrapolating rats data to humans, species differences in toxicodynamics and toxicokinetics should be considered. The lung response to PSLT particles exposure has been well described by the term "lung overload," which is typified by a progressive reduction in particle clearance mediated by alveolar macrophage (AM) and the loss of AM mobility (Morrow, 1988). As rats are known to be more prone to lung overload than other mammals including humans, an assessment factor of 1 has been suggested to account for the species differences in toxicodynamics (Olin, 2000; Gamo, 2011). As for toxicokinetics, the lung burden of rats is first extrapolated to that of humans using species differences in either lung weight or alveolar SA, and then converted to the corresponding air concentration considering anatomical and physiological differences in respiration between rats and humans using the MPPD model (NIOSH, 2011; Oller and Oberdörster, 2016).

NIOSH has selected the lung SA-based approach to evaluate PEL for TiO_2 because insoluble particles are deposited and cleared from the surface of the respiratory tract. Consequently, dose per unit SA is often used as a normalizing factor for comparing particle doses across species (NIOSH, 2011). The US Environmental Protection Agency (EPA) also

Table 1
Particle surface area (SA) Lung burdens at LOAELs of Poorly soluble low toxic (PSLT) particles.

	Nano TiO_2				Nano Carbon black	Bulk TiO_2	Diesel engine exhaust
	Aeroxide P25, NM-105 (Anatase: utile = 80:20, BET: 48 m^2/g)		UV TITAN M212 NM-103 (rutile, BET: 56 m^2/g)	UV TITAN M262 NM-104 (rutile, BET: 46 m^2/g)	Monarch 880 (BET: 220 m^2/g)	Bulk TiO_2 (Rutile, BET: 4.99 m^2/g)	Diesel engine exhaust (BET: 18 m^2/g)
Duration	5 days (6 h/d)	28 days (6 h/d, 5 d/w)	28 days (6 h/d, 5 d/w)	28 days (6 h/d, 5 d/w)	13 weeks (6 hr/d, 5 d/week)	2 years (6 h/d, 5 d/w)	2 years (18 h/d, 5 day/wk)
Dose	2, 10, 50 mg/m^3	3, 12, 48 mg/m^3	3, 12, 48 mg/m^3	3, 12, 48 mg/m^3	1.1, 7.1, 52.8 mg/m	10, 50, 250 mg/m^3	0.8, 2.5, 4.5, 7 mg/m^3
MMAD (GSD)	0.7–1.1 μm (2.3–3.4)	0.59–0.83 μm (4.02–6.19)	0.62–1.17 μm (2.92–4.27)	0.91–1.57 μm (3.26–3.94)	0.88 μm	1.5–1.7 μm	0.25 μm (2.93)
Rat strain, Sex	Wistar, ♂	Wistar, ♂	Wistar, ♂	Wistar, ♂	Fischer 344, ♂♀	SD, ♂♀	Wistar, female
Reference	Ma-Hock et al. (2009)	Creutzenberg (2013)	Creutzenberg (2013)	Creutzenberg (2013)	Driscoll et al. (1996)	Lee et al. (1985)	Heinrich et al. (1995)
Particle SA lung burden[a] (LOAEL[b])	0.0785 m^2/lung (50 mg/m^3)	0.0873 m^2/lung (2 mg/m^3)	0.091 m^2/lung (12 mg/m^3)	0.0781 m^2/lung (12 mg/m^3)	0.40172 m^2/lung (7.1 mg/m^3)	0.103 – 0.161 m^2/lung (10 mg/m^3)	0.113202 m^2/lung (0.8 mg/m^3)

Abbreviations: BET: Brunauer, Emmett, Teller surface area (m^2/g); MMAD (GSD): Mass Median Aerodynamic Diameter (Geometric Standard Deviation).

[a] Reported lung burdens as mass were converted into total particle SA using BET SAs.

[b] LOAELs were evaluated according to the histopathological findings.

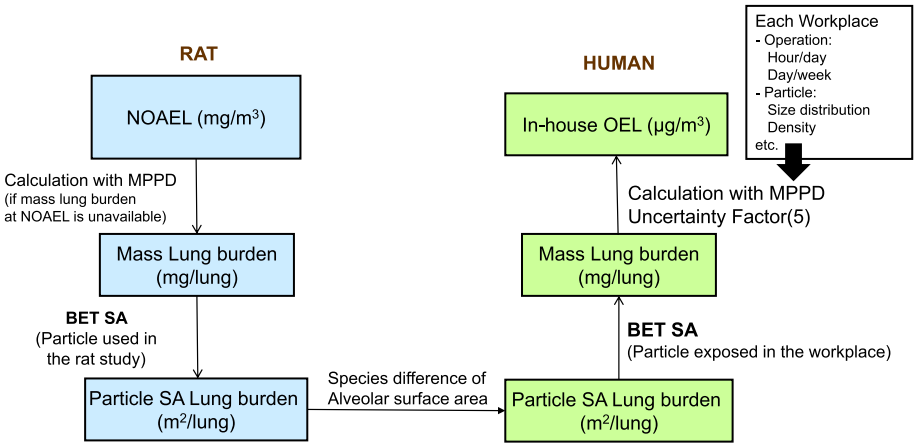

Fig. 1. Schematic diagram for in-house OEL derivation using PSLT particle SA lung burden at a NOAEL. Abbreviations: MPPD; Multiple Path Particle Deposition Model, BET SA; Brunauer, Emmett, Teller surface area (m^2/g).

uses the lung SA-based factor for rat to human extrapolation in risk assessment of chronic exposure to particulates (EPA, 2004). NIOSH and EPA mentioned that extrapolation could also be based on the lung weight of rats relative to that of humans (NIOSH, 2011; EPA, 2004). In that case, the estimates of occupational exposure level equivalent to the rat dose level would be higher by a factor of approximately four (NIOSH, 2011). In other words, estimates would be lower (i.e., OELs would be severer) using the lung SA-based approach than the lung mass-based one.

In our framework, we used the ratio of the alveolar SA (143 m^2 [human]/0.39 m^2 [rat]) (ICRP, 1994) as the assessment factor for toxicokinetics and the MPPD model to convert the mass lung burden at the NOAEL for humans into the equivalent air concentration. The MPPD model includes anatomical parameters, such as angles, radius, and length of respiratory tracts, and physiological parameters, such as tidal volume and breathing frequency, for rats and humans (Anjilvel and Asgharian, 1995), and has been used to calculate the air concentration corresponding to the human-equivalent mass lung burden (NIOSH, 2011; Oller and Oberdörster, 2016).

In summary, we adopted 1 for an assessment factor for the species differences in toxicodynamics, because rats are known to be the most sensitive species (Olin, 2000; Gamo, 2011). As for the differences in toxicokinetics, the alveolar SA ratio (143 m^2 [human]/0.39 m^2 [rat]) (ICRP, 1994) was considered and another anatomical species differences were also taken into account by inputting the species specific parameters into the MPPD model.

2.1.2.3. Derivation of an in-house OEL based on workplace operational conditions. The physico-chemical properties of the particle and operational conditions are taken into account when obtaining the in-house OEL at the workplace (Fig. 1, right side).

The particle SA lung burden (m^2/lung) at the NOAEL for humans, obtained in section 2.1.2.2, was converted into the mass lung burden (mg/lung) using the BET SA of the particle exposed in the workplace. Then, the corresponding air concentration ($\mu g/m^3$) was calculated using the MPPD model. This method is based on the well-known theory that the critical dose to cause lung inflammation is lung burden (EPA, 2004; Oller and Oberdörster, 2016; NIOSH, 2011; Pauluhn, 2011).

Particle characteristics, such as size distribution and density of the material and work condition including the number of hours, frequency and duration of exposure were inputted into the model. In this manner, differences of exposure durations are taken into account.

To calculate in-house OEL, we inputted 20 years for the duration of exposure, which seemed to be enough to evaluate workplace-specific exposure, as it is unlikely that a worker is engaged in the same operation over his entire work life, considering that individual work contents often change in actual workplaces, following employee movement, promotion, and so on. However, depending on workplace situations, an entire work life, 40 or 45 years would be applied. Finally, the remaining uncertainty, differences between individual workers were considered by dividing the human NOAEL ($\mu g/m^3$) by 5 (ECHA, 2012).

Generally, OELs have been evaluated based on the standard work condition, i.e., exposure to the chemical for 8 hours/day, 5 days/week. However, work conditions vary between workplaces. In some workplaces, workers might work 1 hour/day, 5 days/week, and in others 8 hours/day, 1 day/week. A great many models have also been proposed to adjust OEL for unusual work schedules. Some models are based on pharmacokinetic actions (ACGIH, 2017). With regard to particulate matters, the MPPD model prepares parameters to describe various exposure scenarios. The model calculates the deposited, cleared and retained particle mass to respiratory tract not only according to the inputted exposure time or frequency but also to the physico-chemical properties of the particles at the workplace. The model considers anatomical and physiological parameters of the exposure population as well, as described in sections 2.1.2.1 and 2.1.2.2. Utilizing the model, we can obtain corresponding air concentrations to the retained mass lung burden according to each exposure scenario and that enables us to estimate in-house OELs for various work schedules, taking into account of the particle deposition and clearance kinetics in the respiratory tracts.

In our framework, the number of work hours and frequency of exposure were inputted into the MPPD model as the workplace-specific parameters to describe the operational schedule at each workplace. Table 2 shows a wide range of in-house OELs (7–290 $\mu g/m^3$) for workplaces where the material handled is the same but the work conditions are different.

As mentioned in section 2.1.2.1, we suggest using the NOAEL of TiO_2 in the absence of a NOAEL for the material of interest. For example, the

Table 2
In-house OELs obtained for various workplaces assuming that operational time or frequency is different but the same material, Aeroxide P25 (NM-105) is handled.

Workplace	A	B	C	D
Operation time	8 hour/day	1 hour/day	8 hour/day	1 hour/day
Frequency	5 day/week	5 day/week	1 day/week	1 day/week
In-house OEL[a]	7.3 $\mu g/m^3$	59 $\mu g/m^3$	36 $\mu g/m^3$	290 $\mu g/m^3$

Abbreviations: OEL; Occupational Exposure Limit, MPPD; Multiple Path Particle Deposition Model, MMAD; Mass Median Aerodynamic Diameter, GSD; Geometric Standard Deviation.

[a] In-house OELs were calculated with MPPD model, assuming the same size distribution of MMAD1.44 μm and GSD 2.60 as in the subchronic inhalation study of Aeroxide P25 (NM-105) in rats (Bermudez et al., 2004).

particle SA lung burden of Aeroxide P25 (provided by Degussa/Evonik; also provided as NM-105 by the EC Joint Research Centre), 0.0042 m^2/lung (the suggested NOAEL for rats), which we calculated using the MPPD model with data from a subchronic inhalation study in rats (Bermudez et al., 2004), could be proposed. Aeroxide P25 (NM-105) has been widely studied as a representative PSLT nanoparticle and data relating to Aeroxide P25 exposure have been used to calculate OELs or a worker-DNEL of TiO_2 by several agencies and projects (NIOSH, 2011; Gamo, 2011; ENRHES, 2009; JSOH, 2013; Stockmann-Juvala et al., 2014; BSI, 2007).

2.2. Exposure assessment

2.2.1. Measurement of particle concentration in the workplace

As suggested by the OECD, we used a three-tiered approach involving: 1) collection of information about the handled materials and operational activities, 2) conduct of a basic exposure assessment using easy-to-use portable equipment, such as an optical particle counter (OPC) or condensation particle counter (CPC), and 3) sophisticated assessment of exposure using a Scanning Mobility Particle Sizer (SMPS), Aerodynamic Particle Sizer (APS) or chemical analysis using Inductively coupled plasma mass spectrometry (ICP-MS) and so on (OECD, 2015b).

2.2.1.1. Estimation of mass concentration using particle number concentration, obtained with an optical particle counter (OPC). The particle number concentration obtained in Tier 2 in the workplace can be converted to the corresponding mass concentration under some assumptions. If the number concentration is obtained by an OPC, the mass concentration, hereafter referred to as the "OPC mass value", can be roughly estimated from the following formula with the assumption that all particles are spherical in shape, and their size is the median value in each measurement range of the OPC,

$$M = \sum \frac{\pi}{6} \rho_p N_{OPC} D_m{}^3.$$

Here, M is the workplace mass concentration, i.e., the "OPC mass value", ρ_p is particle density, D_m is median diameter, and N_{OPC} is the number concentration obtained in each measurement range. The sum of the mass concentrations in each bin is considered to be the OPC mass value in the workplace.

Table 3 shows the OPC mass values and actual chemical concentrations measured by chemical analysis in a workplace where certain PSLT particles are produced. In this example, the OPC mass value was an underestimate of the actual chemical concentration when particle size was ≤2.5 μm but not when it was >2.5 μm. This means that the OPC mass value could be used as the worst case workplace concentration if the size of most of the particles is >2.5 μm.

On the contrary, if a considerable amount of particle occupies ≤2.5 μm, the OPC mass value would be an underestimate and so it would be necessary to measure total number concentrations of particles with a CPC including those with diameters less than 100 nm, which is out of the range of an OPC.

2.2.2. Assessment of performance of respirators

Exposure can be assessed with respect not only to the workplace concentration but also to the performance of the respirators used by workers. The reduction factor achieved by the use of respirators has also been suggested under the REACH regulation in order to evaluate that the risk associated with the exposure to the material was adequately controlled. It is important to note that personal protective equipment such as a respirator is always the last resort (ECHA, 2016).

Respirator performance is usually determined by measuring the protection factor (PF) of the respirator, which is the ratio of the concentration of an airborne contaminant outside (C_o) to inside (C_i) the respirator (i.e., C_o/C_i). Therefore, a higher PF means respirator use provides more effective protection (OSHA, 2009). Authorities, such as the US Occupational Safety and Health Administration (OSHA) and the Japanese Industrial Standards (JIS) Committee, have provided guidance on assigned protection factors (APFs) (OSHA, 2009; MHLW, 2009). The APF is defined as the expected rate of decrease in the concentration of inhaled substances when a trained worker correctly puts on a properly functioning respirator. The APF has been also used in the European Centre for Ecotoxicity and Toxicology of Chemicals (ECETOC) Targeted Risk Assessment (TRA) tool, which is recommended under the REACH regulation (ECETOC, 2012; ECHA, 2016).

Worker exposure concentration is evaluated as below if a respirator is used as the last resort:

$$\text{Exposure concentration} = \text{Workplace concentration} \times (1/\text{PF}).$$

When the PF of the respirator is unavailable, the worst case alternative is the recommended respirator APF.

2.3. Risk assessment

Risk assessment is conducted by calculating the quotient between the exposure concentration and the in-house OEL, which is called the Hazard Quotient (HQ). If the HQ is less than 1, the risk is considered to be acceptable.

Our proposing scheme for risk assessment of workplace exposure to PSLT particles is provided in Fig. 2. The scheme consists of three elements: in-house OEL (section 2.1), workplace concentration (section 2.2.1), and respirator performance when used as the last resort (section 2.2.2). Each element should start with basic information, that is, NOAEL of TiO_2 suggested using for the in-house OEL determination when there is no NOAEL of the material to be evaluated, an OPC measurement for workplace concentration, and an APF for respirator performance. Even with less information, risk assessment would still be possible by substituting worst case numerical estimates.

OPCs, however, do not explicitly measure size distribution parameters, which are necessary to obtain the aerosol concentration corresponding to the mass lung burden calculated using the MPPD model as described in section 2.1.2.3. In such a case, the in-house OEL should be assessed in each measurement range of the OPC. The rate of alveolar deposition varies depending on the particle size, and this variability results in differences in lung toxicity potential. Therefore, the in-house OEL assessment is based on the worst case assumption that all particles have the same diameter and the highest deposition rate in each measurement range, that is, 2.2 μm for the 0.3–2.5 μm size bin, 2.5 μm for 2.5–5 μm, and 5 μm for 5–10 μm, respectively (Fig. 3). If the sum of the HQ obtained in each range is <1, the risk is considered to be acceptable.

Calculating HQs would also be useful for choosing an appropriate respirator to protect against the workplace hazard if respirators cannot be avoided to mitigate the exposure to the material. For example, if use of the half face type dust mask (APF = 3 or 10) is assumed (MHLW, 2009; OSHA, 2009) and the sum of the HQ is >1, then another type of respirator with a larger APF should be considered. These include the half-facepiece or fan-assisted air-purifying respirator (APF = 50) (MHLW, 2009; OSHA, 2009), which can reduce the exposure concentration to 6 or 20%, respectively, of that measured under half face type dust mask conditions.

Table 3
Workplace concentrations obtained by conversion of number concentration measured by an Optical particle counter (OPC mass value)[a] and actually measurement by chemical analysis of the material.

	≤2.5 μm	2.5–10 μm
OPC mass value	310 μg/m^3	15100 μg/m^3
Chemical analysis (ICP-MS)	810 μg/m^3	11200 μg/m^3

Abbreviations: ICP-MS; Inductively Coupled Plasma-Mass Spectrometry.
[a] OPC mass value was calculated using the formula specified in section 2.2.1.1.

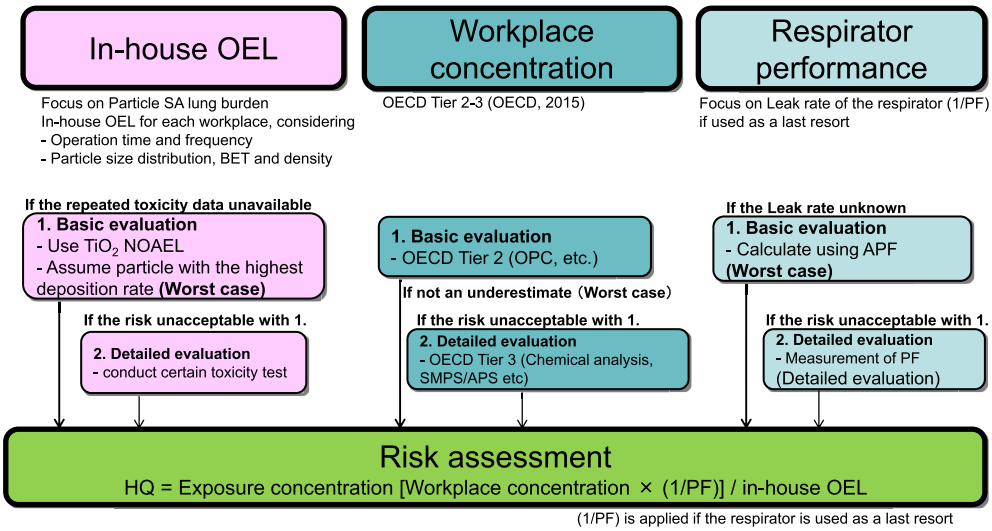

Fig. 2. Risk assessment framework for workers exposed to PSLT particles. Abbreviations: OEL; Occupational Exposure Limit; HQ: Hazard Quotient; SMPS/APS: Scanning Mobility Particle Sizer Spectrometer/Aerodynamic Particle Sizer.

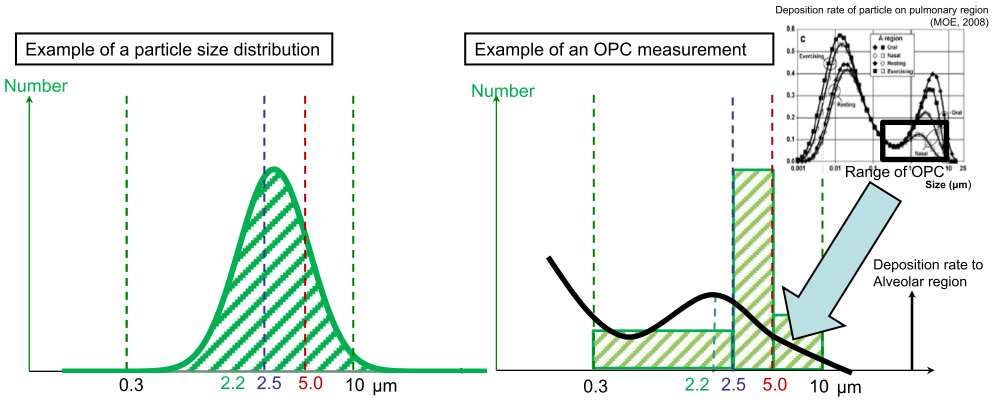

Fig. 3. Risk assessment in each measurement range of an OPC, focusing on the highest deposition rate on alveoli. If the size distribution of the particle at the workplace is available, one in-house OEL can be calculated by using the MMAD and GSD (Left side). However, MMAD and GSD are not available with an OPC, but just particle number in each measurement range (ex. 0.3–2.5, 2.5–5.0 and 5.0–10 μm) is available (Right side). Then, In-house OELs are evaluated by using the highest deposition rate in each size range, ex. 2.2 μm for the 0.3–2.5 μm size bin, 2.5 μm for the 2.5–5 μm, and 5 μm for the 5–10 μm, respectively. The In-house OELs are compared with the OPC mass values at each bin to obtain the HQs. If the sum of the HQ obtained in each range is <1, the risk is considered to be acceptable.

3. Discussion

3.1. Particle SA lung burden as the dose metric

In this framework, an in-house OEL is calculated using the particle SA lung burden at an NOAEL for rats, which is warranted based on the finding that the particle SA lung burdens at LOAELs were not significantly different between PSLT particles.

The most suitable dose metric to describe the pulmonary adverse effect of PSLT particles is still under debate and particle volume has also been suggested to derive a worker-DNEL (Pauluhn, 2011). NIOSH reported that TiO_2 and other PSLT particles with nano and bulk sizes showed a consistent dose-response relationship for adverse pulmonary responses in rats, including persistent pulmonary inflammation and lung tumors when the dose metric was particle SA lung burden, while different dose-response relationships were observed between particles when the dose was expressed as particle mass (NIOSH, 2011). Oberdörster and Yu analyzed the tumor incidences and the different particle parameters, such as particle SA, mass, number and volume lung burden and observed that only SA showed a good correlation with the tumor incidences (Oberdörster and Yu, 1990). The correlations between particle SA lung burden and the lung response have also been well described by others (Tran et al., 2000; Driscoll, 1996; Miller, 2000).

The above correlation characteristic applies to PSLT particles that are insoluble in lungs. As for soluble or partially soluble particles, such as zinc oxide or amorphous silica, their adverse effects whether due to dissolution into ions or to retention as particles firstly should be discussed.

This characteristic should also not be applied to compare the lung responses to identical chemicals with different shapes, including spheres, rods, tubes, fibers and plates as they may have different physical, chemical and biological properties. Ma-Hock et al. compared the lung inflammation to carbon black, graphene, graphite nanoplatelets and multi-wall carbon nanotubes. They could not find the correlation to the particle SA nor the volume of the lung burden and concluded that there is likely to be a complex interaction of several parameters (Ma-Hock et al., 2013).

Particle SA lung burden is calculated by multiplying the mass of the particle retained in the lungs by the BET SA (m^2/g) of the particle as described in section 2.1.1 not by the SA obtained by other methods. The above mentioned relationship between particle SA lung burden and pulmonary adverse effect has been analyzed by BET SA which means "total SA" taking pores and crevices of the particle into account. "Active SA" measured by diffusion chargers or "mobility-based SA" by scanning mobility particle sizers (SMPS)s has also been used in occupational exposure assessment. Diffusion chargers measure only "outer active SA" of the particles but not pores or crevices. SMPSs do not measure particle SA directly but calculate it from the mobility-based size assuming a

spherical particle. LeBouf et al. reported that "active SA" and "mobility-based SA" underestimated the "total SA" of nano TiO_2 measured by BET method (LeBouf et al., 2011).

3.2. Calculation of an in-house OEL for the relevant human population considering each exposure scenario

Particle SA lung burdens at NOAELs in rats are converted into mass lung burdens in humans and the corresponding workplace concentrations are calculated utilizing the MPPD, a particle deposition model, with work time per day, frequency per week, particle size distribution, and particle density found at each workplace serving as parameters. Finally, the concentrations are divided by five, which is the suggested assessment factor for intraspecies differences for workers according to the REACH guidance (ECHA, 2012).

OELs are derived assuming 8 hours exposure per working day, however, not all operations are made under that standard condition as described in section 2.1.2.3. Models to adjust OELs to non-regular work schedules, including pharmacokinetic based ones, have also been suggested but it seems unlikely to utilize such models to adjust OELs to shorter work time than 8 hours per day (ACGIH, 2017).

As described in Chapter 2, lung toxicity of PSLT particles has been well explained by the particle retention in lungs and overload phenomenon. The MPPD model enables us to calculate corresponding air concentration to the lung retention at the NOAEL, according to any exposure situation, taking into account of the particle kinetics in the respiratory tract. Based on the above, it would be practical to estimate an in-house OEL for the PSLT particle according to any set of work conditions including 1 hour/day or 1 day/week, by utilizing the MPPD model.

Assuming such variety of exposure schedules, in-house OELs would vary a lot, for example, from 7 $\mu g/m^3$ (8 hour/day, 5 day/week) to 290 $\mu g/m^3$ (1 hour/day, 1 day/week) for the suggesting representative PSLT material, Aeroxide P25 (TiO_2) as described in section 2.1.2.3 and Table 2.

Using our flow scheme, acceptable concentrations for general people, such as general population-DNELs can also be evaluated by inputting applicable respiratory condition data (appropriate tidal volume and breathing frequency depending on the population), exposure number of hours (24 hours per day), frequency (7 days per week), and duration (70 or 75 years) into the MPPD model.

3.3. TiO_2 as representative PSLT particles

It has been suggested that TiO_2 can be used as a benchmark material to evaluate the lung response to PSLT particles exposure (Kuempel et al., 2012). Aeroxide P25 (NM-105), in particular, has been widely studied as a representative PSLT nanoparticle and data relating to Aeroxide P25 exposure have been used to determine OELs or the worker-DNEL for TiO_2 (NIOSH, 2011; ENRHES, 2009; Gamo, 2011; JSOH, 2013; Stockmann-Juvala et al., 2014; BSI, 2007). Aeroxide P25 (NM-105) was also selected as a principal TiO_2 material in one of the most comprehensive nanomaterial research programs of the OECD Working Party on Manufactured Nanomaterials, "Safety Testing of a Set of Representative Manufactured Nanomaterials" (OECD, 2015a). The rat lung tumor response or inflammation caused by TiO_2 has been described with the same dose-response curve as other PSLT particles when the dose was explained as lung burden SA (NIOSH, 2011; Oberdörster and Yu, 1990). We observed that the particle SA lung burdens at LOAELs (m^2/lung) in the repeated inhalation studies in rats were not so different, as described in section 2.1.1 and Table 1.

The ECETOC also used Aeroxide P25 (NM-105) as a benchmark material in the decision-making framework for the grouping and testing of nanomaterials, known as DF4nanoGrouping, which assigned it to active nanomaterials (Arts et al., 2015, 2016). Aeroxide P25 (NM-105) might cause a slightly stronger inflammation than other PSLTs. If so, using its data instead would be a worst case assumption and would not underestimate the risk associated to the exposure to the PSLT particle.

Considering the above, we suggest using the NOAEL of the TiO_2, Aeroxide P25 (NM-105), when the NOAEL of the PSLT material of concern is unavailable.

3.4. OPC value as the workplace concentration

According to the published literature on exposure to nanomaterials in workplaces, nanoparticles are not likely to be present as primary particles; rather, agglomerates or aggregates are likely to be the dominant airborne particle (Seipenbusch et al., 2008; Brouwer, 2010; Ogura et al., 2012). Ogura et al. measured size distributions of airborne particles resulting from nineteen kinds of operations using carbon nanotubes, fullerene, carbon black, titanium dioxide, zinc oxide, silicon carbide, or lithium iron phosphate. They reported that particles with the size of $<$300 nm could not be differentiated from background particles in the most workplaces. The particle size distributions measured by an OPC were roughly comparable to those measured by a SMPS in the bin of $>$0.3 μm. Furthermore, the mass size distributions revealed that most particles were $>$2.5 μm (Ogura et al., 2012). We found that certain particles $>$2.5 μm did not have an underestimated OPC mass value as mentioned in section 2.2.

Hence, OPC values seemed to be useful in many workplaces where nanomaterials are handled. There is also an ongoing project to evaluate optical measurement devices including OPCs for the determination of particle size distribution of hazardous substances including workplace nanomaterials (BauA, 2018).

On the other hand, OPC mass values might be useless at some workplaces, where, e.g., primary nanoparticles with narrow size distribution (geometric standard deviation $\approx$1) are produced and workers are in close proximity to the nanomaterial generator (Seipenbusch et al., 2008). In such a case, a CPC, which counts the total number of particles including nano size particles ($<$100 nm), should be the first choice for Tier 2 exposure assessment, and the in-house OEL should be assessed on the assumption that all particles are around 20 nm, a size associated with the highest pulmonary deposition rate (ICRP, 1994).

The sensitivity of an OPC to particles depends not only on the size of the particle but also on the refractive index of the material (Hinds, 1999). When the refractive index is available, suitable calibration will permit an accurate measurement of the size distribution. For aerosol particles of unknown refractive index, the error in size estimation can be significant. In the case of carbon materials, the OPC was reported to be less sensitive than the standard particle in the bin of $>$0.5 μm (Hinds, 1999) and the OPC mass value could be underestimated without suitable calibration of the counter.

3.5. Assessment of the performance of respirators

Generally, workplace concentrations of chemicals have been compared with the OELs for occupational risk assessment. However, we suggest including the performance of respirators in the evaluation of exposure concentration, when the respirators cannot be avoided to mitigate the risk to the material. REACH guidance recommends taking into account the reduction factor achieved by the respirator use in order to assess that the risk has been appropriately controlled (ECHA, 2016). In one of the models suggested in the ECETOC TRA guidance, APFs are used in the risk management evaluation (ECETOC, 2012). Considering reduction factors would optimize the respirator choice for the workplace as described in section 2.3, and that would facilitate better self-management of nanomaterials at workplaces where engineering controls (e.g. containment of the source, local exhaust ventilation, mechanical ventilation) are almost impossible.

4. Conclusions

A risk assessment framework for self-management of PSLT particles was developed. This framework takes into account operational variables

and particle conditions at each workplace, such as operational time, frequency, and particle size, density, and SA. If a respirator is used as a last resort, the performance is also considered. Even with limited data, an efficient basic assessment can be carried out by assuming the worst case at each step of the hazard and exposure assessment, and a more sophisticated assessment can be carried out when the evaluated risk is unacceptable.

Declarations

Author contribution statement

Satomi Kawai: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Masanori Niwano: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Masayuki Sato: Analyzed and interpreted the data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

ACGIH, 2017. TLVs and BEIs. Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices.

Anjilvel, S., Asgharian, B., 1995. A multiple-path model of particle deposition in the rat Lung. Fundam. Appl. Toxicol. 28, 41–50.

Arts, J.H., Hadi, M., Irfan, M.-A., Keene, A.M., Kreiling, R., Lyon, D., Maier, M., Michel, K., Petry, T., Sauer, U.G., Warheit, D., Wiench, K., Wohlleben, W., Landsiedel, R., 2015. A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping). Regul. Toxicol. Pharmacol. 71, S1–S27.

Arts, J.H., Irfan, M.-A., Keene, A.M., Kreiling, R., Lyon, D., Maier, M., Michel, K., Neubauer, N., Petry, T., Sauer, U.G., Warheit, D., Wiench, K., Wohlleben, W., Landsiedel, R., 2016. Case studies putting the decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping) into practice. Regul. Toxicol. Pharmacol. 76, 234–261.

BauA, 2018. Evaluation of Optical Measurement Devices for the Determination of Particulate Hazardous Substances at Workplaces. Project number: F 2405, Status: ongoing. https://www.baua.de/EN/Tasks/Research/Research-projects/f2405.html. (Accessed 24 August 2018).

Bermudez, E., Mangum, J.B., Wong, B.A., Asgharian, B., Hext, P.M., Warheit, D.B., Everitt, J.I., 2004. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. Toxicol. Sci. 77, 347–357.

Brouwer, D., 2010. Exposure to manufactured nanoparticles in different workplaces. Toxicology 269, 120–127.

BSI, 2007. Nanotechnologies – Part 2: guide to safe handling and disposal of manufactured nanomaterials. PD 6699-2:2007.

Creutzenberg, O., 2013. Toxic Effects of Various Modifications of a Nanoparticle Following Inhalation. Research Project F 2246, BauA.

Driscoll, K.E., 1996. Role of inflamation in the development of rat lung tumors in response to chronic particle exposure. Inhal. Toxicol. 8 (SUP), 139–153.

ECETOC, 2012. ECETOC TRA Version 3: Background and Rationale for the Improvements. Technical Report No. 114.

ECHA, 2008. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of Dose[concentration]-Response for Human Health.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of Dose[concentration]-Response for Human Health.

ECHA, 2016. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.14: Occupational Exposure Assessment.

ENRHES, 2009. The EU Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES).

EPA, 2004. Air Quality Criteria for Particulate Matter. October 2004, Volume II. EPA/600/P-99/002bF.

Gamo, M., 2011. Risk Assessment of Manufactured Nanomaterials: Titanium Dioxide. Final report issued on July 22, 2011. NEDO project (P06041) "Research and Development of Nanoparticle Characterization Methods".

Heinrich, U., Fuhst, R., Rittinghausen, S., Creutzenberg, O., Bellmann, B., Koch, W., Levsen, K., 1995. Chronic inhalation exposure of wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal. Toxicol. 7, 533–556.

Hinds, W.C., 1999. Aerosol Technology. Properties, Behavior, and Measurement of Airborne Particles, second ed.

ICRP, 1994. Human Respiratory Tract Model for Radiological protection. A Report of a Task Group of the International Commission on Radiological protection.

JSOH, 2013. Titanium dioxide nano particle. Sangyou Eiseigaku Zasshi 55, 234–239.

Keller, J., Wohlleben, W., Ma-Hock, L., Strauss, V., Gröters, S., Küttler, K., Wiench, K., Herden, C., Oberdörster, G., van Ravenzwaay, B., Landsiedel, R., 2014. Time course of lung retention and toxicity of inhaled particles: short-term exposure to nano-Ceria. Arch. Toxicol. 88, 2033–2059.

Kuempel, E.D., Castranova, V., Geraci, C.L., Schulte, P.A., 2012. Development of risk-based nanomaterial groups for occupational exposure control. J. Nanoparticle Res. 14, 1029–1053.

LeBouf, R.F., Ku, B.K., Chen, B.T., Frazer, D.G., Cumpston, J.L., Stefaniak, A.B., 2011. Measuring surface area of airborne titanium dioxide. J. Nanoparticle Res. 13, 029–7039.

Lee, K.P., Trochimowicz, H.J., Reinhardt, C.F., 1985. Pulmonary response of rats exposed to titanium dioxide by inhalation for two years. Toxicol. Appl. Pharmacol. 79 (2), 179–192.

Ma-Hock, L., Burkhardt, S., Strauss, V., Gamer, A.O., Wiench, K., van Ravenzwaay, B., Landsiedel, R., 2009. Development of a short-term inhalation test in the rat using nano-titanium dioxide as a model substance. Inhal. Toxicol. 21 (2), 102–118.

Ma-Hock, L., Strauss, V., Treumann, S., Küttler, K., Wohlleben, W., Hofmann, T., Gröters, S., Wiench, K., van Ravenzwaay, B., Landsiedel, R., 2013. Comparative inhalation toxicity of multi-wall carbon nanotubes, graphene, graphite nanoplatelets and low surface carbon black. Part. Fibre Toxicol. 10, 23.

MHLW, 2009. RE: Notification on Precautionary Measures for Prevention of Exposure Etc. To Nanomaterials. LSB Notification No.0331013, March 31st. Japan Ministry of Health, Labour and Welfare.

Miller, J.F., 2000. Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review. Inhal. Toxicol. 12, 19–57.

Morrow, P.E., 1988. Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10, 369–384.

Nakanishi, J., 2011. Risk Assessment of Manufactured Nanomaterials: "Approaches" - Overview of Approaches and REsults - . Final Report Issued on August 17, 2011. NEDO Project (P06041). "Research and Development of Nanoparticle Characterization Methods".

NIOSH, 2011. Occupational exposure to titanium dioxide. Curr. Intell. Bull. 63.

Oberdörster, G., Yu, C.P., 1990. The carcinogenic potential of inhaled diesel exhaust: a particle effect? J. Aerosol Sci. 21 (Suppl. 1), S397–S401.

OECD, 2015a. Dossier on Titanium Dioxide- Part 1/3 - NM 105. Series on the Safety of Manufactured Nanomaterials. No. 54.

OECD, 2015b. Harmonized Tiered Approach to Measure and Assess the Potential Exposure to Airborne Emissions of Engineered Nano-Objects and Their Agglomerates and Aggregates at Workplaces. Series on the Safety of Manufactured Nanomaterials. No. 55.

Ogura, I., Kotake, M., Sakurai, H., Gamo, M., 2012. Emission and Exposure Assessment of Manufactured Nanomaterials. English Version. October 26, 2012. NEDO project (P06041) "Research and development of nanoparticle characterization methods".

Olin, S.S., 2000. The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. Inhal. Toxicol. 12, 1–17.

Oller, A.R., Oberdörster, G., 2016. Incorporation of dosimetry in the derivation of reference concentrations for ambient or workplace air: a conceptual approach. J. Aerosol Sci. 99, 40–45.

OSHA, 2009. Assigned Protection Factors for the Revised Respiratory Protection Standard. OSHA 3352-02.

Pauluhn, J., 2011. Poorly soluble particulates: searching for a unifying denominator of nanoparticles and fine particles for DNEL estimation. Toxicology 249, 176–188.

Seipenbusch, M., Binder, A., Kasper, G., 2008. Temporal evolution of nanoparticle aerosols in workplace exposure. Ann. Occup. Hyg. 52 (8), 707–716.

Stockmann-Juvala, H., Taxell, P., Santonen, T., 2014. Formulating Occupational Exposure Limits Values (OELs) (Inhalation & Dermal). Scaffold D.3.11.

Tran, C., Buchanan, D., Cullen, R., Searl, A., Jones, A., Donaldson, K., 2000. Inhalation of poorly soluble particles. II. Influence of particle surface area on inflammation and clearance. Inhal. Toxicol. 12 (12), 1113–1126.

Winter-Sorkina, R., Cassee, F., 2002. From Concentration to Doses: Factors Influencing Airborne Particulate Matter Deposition in Humans and Rats. RIVM report 650010031/2002.