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Derivation of occupational exposure limits for multi-walled carbon nanotubes and graphene using subchronic inhalation toxicity data and a multi-path particle dosimetry model

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In this study, we aimed to provide the recommended occupational exposure limits (OELs) for multi-walled carbon nanotubes (MWCNTs) and graphene nanomaterials based on data from a subchronic inhalation toxicity study using a lung dosimetry model. We used a no observed adverse effect level (NOAEL) of 0.98 mg m^{-3} and 3.02 mg m^{-3} in rats for MWCNTs and graphene, respectively. The NOAELs were obtained from a 13-week inhalation study in rats. The deposition fractions of MWCNTs and graphene in the respiratory tract of rats and humans were calculated by using the multi-path particle dosimetry model (MPPD model, v3.04). The deposition fraction in the alveolar region was 0.0527 and 0.0984 for MWCNTs and 0.0569 and 0.1043 for graphene in rats and human lungs, respectively. Then, the human equivalent exposure concentrations (HECs) of MWCNTs and graphene were calculated according to the method by the National Institute for Occupational Safety and Health (NIOSH). The HEC was estimated to be 0.17 mg m^{-3} for MWCNTs and to be 0.54 mg m^{-3} for graphene, which was relevant to the rat NOAEL of 0.98 mg m^{-3} and 3.02 mg m^{-3} for MWCNTs and graphene, respectively. Finally, we estimated the recommended OELs by applying uncertainty factors (UFs) to the HEC as follows: an UF of 3 for species differences (rats to humans), 2 for an experimental duration (subchronic to chronic), and 5 for inter-individual variations among workers. Thus, the OEL was estimated to be 6 μg m^{-3} for MWCNTs and 18 μg m^{-3} for graphene. These values could be useful in preventing the adverse health effects of nanoparticles in workers.

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Introduction

Nanoparticles are defined as primary particles with at least one dimension less than 100 nm.[1] Carbon nanomaterials, such as carbon nanotubes and graphene, are the most widely used material type and can have a significant impact on various fields, such as electronics, polymer composites, aerospace materials, and the textile and medical industries. Each carbon nanomaterial can have different physical, morphological, and chemical properties due to the distinct arrangement of sp^2-bonded carbon atoms.[2,3]

Carbon nanotubes (CNTs) are nanoscale cylinders of carbon that can produce very large aspect ratios. Single-walled carbon nanotubes (SWCNTs) comprise a single rolled graphene sheet and have a typical diameter of approximately 1–2 nm. Multi-walled carbon nanotubes (MWCNTs) comprise many SWCNTs with diameters in the range of 2–100 nm. SWCNTs and MWCNTs may vary in length, some of which can be up to several tens of micrometers in length.[4] The global market of CNT products is increasing; it reached $ 2.26 billion in 2015 and is expected to reach $ 5.64 billion by 2020.[5] Graphene is a two-dimensional crystal comprising a single layer of carbon atoms arranged in a honeycomb network with six-membered rings.[6] It was first produced using the "scotch tape method" by Novoselov *et al.*[7] Two-dimensional graphene exhibits exceptional properties such as chemical inertness, mechanical strength, high thermal conductivity, and excellent transmittance compared to zero-dimensional fullerenes and one-dimensional nanotubes.[8] Graphene can be produced in large quantities and its market is rapidly increasing. The global market of graphene accounted for $ 23.7 million in 2015 and is expected to reach $ 311.2 million by 2022.[9]

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Several studies have suggested the potential hazardous impacts of MWCNTs and graphene on human health. Pauluhn[10] observed increases in neutrophil granulocytes (PMNs) and collagen associated with exposure to Baytubes, a MWCNT type. The no-observed-adverse-effect-level (NOAEL, 0.1 mg m^{-3}) and occupational exposure limit (OEL, 0.05 mg m^{-3}) for MWCNTs were set based on these data. The National Institute for Occupational Safety and Health (NIOSH)[11] suggested a recommended exposure limit (REL) of 8 h TWA 1 μg m^{-3} elemental carbon (EC) for CNTs based on Pauluhn's study.[10] Kasai *et al.*[12] observed granuloma and focal fibrosis of lungs during 90-day inhalation exposure to Mitsui MWCNT-7 in Fisher 344 rats. In the case of graphene, inflammatory lung damage and oxidative stress in mice were reported in previous studies.[13–15] Other studies reported an increase of graphene in the alveolar macrophage and in transport to the pulmonary lymph node after graphene exposure in rats.[16–18] Despite the increasing production/use of nanomaterials, such as MWCNTs and graphene, and their possible impact on human health, there are limited studies on the standard exposure level or guideline to protect humans from nanomaterials, in both industry and the environment.[10,11]

Anjilvel and Asgharian[19] first introduced the multiple-path model in estimating particle deposition in the lower respiratory tract of rats. This model has been improved further and validated to estimate the deposition of particles in the respiratory tract of rats and humans by several researchers.[20–22] Furthermore, this model has been used in estimating the alveolar lung deposition of poorly soluble particles, such as MWCNTs and graphene ranging in size from ultrafine (0.01 μm) to coarse (20 μm), in the previous studies.[10,18,23] It is a reliable and relatively simple model.[24,25]

Therefore, in the present study, we aimed to estimate OELs by using a multi-path particle dosimetry (MPPD) model based on NOAELs from an animal study to provide minimum safety guidelines in the working environment for workers dealing with carbon nanomaterials such as MWCNTs and graphene.

Experimental

Inhalation study

A subchronic inhalation study of MWCNTs and graphene, respectively, was conducted in Fisher 344 rats [MWCNT: 8-week-old, sixty males (160.20 ± 1.07 g) and forty females (128.32 ± 0.79 g), graphene: 7-week-old, forty males (134.65 ± 4.58 g) and forty females (120.32 ± 3.41 g)] by the Korea Conformity Laboratory, which is a Good Laboratory Practice testing institute. The rats were exposed to MWCNTs [CM-100, density 0.01 g cm^{-3}, mass median aerodynamic diameter (MMAD) 0.24 μm, geometric standard deviation (GSD) 2.00, equivalent diffusion diameter 0.42 μm] at concentrations of 0.17, 0.51, and 0.98 mg m^{-3}, and to graphene (graphene oxide powder, density 1.7 g cm^{-3}, MMAD 0.20 μm, GSD 2.01, equivalent diffusion diameter 0.35 μm) at concentrations of 0.34, 1.01, and 3.02 mg m^{-3}. They were exposed to MWCNTs or graphene nanoparticles for 6 h per day, 5 days per week for 13 weeks by a nose-only inhalation. Clinical symptoms and signs, body weight, food consumption, ophthalmic findings, urinalysis, hematologic examination, blood coagulation test, blood biochemical test, bronchoalveolar lavage (BAL) analysis, and histopathological findings were examined. These studies were performed in accordance with the Organization for Economic Co-operation and Development Test Guideline 413 (OECD TG 413)[26] and were approved by the Institutional Animal Care and Use Committees of Korea Conformity Laboratories (Incheon, Korea).

Lung deposition fraction

The deposition fractions of MWCNTs and graphene in rats and human lungs were calculated using the MPPD program (version 3.04) provided by the Applied Research Associates.[27] The aerosol concentration of MWCNTs or graphene was applied to the MPPD model with each NOAEL value obtained from subchronic animal inhalation studies. Specific parameters applied to the MPPD model are listed in Table 1. An airway morphometry model was used in asymmetric Sprague Dawley rats[28] and a Yeh/Schum 5-lobe lung model[29] was used for rats and humans, respectively. The rats showed a functional residual capacity (FRC) of 3.4 mL,[20] an upper respiratory tract (URT) volume of 0.4 mL,[20] a breathing frequency of 166 per minute, and a tidal volume of 2.0 mL.[30] In humans, the FRC and URT volume were 3300 mL and 50 mL, respectively.[31] The breathing frequency and tidal volume were 19 per minute and 1000 mL, respectively, which corresponded to a light exercise state in the workplace.[20]

Estimation of human equivalent concentration (HEC)

The HECs of MWCNTs and graphene are the human exposure concentrations showing effects identical to the exposure concentrations in experimental animals. HECs relevant to NOAELs of MWCNTs and graphene were calculated from NOAELs by adjusting for physiological and anatomical differences between rats and humans, including ventilation rate, clearance rate, deposition fraction, retention half-time of particles, and alveolar surface area, as follows:[11]

$$\mathrm{HEC_{NOAEL}} = \mathrm{NOAEL} \times \frac{\mathrm{VR_R}}{\mathrm{VR_H}} \times \frac{\mathrm{DF_R}}{\mathrm{DF_H}} \times \frac{\left(\frac{1-k_R^n}{1-k_R}\right)}{\left(\frac{1-k_H^n}{1-k_H}\right)} \times \frac{\mathrm{RH_R}}{\mathrm{RH_H}} \times \frac{\mathrm{SA_H}}{\mathrm{SA_R}} \quad (1)$$

(VR: ventilation rate, DF: deposition fraction, k: (1-clearance rate), RH: retention half-time of particles, SA: alveolar surface area, n: exposure days, R: rat, H: human)

Derivation of OEL

OEL was derived by dividing by uncertainty factors (UFs) based on the calculated $\mathrm{HEC_{NOAEL}}$ according to the approach by NIOSH[11] and Weldon *et al.*[32] UFs were considered for species differences from rats to humans, the experimental duration from subchronic to chronic, and inter-individual variations among workers.

Table 1 Conditions in multiple-path particle dosimetry (MPPD) and exposure models

	MWCNTs		Graphene	
Mode parameter	Rats	Humans	Rats	Humans
Airway morphometry				
Model	Asymmetric Sprague–Dawley	Yeh/Schum 5-lobe	Asymmetric Sprague–Dawley	Yeh/Schum 5-lobe
Weight of rats sacrificed (g)	282		282	
Functional residual capacity (FRC)	3.4 mL	3300 mL	3.4 mL	3300 mL
Upper respiratory tract (URT)	0.4 mL	50 mL	0.4 mL	50 mL
Particle properties				
Density	0.01 g cm^{-3}	0.01 g cm^{-3}	1.7 g cm^{-3}	1.7 g cm^{-3}
Diameter, MMAD	0.24 μm	0.24 μm	0.20 μm	0.20 μm
GSD	2.00	2.00	2.01	2.01
Equivalent diffusion diameter	0.42 μm	0.42 μm	0.35 μm	0.35 μm
Exposure scenario				
Aerosol concentration	NOAEL		NOAEL	
Breathing frequency (min^{-1})	166	19	166	19
Tidal volume	2.0 mL	1000 mL	2.0 mL	1000 mL
Breathing scenario	Nose only	Light exercise	Nose only	Light exercise

MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation.

Results

NOAELs of MWCNTs and graphene

In the inhalation study, rats were exposed to MWCNTs (0, 0.17, 0.51, and 0.98 mg m^{-3}) and graphene (0, 0.34, 1.01, and 3.02 mg m^{-3}), respectively, for 13 weeks. No significant clinical symptoms and signs, weight change, food consumption changes, and abnormal laboratory findings in urinalysis, hematology, blood coagulation test, blood chemistry, and BAL analysis were observed compared to the control during the experimental period. In addition, no abnormal morphological findings were observed. Thus, the NOAELs of MWCNTs and graphene were suggested to be 0.98 mg m^{-3} and 3.02 mg m^{-3}, respectively, in the subchronic inhalation study of rats.

Deposition fractions of MWCNTs and graphene in the respiratory tract

The deposition patterns of MWCNTs and graphene were calculated in the lungs of rats and humans after exposure to NOAEL concentrations by using the MPPD model (Table 2). The total deposition fraction of MWCNTs in the respiratory tract of rats was 0.3923, and the regional specific deposition fraction was 0.2829, 0.0567, and 0.0527 in extrathoracic, tracheo-bronchial, and alveolar regions, respectively. For humans, the total deposition fraction of MWCNTs in the respiratory tract was 0.4261 and the regional specific deposition fraction was 0.2861, 0.0416, and 0.0984 in extrathoracic, tracheo-bronchial, and alveolar regions, respectively. The total deposition fraction of inhaled graphene in the respiratory tract was 0.3976 and 0.4340 in rats and humans, respectively. The specific regional deposition fraction was 0.2831, 0.0576, and 0.0569 in the extrathoracic, tracheo-bronchial, and alveolar regions of rats, and 0.2865, 0.0432, and 0.1043 in the extrathoracic, tracheo-bronchial, and alveolar regions of humans. In this study, deposition fractions in alveolar regions were used to calculate the retained particles in the lungs of rats and humans.

Table 2 Deposition fractions of MWCNTs and graphene in the respiratory tract of rats and humans from the MPPD model

	MWCNTs		Graphene	
Regions	Rats	Humans	Rats	Humans
Extrathoracic region	0.2829	0.2861	0.2831	0.2865
Tracheo-bronchial region	0.0567	0.0416	0.0576	0.0432
Alveolar region	0.0527	0.0984	0.0569	0.1043
Total respiratory tract	0.3923	0.4261	0.3976	0.4340

Estimation of HECs of MWCNTs and graphene

The HEC of MWCNTs and graphene, respectively, was estimated based on the deposition fraction in the alveolar region calculated from the respective NOAEL. In this process, the physiological and anatomical differences between rats and humans were normalized by using the ventilation rate, clearance rate, retention half-time of particles, and alveolar surface area as well as deposition fraction (Table 3). The ventilation rate of rats (0.12 m^3 day^{-1}) was calculated using the method by NIOSH,[11] and a breathing frequency of 166 per minute, a tidal volume of 2.0 mL, and 6 h exposure per day were used in the MPPD model. In humans (light exercise condition), the ventilation rate of 9.12 m^3 day^{-1} was calculated from the breathing frequency of 19 per minute, the tidal volume of 1000 mL, and 8 h exposure per day used in the MPPD model. The clearance rates, 0.001057 and 0.000020 in rats and humans, respectively, were provided in MPPD.[27] The ratio of the retention half-time of particles in rats to humans was applied as 1/10.[11] The alveolar surface area was applied as 2422 cm^2 and 634 620 cm^2 in rats and humans, respectively.[33] Taken together, the HEC rele-

Table 3 Normalizing parameters between rats and humans in estimating human equivalent concentrations (HECs) from $NOAEL_{rat}$ of MWCNTs and graphene

	MWCNTs		Graphene	
Parameters	Rats	Humans	Rats	Humans
Ventilation rate (m^3 day^{-1})	0.12	9.12	0.12	9.12
Deposition fraction	0.0527	0.0984	0.0569	0.1043
Clearance rate	0.001057	0.000020	0.001057	0.000020
Retention half-time of particles (ratio)	1	10	1	10
Alveolar surface area (cm^2)	2422	634 620	2422	634 620
Human equivalent concentration (HEC) (mg m^{-3})		0.17		0.54

vant to $NOAEL_{rat}$ of MWCNTs and graphene was estimated to be 0.17 mg m^{-3} and 0.54 mg m^{-3}, respectively, as given below:

$$\mathrm{HEC_{MWCNT}} = 0.98\ \mathrm{mg\ m^{-3}} \times \frac{0.12\ \mathrm{m^3\ day^{-1}}}{9.12\ \mathrm{m^3\ day^{-1}}} \times \frac{0.0527}{0.0984} \times \frac{\dfrac{1-(1-0.001057)^{90}}{1-(1-0.001057)}}{\dfrac{1-(1-0.000020)^{90}}{1-(1-0.000020)}} \times \frac{1}{10} \times \frac{634620\ \mathrm{cm^2}}{2422\ \mathrm{cm^2}} = 0.17\ \mathrm{mg\ m^{-3}} \quad (2)$$

$$\mathrm{HEC_{graphene}} = 3.02\ \mathrm{mg\ m^{-3}} \times \frac{0.12\ \mathrm{m^3\ day^{-1}}}{9.12\ \mathrm{m^3\ day^{-1}}} \times \frac{0.0569}{0.1043} \times \frac{\dfrac{1-(1-0.001057)^{90}}{1-(1-0.001057)}}{\dfrac{1-(1-0.000020)^{90}}{1-(1-0.000020)}} \times \frac{1}{10} \times \frac{634620\ \mathrm{cm^2}}{2422\ \mathrm{cm^2}} = 0.54\ \mathrm{mg\ m^{-3}} \quad (3)$$

In this study, the retention patterns of particles were calculated in the alveolar region after exposure of rats and humans (light exercise condition) to MWCNTs and graphene at the $NOAEL_{rat}$ or HEC level during the exposure period of 13 weeks (Fig. 1). The retained amounts of particles (MWCNTs and graphene) were significantly increased in the alveolar regions of rats and humans during the exposure period. Although the total retention amounts of particles (MWCNTs and graphene) in the alveolar regions were much higher in humans (exposed to HEC or $NOAEL_{rat}$) than in rats (exposed to NOAEL), the retention amounts of particles per alveolus were observed at relatively similar levels between rats exposed to NOAEL and humans exposed to the HEC of both MWCNTs and graphene. The amounts of retained particles (MWCNTs and graphene) per alveolar surface area were lower in humans than in rats.

Derivation of OELs for MWCNTs and graphene

The OEL recommended to protect workers from nanoparticles in workplaces handling MWCNTs or graphene was derived by dividing the HEC estimated, under a light exercise condition in humans, from the $NOAEL_{rat}$ by UFs according to the method used by NIOSH[11] and Weldon *et al.*[32] A UF of 3 was applied to account for the toxicodynamic effects between rats and humans as well as uncertainty for the clearance kinetic factor and breathing rate;[34–36] a UF of 2 was used to account for the differences in the exposure period from subchronic to chronic; and a UF of 5 was used to account for inter-individual variations among workers.[2,37] From the findings of this study, the OEL of MWCNTs and graphene in the workplace was suggested to be 6 μg m^{-3} and 18 μg m^{-3}, respectively.

Discussion

In this study, we aimed to estimate the recommended OELs of MWCNTs and graphene in workplace by applying subchronic inhalation toxicity data in rats to a lung dosimetry model. We found the OELs of MWCNTs and graphene that could prevent adverse health effects of nanoparticles in workers.

NOAELs of 0.98 mg m^{-3} for MWCNTs and 3.02 mg m^{-3} for graphene obtained from 13-week inhalation studies in rats were applied to the MPPD model to obtain deposition fractions of nanoparticles in the alveolar region of lungs in rats and humans (under light exercise conditions). Then, HECs in humans (light exercise conditions) corresponding to NOAELs in rats were estimated. Finally, OELs of 6 μg m^{-3} for MWCNTs and 18 μg m^{-3} for graphene were derived by applying UFs to HECs. No significant critical endpoints or target organ (lung) were observed during the 13-week exposure period using MWCNT concentrations of 0.17, 0.51, and 0.98 mg m^{-3}. Pauluhn[10] suggested a NOAEL of 0.1 mg m^{-3} for MWCNTs (Baytubes®, Bayer Material Science, Leverkusen, Germany, density 0.11 g m^{-3}, MMAD 1.7–3.4 μm, GSD 1.7–2.1) in a 13-week inhalation study using doses of 0.1, 0.4, 1.62, and 5.98 mg m^{-3}. Inflammatory changes in BAL were observed at concentrations above 0.4 mg m^{-3}. Ma-Hock *et al.*[23] reported a no observed effect concentration of 0.1 mg m^{-3} for MWCNTs (Nanocyl NC 7000, Nanocyl S.A., Sambreville, Belgium, MMAD 0.5–1.3 μm, GSD 3.1–5.4) based on the findings of minimal granulomatous inflammation in the lungs of rats in a subchronic inhalation study at doses of 0.1, 0.5, and 2.5 mg m^{-3}. The NOAEL of MWCNTs was relatively higher in this study than in previous studies. It has been understood that particles with a smaller size show an increased particle surface area, therefore smaller particles may exhibit greater biological effects than larger particles.[38,39] However, the particle size with regard to the MMAD of MWCNTs used in this subchronic inhalation study was smaller than those reported by Pauluhn[10] and Ma-Hock *et al.*[23], while the value of NOAEL was greater than those in both studies. The MWCNTs have different shapes and various properties such as rigidity, contents of catalysts, aspect ratio, density, surface area and so on, as well as size, depending on the manufacturing process; therefore, the biological effects of MWCNTs could differ depending on the products.[4] So, it might be hard to compare the toxicity of particles directly according to the size, but it need further studies. The NOAEL

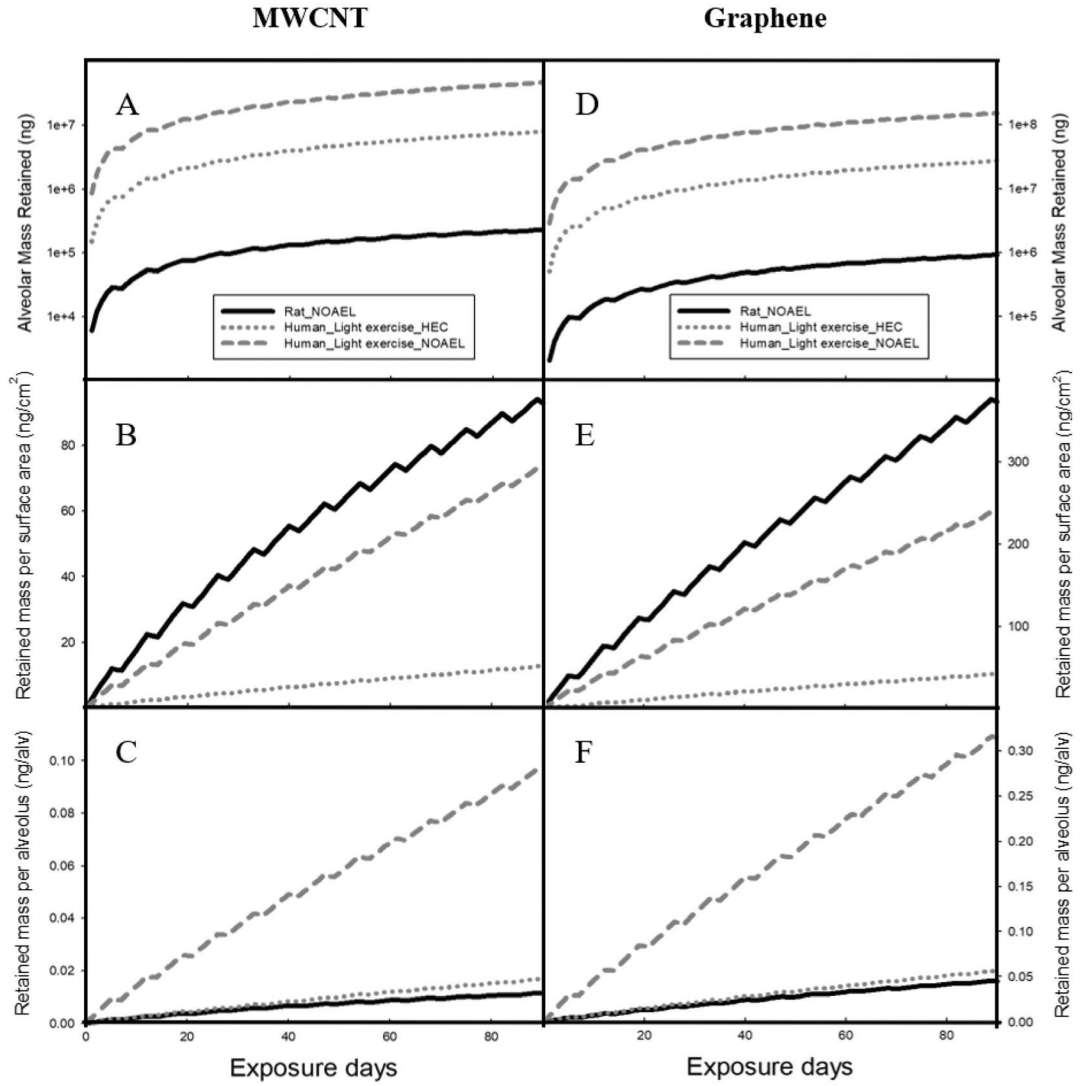

Fig. 1 Retention patterns of inhaled particles in the lung alveolar region over time after exposure to MWCNTs and graphene in rats and human lungs (under light exercise conditions). Total retained mass in the total alveolar region (A, D), per lung surface area (B, E), and per alveolus (alv) (C, F).

of graphene used in this inhalation study was suggested to be 3.02 mg m^{-3}. Any significant endpoint was not observed in rats during the 13-week experimental period with different doses of graphene (0.34, 1.01, and 3.02 mg m^{-3}). There are limited data on the critical toxic endpoint of graphene. Kim *et al.*[18] suggested that the NOAEL of graphene (GPX-205, Cabot Corporation, Boston, MA, USA, MMAD 0.123 μm, GSD 3.63) might be higher than 1.88 mg m^{-3} based on a 28-day inhalation study at concentrations of 0.12, 0.47, and 1.88 mg m^{-3}.

In the present study, the deposition fraction of MWCNTs used at $NOAEL_{rat}$ in the alveolar region of lungs was 0.0527 and 0.0984 in rats and humans (light exercise conditions), respectively. The deposited proportions of inhaled MWCNTs in the alveolar region were similar to those in previous studies. Pauluhn[10] reported that 0.057 and 0.118 of inhaled MWCNTs (Baytubes®) in rats and humans, respectively, were deposited in the alveolar region. NIOSH[11] suggested a deposition fraction of 0.046 (rats) and 0.086 (humans) for CNTs. However, the deposited fraction of inhaled MWCNTs in the alveolar region was different between species—relatively higher in humans than in rats. This finding is in agreement with the results of the previous studies.[10,11] In the present study, the deposition pattern of graphene was similar to that of MWCNTs. The deposited proportion of inhaled graphene in the alveolar region was 0.0569 and 0.1043 in rats and humans, respectively, and was higher in humans than in rats. As there are limited studies on the deposition of inhaled graphene in the respiratory tract, it is difficult to draw a comparison. Previously, Weldon *et al.*[32] indicated a relatively high proportion of the deposition fraction of inhaled silver nanoparticles in the alveolar region (0.290 and 0.348 in rats and humans, respectively) compared to the carbon nanomaterials. These findings suggest that the deposition pattern of inhaled nanoparticles in the lungs might be different, especially their solubility.[40]

In the present study, the HEC (under light exercise conditions) was estimated to be 0.17 mg m^{-3} and 0.54 mg m^{-3} for MWCNTs and graphene, respectively, which was approximately 6 times lower than NOAELs of both MWCNTs and graphene. The ratio of NOAEL to HEC in particles could be useful to simplify the extrapolation process from animals to humans.

The amount of the total retained mass of MWCNTs and graphene in the alveolar region of lungs was higher in HEC or NOAEL exposed humans than in NOAEL exposed rats during the experimental period (Fig. 1A and D). The retained mass per alveolus was also higher in NOAEL exposed humans than in NOAEL exposed rats, but the retained mass per alveolus in HEC exposed humans (light exercise conditions) was relatively similar to that in NOAEL exposed rats in both MWCNTs and graphene (Fig. 1C and F). However, the retained mass per alveolar surface area was higher in NOAEL exposed rats than in HEC or NOAEL exposed humans (Fig. 1B and E). Accordingly, the retained mass estimates in the alveolar region of NOAEL exposed rats and HEC exposed humans corresponded to the dose metrics adjusted by the number of alveoli rather than the alveolar surface area in this study. Ji and Yu[41] reported that the deposited mass in the alveolar region after exposure to silver nanoparticles at NOAEL in rats and HEC in humans was similar to dose metrics adjusted by the alveolar surface area. Although HEC estimation can depend on various factors, such as lung surface area, lung volume, lung weight, number of alveoli, total area surfactant, particle size, ventilation rate and so on,[35,36,42] a further study is warranted to clarify why the mass unit adjusted by the number of alveoli is more compatible than that adjusted by the alveolar surface area, which was extrapolated across species to estimate the HEC in this study.

Previously, OEL was reported by dividing NOAEL by UF directly.[10,43] HEC could be a more reasonable index as a point of departure (POD) rather than NOAEL, and it was normalized for physiological/anatomical differences across species from rats to humans. Furthermore, UFs of 30 were applied to HEC.[2,34–37] Finally, the recommended OEL was estimated to be 6 μg m^{-3} and 18 μg m^{-3} for MWCNTs and graphene, respectively.

There are certain limitations to this study. First, strict OELs of nanoparticles have not been established despite their widespread use in various fields, because there are limited studies on the toxicokinetics/dynamics of nanoparticles, and these findings were also obtained from specific nanoparticles used in the subchronic inhalation study. Second, because EC was not measured in this study, it is difficult to directly compare OELs from this study with that from previous studies. Relatively similar levels as well as a high correlation were observed between the mass concentration and EC after exposure to graphene particles in the inhalation chamber.[18] However, it is necessary to revise OELs continuously through further extensive studies.

Conclusion

In summary, we proposed the recommended OELs for MWCNTs (6 μg m^{-3}) and graphene (18 μg m^{-3}) from subchronic inhalation study data in rats by using the MPPD model, which is a simple and reliable tool in estimating the lung deposition of poorly soluble particles. Thus, OELs from this study could be useful as a putative safety guideline to prevent health effects and to maintain workers' health in the nanoparticle industry.

Conflicts of interest

There are no conflicts to declare.

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