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*Research Article*

# Estimates of Inhaled and Deposited Doses following Exposure to Humidifier Disinfectant Containing Polyhexamethylene Guanidine (PHMG)

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We estimated the inhaled and deposited dose in humans using the International Commission on Radiological Protection (ICRP) and multiple-path particle dosimetry (MPPD) models following exposure to humidifier disinfectant containing polyhexamethylene guanidine (PHMG). The disinfectant has caused at least 1,810 deaths, with an odds ratio of lung injury of 47.3 (95% confidence interval: 6.1–369.7), because of its application in Korea. In this study, the Oxy product, which is regarded as the causative agent of most lung diseases, was sprayed into a cleanroom at normal (6.5 ppm in solution) and worst case (65 ppm in solution) dilutions; the airborne aerosol was monitored with direct reading instruments. Areas of deposition were divided into the head airway, tracheobronchial, and alveolar regions. Four dose scenarios were considered in this study: adults and children in both daily average and sleep conditions. Most PHMG aerosols were smaller than PM1 (96%). Number-based concentration analysis showed that <100 nm nanoparticles comprised 81% and 69% of the aerosol when the 6.5 and 65 ppm solutions were used, respectively. In all scenarios, the number-based deposited dose increased in the order of alveolar, tracheobronchial, and head airway regions; the mass-based deposited dose increased in the order of the head airway, alveolar, and tracheobronchial regions. The deposited dose per unit body weight was higher in children than in adults in terms of both number- and mass-based concentrations. When the humidifier was sprayed, the highest number-based concentration was found at a particle size of 15.4 nm; the highest deposition fraction or dose by PM1 was observed in the pulmonary and head airways in both models.

## 1. Introduction

Humidifier disinfectants were first developed in 1994 as a consumer product to prevent the growth of microbes in ultrasonic humidifiers, but they were withdrawn from the Korean market in 2011 because they were found to cause lung disease [1, 2]. As of July 2023, 1,810 deaths had resulted from lung injuries associated with humidifier disinfectant; this number is expected to increase because severe lung disease has occurred in many people who used humidifier disinfectants in the past (ACCEH, accessed 3 July 2023). The Korea Centers for Disease Control and Prevention (KCDC) reported an odds ratio of lung disease of 47.3 (95% confidence interval: 6.1–369.7) in a case-controlled epidemiologic study investigating the occurrence of lung disease associated with humidifier disinfectant in 2011 [3]. The use of humidifier disinfectants comprises one of the worst public health incidents involving inhalation exposure to consumer products in Korea; it has been the focus of epidemiological studies, clinical reports, and toxicological studies. Although it has been more than a decade since the products were withdrawn from the market, only a few studies have assessed actual exposure concentrations and the inhaled and deposited doses in similar environments [4, 5]. In addition, there is a

need to consider the characteristics of each population in exposure assessments because the affected individuals were mainly children and pregnant women.

Various exposure assessment models have been developed to complement experimental measurements [6]. There are several advantages of modeling particle deposition in the human respiratory tract. Health risk assessments and aerosol therapies for inhaled particles require information regarding local deposition patterns within the lungs.

Although experimental studies are not feasible due to ethical considerations or for health reasons, there is a need to obtain information on particle deposition for all population members (e.g., children to the elderly) and for all particle sizes and respiratory conditions [7].

The International Commission on Radiological Protection (ICRP) model is widely used to evaluate particle deposition in the respiratory tract among the general population. The model uses empirical equations based on experimental data and theory to characterize deposition via settling, inertia, and diffusion in the respiratory tract [8]. Additionally, the multiple-path particle dosimetry (MPPD) model uses the multiple-path method to calculate particle deposition in all airways of the lungs; it provides lobar- and airway-specific information. In version 3.04 of the MPPD model, deposition in each airway is calculated using theoretically derived efficiencies based on diffusion, sedimentation, impaction, and interception within the airway or airway bifurcation.

The humidifier disinfectant incident led to the development of various lung diseases in a large number of patients following inhalation exposure to consumer products. There is a need to estimate the inhaled and deposited doses of humidifier disinfectants because inhalation exposure has not been assessed using real data in cases of lung disease. Therefore, this study estimated inhaled and deposited doses in the human respiratory tract using the ICRP and MPPD models for particles generated when a humidifier disinfectant containing polyhexamethylene guanidine (PHMG) was sprayed in an indoor environment.

## 2. Methods

*2.1. Preparation of PHMG.* The experiment was conducted with one product containing PHMG. This product is known to be responsible for most cases of lung disease associated with humidifier disinfectants. Because there was no legal requirement to produce a safety data sheet for the Oxy product at the time of sale, no specific safety information was available; however, available data concerning the raw materials indicated that the PHMG concentration was approximately 1,300 ppm. The recommended dilution for the Oxy product was 200 : 1, but the dilution ratio used by consumers varied from 200 : 1 to 20 : 1. The concentrations of Oxy product were calculated to be approximately 6.5 ppm at 200 : 1 dilution and approximately 65 ppm at 20 : 1 dilution [4]. PHMG exposure from the typical use of the disinfectant was estimated using the typical amount sprayed each day and the PHMG concentration in the product. Due to the difficulty of obtaining a standard solution for each polymer unit of PHMG, quantitative aerosol chemical analysis was not performed, and the calculated concentrations are used. The low dilution was used to simulate a "worst-case scenario." Distilled water, generated by a commercial purification system (Milli-Q; Merck Millipore, Germany), was used to dilute PHMG in all experiments.

*2.2. Experimental Framework and Measurement.* The cleanroom used in this study was the same exposure chamber used in our previous humidifier disinfectant study; it has been described in detail elsewhere [4]. In brief, the experiments were conducted in a 40.3 $m^3$ (7.0 m (L) × 2.4 m (W) × 2.4 m (H)) class 1,000 cleanroom (Figure S1). The cleanroom was ventilated before measurements were conducted to ensure that the background concentration was maintained below 100 particles/$cm^3$ (#/$cm^3$); the concentration was measured by a scanning mobility particle sizer (Nanoscan; TSI, USA). When the background concentration was low and stable, the ventilation system was switched off. The temperature and humidity in the cleanroom before the humidifier began operating were maintained at approximately 20°C and 50%, respectively. At the beginning of the operation, humidity was increased to 100% and then decreased to approximately 60% at the sampling site.

The scanning mobility particle sizer and an optical particle sizer (Model 3330; TSI) were used for real-time monitoring of the particle number-based concentration in the ranges of 10–420 nm and 0.3–10 $\mu$m, respectively. The particle cut points of the optical particle sizer were set at 0.3, 0.5, 1.0, 3.0, 5.0, and 10.0 $\mu$m (i.e., six total channels). A portable aerosol spectrometer (model 1.109; Grimm, Germany) was used to measure the mass concentrations of the PM1, PM2.5, and PM10 fractions. In the case of PM measurement, as a result of measuring the weight of the filter before and after the experiment according to the manufacturer's recommendation to obtain the C-factor, the value was close to 1, so concentration correction was not performed. All real-time instruments logged data at 1 min intervals.

A diffusion dryer and thermodenuder were connected to the inlets of all measuring equipment to minimize the effect of moisture when operating the humidifier. The silica gel in the diffusion dryer was replaced periodically (i.e., when it became pink). In a previous study, we investigated the most efficient combination of dryer and thermodenuder. Optimal efficiency was obtained when the diffusion dryer was connected ahead of the thermodenuder [9, 10].

The ultrasonic humidifier (H-U977, Ohsung, Korea) used for the experiment had a 6.5 L tank containing the spray liquid; its design is commonly used in household humidifiers. The humidifier could be operated at a spray output rate of 320 ml/h, and the spray volume was set at the maximum value in this study.

The sampling zone was set at 0.5 m from the instrument for the scanning mobility particle sizer, optical particle sizer, and portable aerosol spectrometer. The real-time monitoring instruments were sampled for a total duration of 5 h 30 min. The background concentration was measured for 30 min before operating the humidifier. The humidifier was

Table 1: Inhaled dose expressed as the mass concentration for Oxy product by the ICRP model (unit: ng/kgbw/day).

| Scenario | | | 6.5 ppm (average (SD)) | | | 65 ppm (average (SD)) | | |
|---|---|---|---|---|---|---|---|---|
| | | | PM 1 | PM 2.5 | PM 10 | PM 1 | PM 2.5 | PM 10 |
| Humidifier on | Adult | Average | 4.9E + 06 | 5.0E + 06 | 5.1E + 06 | 5.6E + 07 | 5.7E + 07 | 5.8E + 07 |
| | | | (7.6E + 05) | (7.1E + 05) | (6.9E + 05) | (3.3E + 06) | (3.1E + 06) | (2.7E + 06) |
| | | Sleeping | 2.0E + 06 | 2.0E + 06 | 2.0E + 06 | 2.2E + 07 | 2.3E + 07 | 2.3E + 07 |
| | | | (3.0E + 05) | (2.8E + 05) | (2.8E + 05) | (1.3E + 06) | (1.2E + 06) | (1.1E + 06) |
| | Child | Average | 1.5E + 07 | 1.5E + 07 | 1.5E + 07 | 1.7E + 08 | 1.7E + 08 | 1.7E + 08 |
| | | | (2.3E + 06) | (2.1E + 06) | (2.1E + 06) | (9.8E + 06) | (9.3E + 06) | (8.1E + 06) |
| | | Sleeping | 4.8E + 06 | 4.9E + 06 | 5.0E + 06 | 5.4E + 07 | 5.5E + 07 | 5.6E + 07 |
| | | | (7.4E + 05) | (6.9E + 05) | (6.8E + 05) | (3.2E + 06) | (3.0E + 06) | (2.6E + 06) |
| Humidifier off | Adult | Average | 1.3E + 06 | 1.3E + 06 | 1.3E + 06 | 8.7E + 06 | 8.9E + 06 | 9.0E + 06 |
| | | | (5.0E + 05) | (5.5E + 05) | (5.9E + 05) | (1.8E + 06) | (1.9E + 06) | (1.9E + 06) |
| | | Sleeping | 5.0E + 05 | 5.2E + 05 | 5.3E + 05 | 3.5E + 06 | 3.6E + 06 | 3.6E + 06 |
| | | | (2.0E + 05) | (2.2E + 05) | (2.4E + 05) | (7.2E + 05) | (7.5E + 05) | (7.8E + 05) |
| | Child | Average | 3.7E + 06 | 3.9E + 06 | 4.0E + 06 | 2.6E + 07 | 2.7E + 07 | 2.7E + 07 |
| | | | (1.5E + 06) | (1.6E + 06) | (1.8E + 06) | (5.4E + 06) | (5.6E + 06) | (5.8E + 06) |
| | | Sleeping | 1.2E + 06 | 1.3E + 06 | 1.3E + 06 | 8.5E + 06 | 8.7E + 06 | 8.8E + 06 |
| | | | (4.9E + 05) | (5.3E + 05) | (5.7E + 05) | (1.8E + 06) | (1.8E + 06) | (1.9E + 06) |

then operated for 4 h. After the humidifier had been switched off, the airborne concentration was measured for an additional 1 h. The data used in this study were measured for 4 h during humidifier operation and for an additional 1 h after the humidifier had been switched off. All experiments were repeated three times under the same conditions. The airborne concentration of particles according to the operation of the humidifier and the concentration of PHMG in the humidifier solution is summarized in supporting information Table S1.

*2.3. Estimation of Inhaled and Deposited Doses.* Inhaled dose refers to the amount of a substance present for a specific period of time in the breathing zone (outside of nose or mouth); deposited dose refers to the amount of a substance deposited on a specific part of the respiratory tract. To estimate PHMG exposure via inhalation during humidifier use, we modeled the inhaled dose in the breathing zone using the ICRP model; we modeled deposited doses in different parts of the respiratory tract using the ICRP and MPPD models. The ICRP model uses semiempirical equations based on experimental data and theory to characterize regional and total deposition through settling, inertia, and diffusion in three regions of the respiratory system: (1) head airway, including the nose, mouth, throat, and upper airways; (2) tracheobronchial region; and (3) alveolar region [8, 11]. The equation in the ICRP model has two parts: one for inhaled dose and one for deposited dose [8, 11, 12].

Details of the ICRP and MPPD models are provided in the supporting information (Tables S2 and S3). The inhalation rate was divided into the categories of adults and children and then average daily (24 h mean) and during sleep. The exposure factors for adults and children were based on the Korean Exposure Factors Handbook, published by the Korea Ministry of Environment [13–15]. The average inhalation rate in adults was 9.9 L/min, and the sleeping inhalation rate in adults was 7.5 L/min. The daily average inhalation rate in children was 7.0 L/min; the corresponding value during sleep was 4.3 L/min. The exposure times were based on measurements from a previous study: 660 min (11 h) for the daily average and 480 min (8 h) for sleeping [5, 16, 17].

The inhaled doses are presented as the mass metric dose (ng/kgbw/day) according to particle size (PM1, PM2.5, and PM 10); the deposited doses are presented as the mass metric doses (ng/kgbw/day) in the different respiratory regions (head airway, tracheobronchial, and alveolar). The inhaled dose is presented as a number count (particles/kgbw/day), as shown in Table S4.

The MPPD model calculates the deposition and clearance of mono- and polydispersed aerosols in the human respiratory tract (https://www.ara.com/mppd/). To idealize the human lung, eight options are available in the model, including the Yeh-Schum, stochastic, age-specific, Weibel, and Pacific Northwest National Laboratories models. In this study, the Yeh-Schum 5-lobe and age-specific 5-lobe models (i.e., the most commonly used MPPD models) were used in a multimodal mode. Body orientation was selected as "upright" for the daily dose and "on back" for the sleeping dose. The particle properties in the MPPD model were adapted from experimental data. For example, the multimodal mode was used because the measurement data indicated a trimodal mode in the 6.5 ppm case and bimodal mode in the 65 ppm case.

The estimates of the MPPD model are presented as the deposition fractions and deposited mass at five lobes in the Yeh-Schum model and each bronchiole generation in the age-specific model.

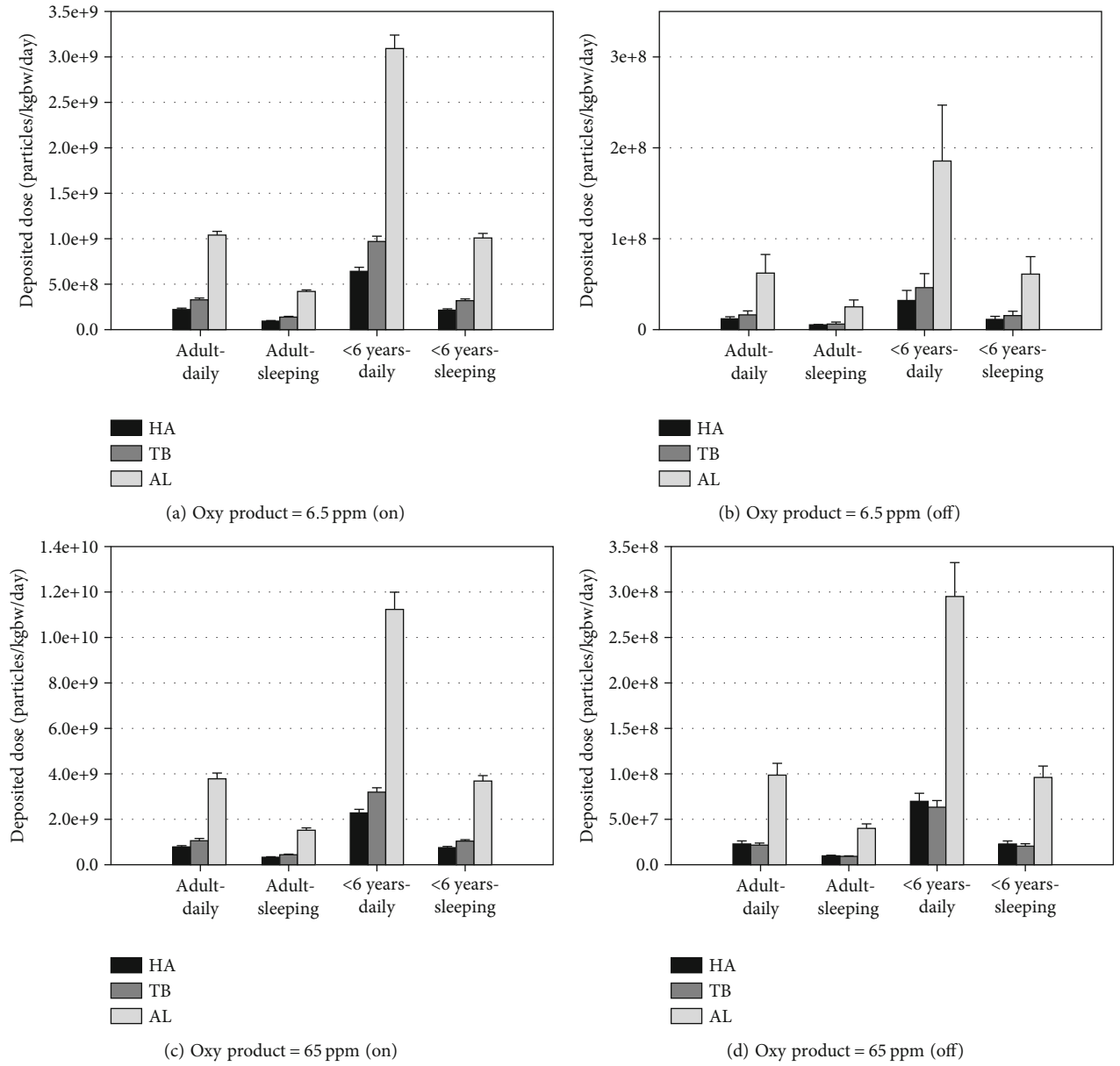



Figure 1: Number-based deposited doses estimated by the International Commission on Radiological Protection (ICRP) model in the head airway region (HA), tracheobronchial region (TB), and alveolar region (AL) during (on) and after (off) humidifier use.

## 3. Results

*3.1. ICRP Model Estimate.* The inhaled dose of particle mass in the Oxy product is shown in Table 1. Most of the inhaled dose expressed by the mass dose (ng/kgbw/day) comprised PM1 particles. When the PHMG concentration was 6.5 ppm, the proportion of PM1 in PM10 was 96.4 ± 3.3%; this proportion was 96.9 ± 1.3% when the PHMG concentration was 65 ppm. The inhaled dose was higher during humidifier use than after use. For example, the inhaled doses of PM1 were 3.96 ± 0.13-fold higher at 6.5 ppm PHMG and 6.40 ± 0.11-fold higher at 65 ppm PHMG during humidifier use, compared with after use.

When the humidifier was operating, most of the inhaled dose, expressed as the number dose (number/kgbw/day), was <100 nm nanoparticles: 81.0 ± 0.4% at 6.5 ppm and 68.5 ± 6.94% at 65 ppm. The proportion of nanoparticles in the inhaled dose decreased after use: 69.8 ± 0.70% at 6.5 ppm and 42.4 ± 0.51% at 65 ppm (Table S4).

The deposited doses in the head airway, tracheobronchial, and alveolar regions are shown in Figure 1 as the number dose (measured using the scanning mobility particle sizer and optical particle sizer) and in Figure 2 as the mass dose (measured using the portable aerosol spectrometer).

In all scenarios, the number-based deposited dose increased in the order of alveolar, tracheobronchial, and head airway regions (Figure 1); the mass-based deposited dose increased in the order of head airway, alveolar, and tracheobronchial regions (Figure 2). The deposited dose per unit body weight was higher in children than in adults for

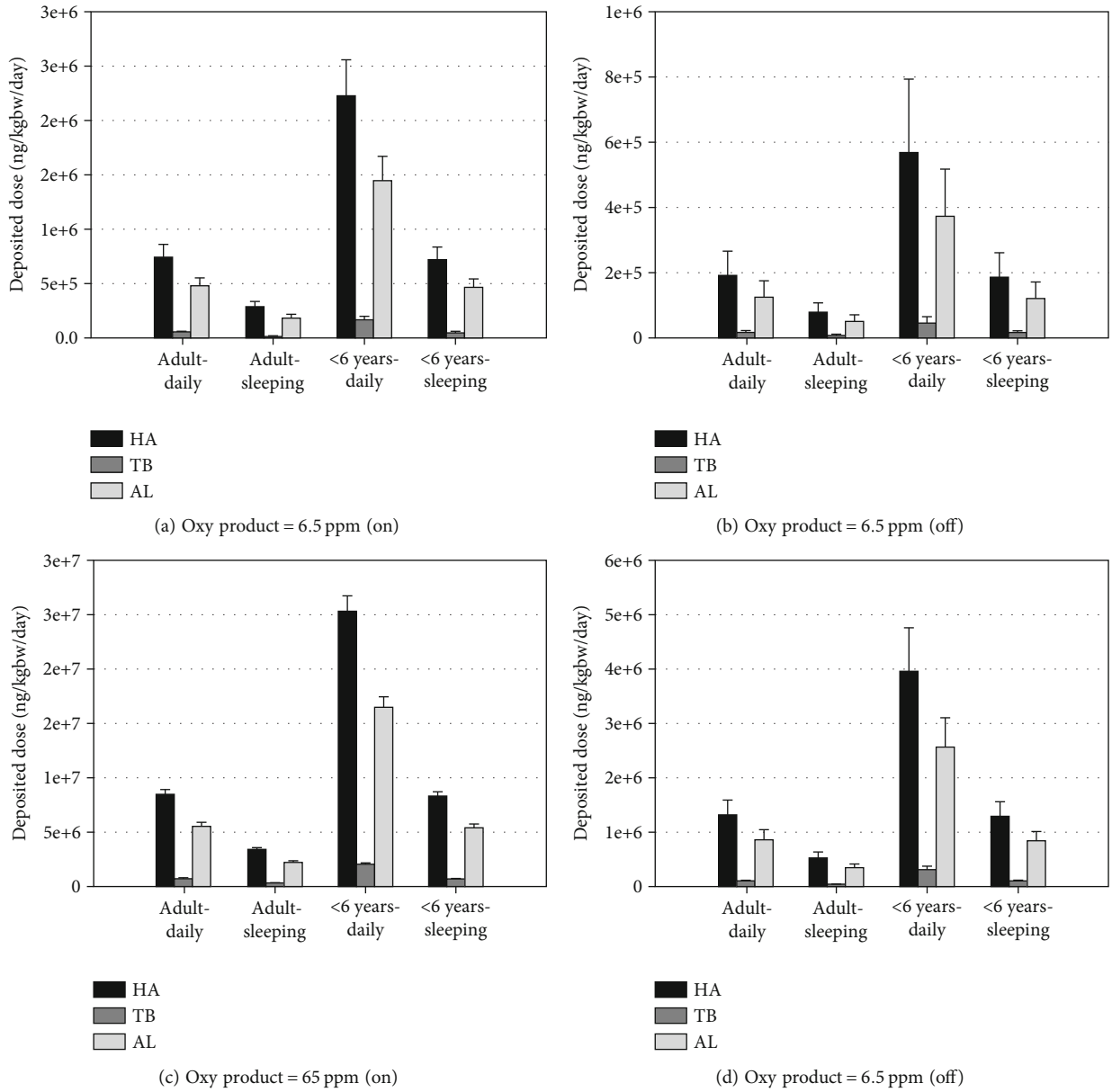
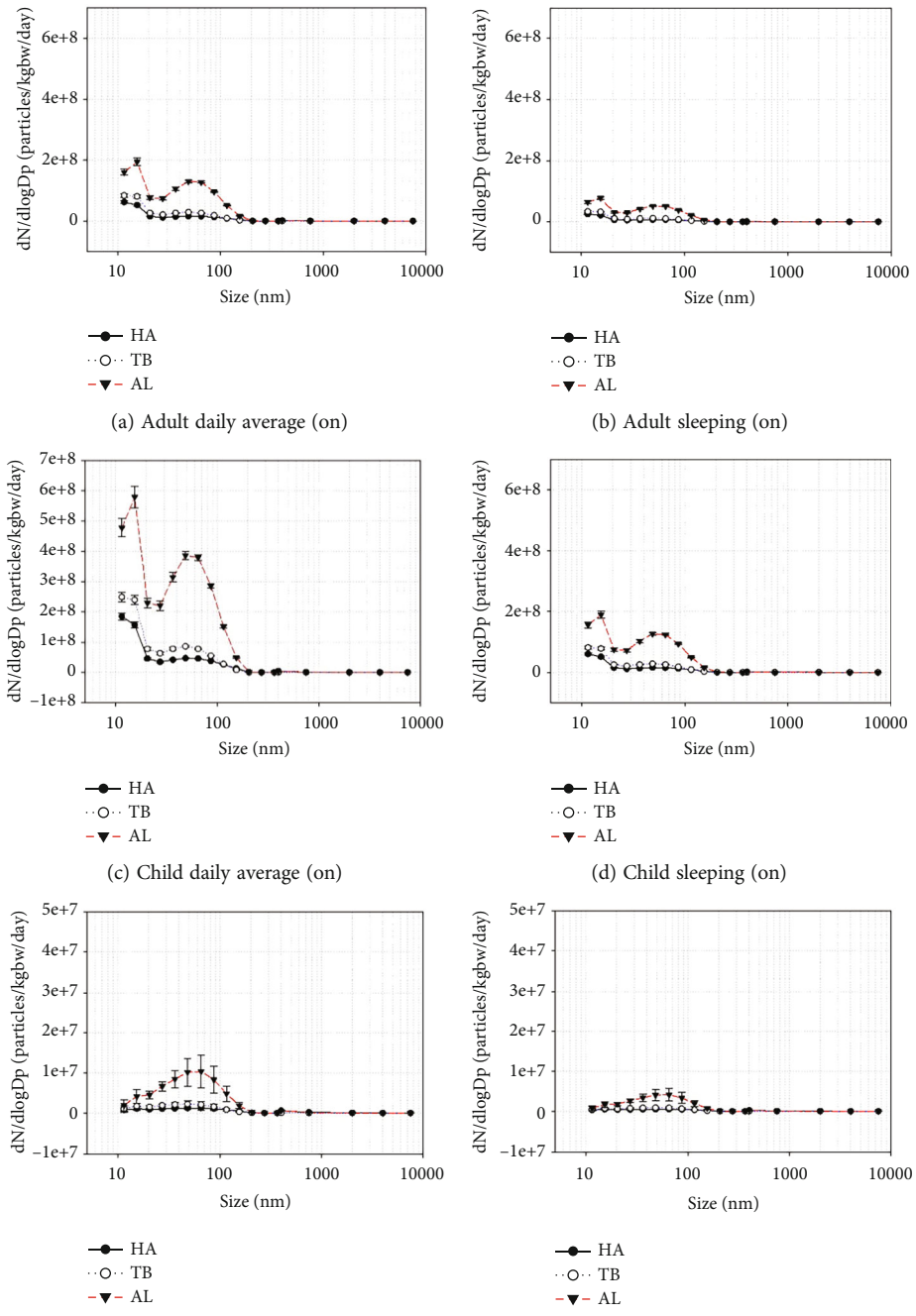



Figure 2: Mass-based deposited doses estimated by the International Commission on Radiological Protection (ICRP) model in the head airway region (HA), tracheobronchial region (TB), and alveolar region (AL) during (on) and after (off) humidifier use.

both the number- and mass-based doses. For example, with PHMG concentrations of 6.5 and 65 ppm, the daily average number- and mass-based deposited doses were approximately three-fold higher in children than in adults. The deposited dose was highest for the daily average of children under 6 years of age, with similar estimated values for the daily average of adults and for children under 6 years of age during sleep, followed by the lowest estimate for adults during sleep.

Figures 3 and 4 present the number-based deposited dose according to particle size distribution under the different scenarios and PHMG spraying concentrations of 6.5 and 65 ppm, respectively. As shown in both figures, the deposited dose mainly consisted of nanosized particles of <100 nm, which were mainly deposited in the alveolar region at all concentrations and in all scenarios. For example, the deposited dose in the alveolar region was 65.8% of the total deposited dose at 6.5 ppm and 67.2% of the total deposited dose at 65 ppm. At 6.5 ppm, the particle distribution was bimodal when the humidifier was in use (Figure 3); after use, the particle peak at the small size disappeared, and the particle size distribution shifted slightly to the right, thus becoming unimodal. The particle size increased slightly. As shown in Figure 4, the particle size distribution shifted slightly to the right at 65 ppm, but a bimodal distribution persisted during or after humidifier use. However, the peak at the small size (<30 nm) became smaller, and the peak at the large size (nanosized particles 80–100 nm) became slightly larger. The third peak at 400 nm only appeared after humidifier use.




(a) Adult daily average (on)

(b) Adult sleeping (on)

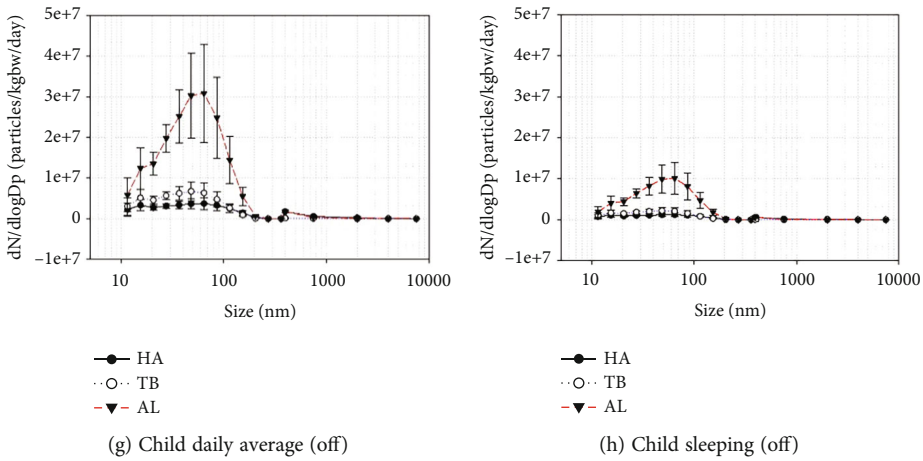
(c) Child daily average (on)

(d) Child sleeping (on)

(e) Adult daily average (off)

(f) Adult sleeping (off)

Figure 3: Continued.




(g) Child daily average (off) (h) Child sleeping (off)

FIGURE 3: Particle size distributions under various scenarios at an Oxy product concentration of 6.5 ppm during (on) and after (off) humidifier use (head airway region (HA), tracheobronchial region (TB), and alveolar region (AL)).

*3.2. MPPD Model Estimate.* The deposition fractions of the mass-based dose in the age-specific five-lobe model and the Yeh-Schum five-lobe model are presented in Figure 5. The Yeh-Schum five-lobe model had a lower overall deposition fraction than did the age-specific five-lobe model. For example, the deposition fraction at each of the five lobes was in the range of 10–16% at 6.5 ppm and 22–35% at 65 ppm for the age-specific five-lobe model; it was only 8% at 6.5 ppm and 19% at 65 ppm for the Yeh-Schum five-lobe model, as shown in Figures 5(a) and 5(b). There was a similar trend when the deposition fraction was estimated according to respiratory tract region, as shown in Figures 5(c) and 5(d). The estimated deposition fractions were higher in both models for the ages of 3 months, 21 months, 8 years, and 9 years than for the ages of 23 months, 28 months, 3 years, and 14–21 years. For all age groups, the estimated deposition fraction according to the lobe of the lung was highest in the left lower and right lower lobes, followed by the left upper and right upper lobes; it was lowest in the right middle lobe.

When the respiratory tract was divided into head airway, tracheobronchial, and alveolar regions, the deposition fraction in each region increased in the order of head airway, alveolar, and tracheobronchial regions.

The deposition fraction tended to increase by more than two-fold in all scenarios when the PHMG concentration was increased from 6.5 to 65 ppm, as shown in Figures 5 and 6. Figure 6 shows the deposition fractions and deposited mass per unit surface area at each lung generation. In all scenarios, the deposition fraction was approximately 1.5–3-fold higher at 65 ppm PHMG than at 6.5 ppm PHMG; it tended to gradually increase between the $20^{th}$ and $24^{th}$ generations in the respiratory zone and then decrease. In contrast, the deposited mass per unit surface area at each generation was highest in the $2^{nd}$ to $6^{th}$ generations, which are the conducting zones of the respiratory tract, and then decreased gradually according to the generation.

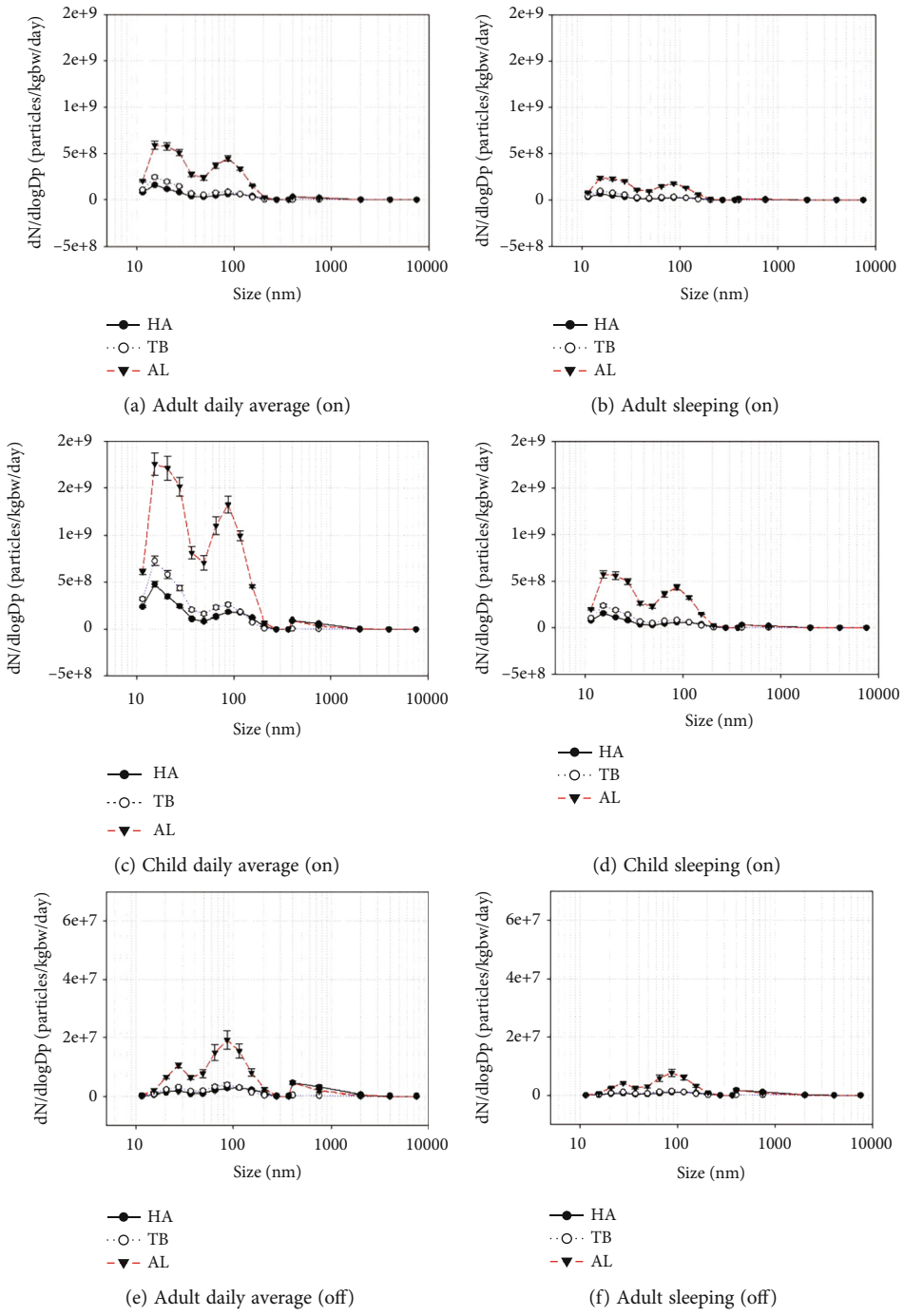
Figure 7 shows a visualization of the mass-based deposited dose in the respiratory tract for the daily average exposure using the MPPD model. When 6.5 ppm PHMG was applied, the bronchial deposited mass was comparatively large; for the 65 ppm PHMG exposure, the deposited dose was higher in the lungs than in the bronchi. Red color indicates a large deposited dose; it is apparent that younger age is associated with more PHMG deposition in the lungs. During sleeping, the distribution of deposited dose in the respiratory tract was similar among age groups (supporting information: Figure S2).

## 4. Discussion

This study estimated the inhaled and lung-deposited doses in humans using the ICRP and MPPD models for particles generated when a humidifier disinfectant containing PHMG was applied as a spray. It is difficult to determine inhaled and deposited doses in the human lung because of uncertain airborne particle behavior and lung structure complexity [18].

Our previous study characterized the behavior of PHMG in the air. It showed that most airborne PHMG was present in nanoparticle form, with a bimodal distribution at or below 100 nm; 99% of the mass concentration was smaller than 1 $\mu$m, including when the aggregated form appeared during and after humidifier use [4]. The present follow-up study attempted to estimate how airborne PHMG-containing particles can be deposited in each part of the respiratory tract.

The advantages and disadvantages of direct measurement and modeling in inhalation exposure have previously been discussed in detail [9], but it is not possible to measure the amounts deposited in the lungs of a living person. The ICRP model was developed to estimate both inhaled and deposited doses by means of semiempirical equations based on experimental data; it assumes symmetric lung geometry in both adults and children. The MPPD model was established based on actual lung morphology; it predicts both total and regional deposition, assuming an overall symmetric and five-lobe asymmetric structure in both humans and other species [18–21]. Estimates produced by the models




(a) Adult daily average (on)

(b) Adult sleeping (on)

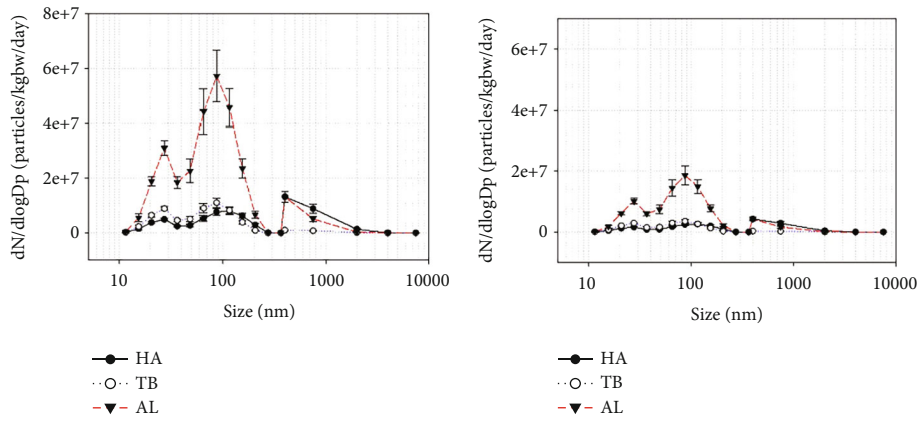
(c) Child daily average (on)

(d) Child sleeping (on)

(e) Adult daily average (off)

(f) Adult sleeping (off)

Figure 4: Continued.




(g) Child daily average (off) (h) Child sleeping (off)

FIGURE 4: Particle size distributions under various scenarios at an Oxy product concentration of 65 ppm during (on) and after (off) humidifier use (head airway region (HA), tracheobronchial region (TB), and alveolar region (AL)).

vary according to the input variables, but both models showed similar trends in this study when using the results of chamber experiments as inputs.

A previous study reported that typical-path and five-lobe symmetric lung geometry models predicted similar regional and generation-by-generation deposition results [22]. In a comparison of the ICRP and MPPD models for nanomaterials generated from a consumer spray product, the deposition results were similar between the two models [6]. In the present study, the production of an age-specific deposition fraction and deposition dose was considered a strength of the MPPD model because health effects have been reported in infants. A notable benefit of the ICRP model is the ease of use, regardless of particle size.

It has been reported that the nanoparticles generated from spray-type household chemicals or 3D printing are present as individual particles in the air, as well as agglomerates. It has also been confirmed by electron microscopy that PHMG particles are present as both agglomerates and individual particles during humidifier use [4, 9, 12, 23]. This phenomenon has also been observed in lung deposition modeling. As shown in Figures 3 and 4, the peak in the 10–40 nm size range, which was clearly visible during the use of the humidifier (4 h), became significantly smaller after use (1 h); the peak in the 70–100 nm size range was slightly shifted to the right. In addition, at the high concentration of 65 ppm, a new peak was formed above 400 nm after humidifier use, indicating that small individual particles had gradually agglomerated.

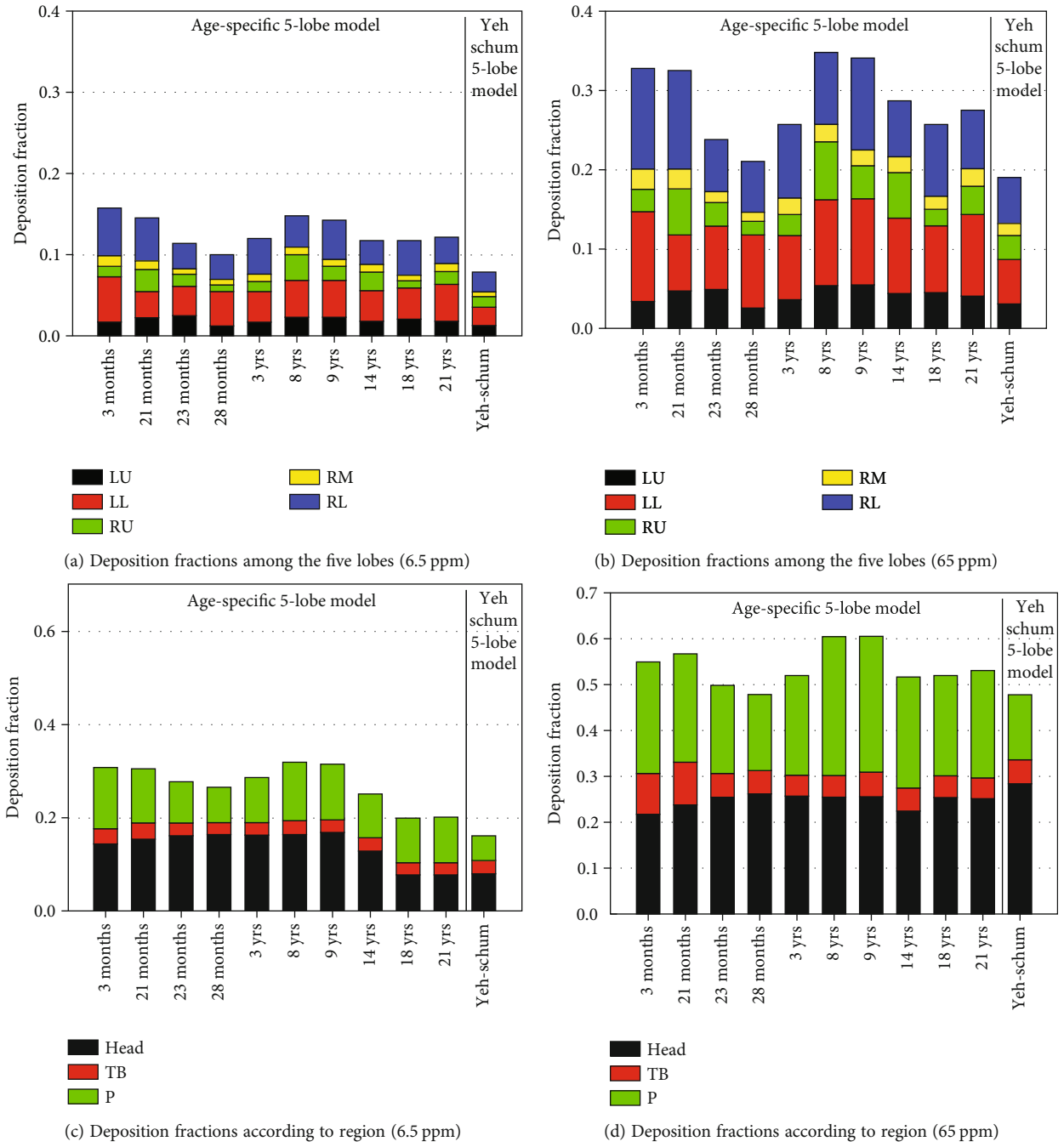
As shown in Table 1, when the humidifier was turned off, the average inhaled dose decreased compared to when the humidifier was used. When the humidifier is stopped, the airborne concentration decreases gradually. The inhaled dose with the humidifier off in Table 1 is calculated as the average concentration over the hour of measurement (see supporting information Table S1). The gradual decrease in concentration can be attributed to the disappearance of the initial inertial force, settling, and diffusion of the particles after particle emission. This decline is well documented in a previous paper, which shows a steep initial decline in concentration after the humidifier was off, followed by a gradual decrease in slope [4].

The airborne particle concentration due to the use of a humidifier can vary according to time and distance. In this study, the change in time during and after the use of the humidifier was reflected, but the change in concentration according to the distance was not reflected. This study only showed the results at the minimum distance of 0.5 m observed in previous epidemiological studies [17]. As shown in previous study [4], the concentration and particle size will change as the distance increases, so the deposited dose will also change.

The diffusion dryer and thermodenuder attached in front of the real-time measuring equipment to remove moisture can evaluate airborne particles in a state different from the conditions when actual consumers use it. Due to the attachment of the moisture removal equipment, it was found that the number concentration of airborne particles was greatly reduced, but there was little change in particle size [10]. That is, due to the moisture removal device, particles in the air enter the respiratory tract differently from actual conditions of use, but overestimation of the concentration of airborne particles could be prevented. There may still be controversy over whether or not to attach a moisture removal device, but we thought it was correct to attach a moisture remover when investing in the behavior of airborne particles.

The daily inhaled and deposited doses in the ICRP model were high in children aged <6 years in all cases; they were approximately three-fold higher than in adults. In the MPPD model, infants aged <3 years also tended to have a higher deposition fraction, compared with adults. Compared with adults, children generally have a higher inhalation rate per body weight or pulmonary surface area [21]. The results of the present study also support the evidence from previous epidemiologic studies that a large number of children aged <6 years have developed lung disease because of humidifier disinfectant exposure [2].

In contrast to the ICRP model, the MPPD model can visualize a detailed image of the lung and identify deposition




(a) Deposition fractions among the five lobes (6.5 ppm)

(b) Deposition fractions among the five lobes (65 ppm)

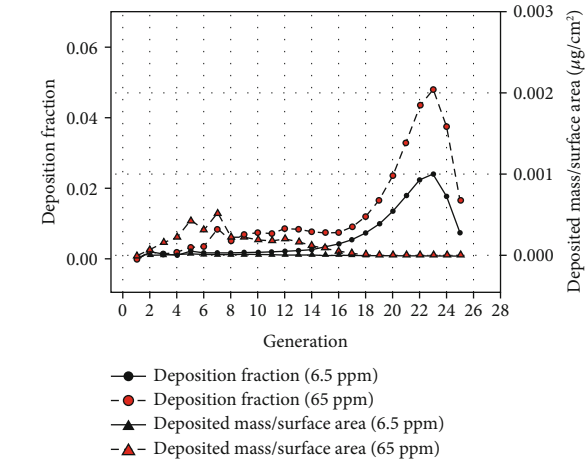
(c) Deposition fractions according to region (6.5 ppm)

(d) Deposition fractions according to region (65 ppm)

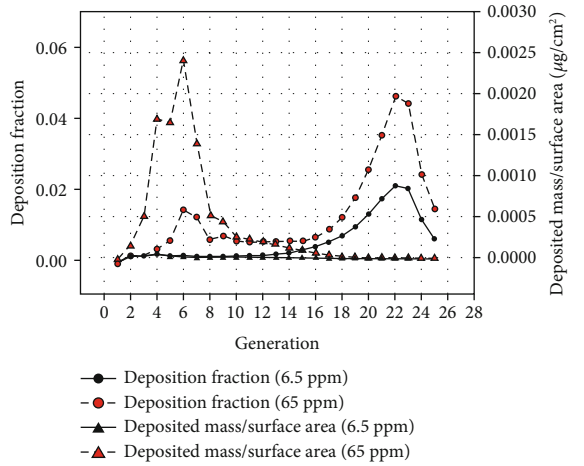
Figure 5: Deposition fractions in each of the five lobes and regions: (a, b) LU (left upper lobe), LL (left lower lobe), RU (right upper lobe), RL (right lower), and RM (right middle lobe); (c, d) head (head airway region), TB (tracheobronchial region), and P (pulmonary region).

fractions in various parts of the lung. In this study, the deposited mass was greater in the bronchus than in the lungs at the recommended dilution concentration. There has been considerable interest in the possible occurrence of asthma as a consequence of exposure to humidifier disinfectants. In a recent study, children < 3 years of age with acute bronchiolitis and humidifier disinfectant exposure also had a significantly increased risk for developing asthma in the following 12 months [24]. Therefore, based on the results of the MPPD model, exposure to the humidifier disinfectant presumably increased the risk of asthma and lung disease. Previous studies have not estimated inhaled and deposited doses or fractions from measured data in a similar environment, although there have been many reports of PHMG-exposed patients.

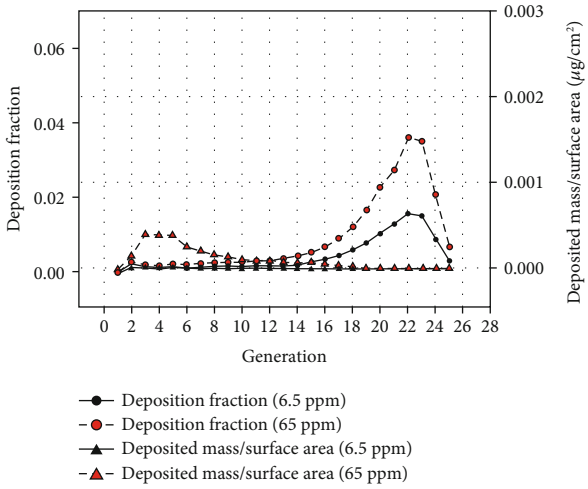
In summary, we achieved the original aim of the study. Despite differences in the input variables, the absolute deposition amount was different, but the deposition tendency was similar in the two models. In addition, most particles produced by the spray were nanoparticles (Figures 3 and 4), and most were deposited in the alveolar region, followed by the tracheobronchial and head airway regions, according



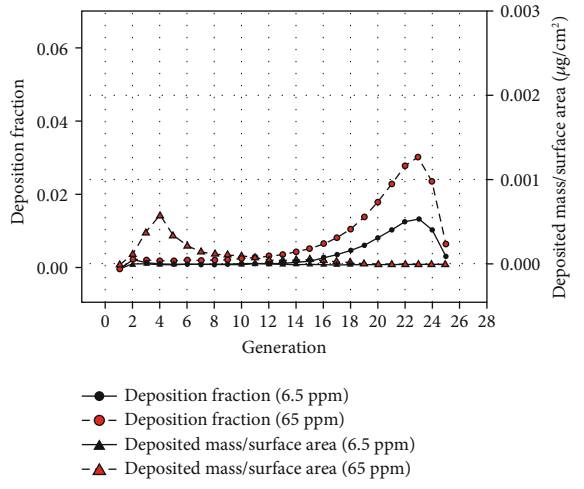

(a) 3 months



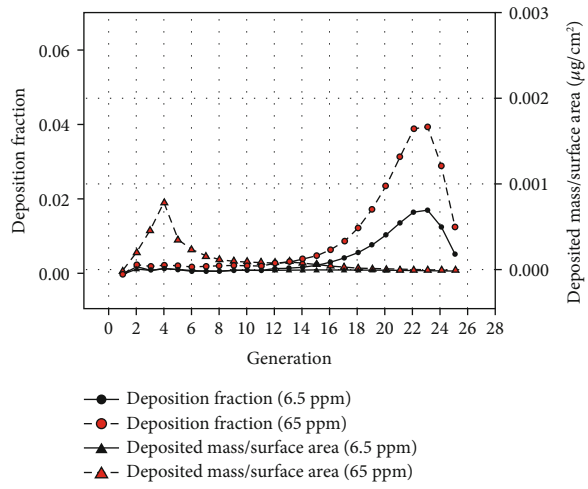

(b) 21 months



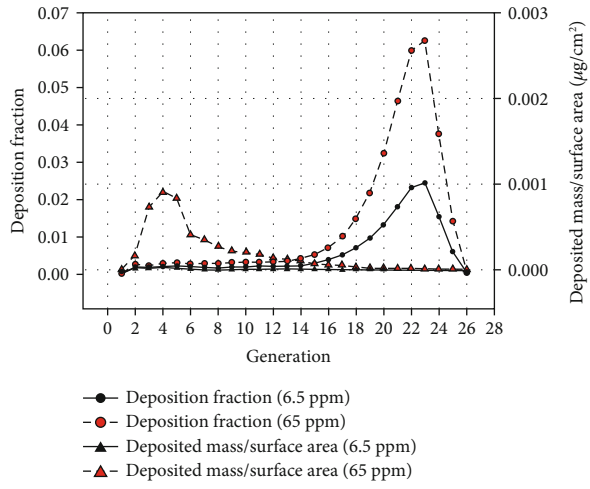

(c) 23 months




(d) 28 months




(e) 3 years




(f) 8 years

Figure 6: Continued.

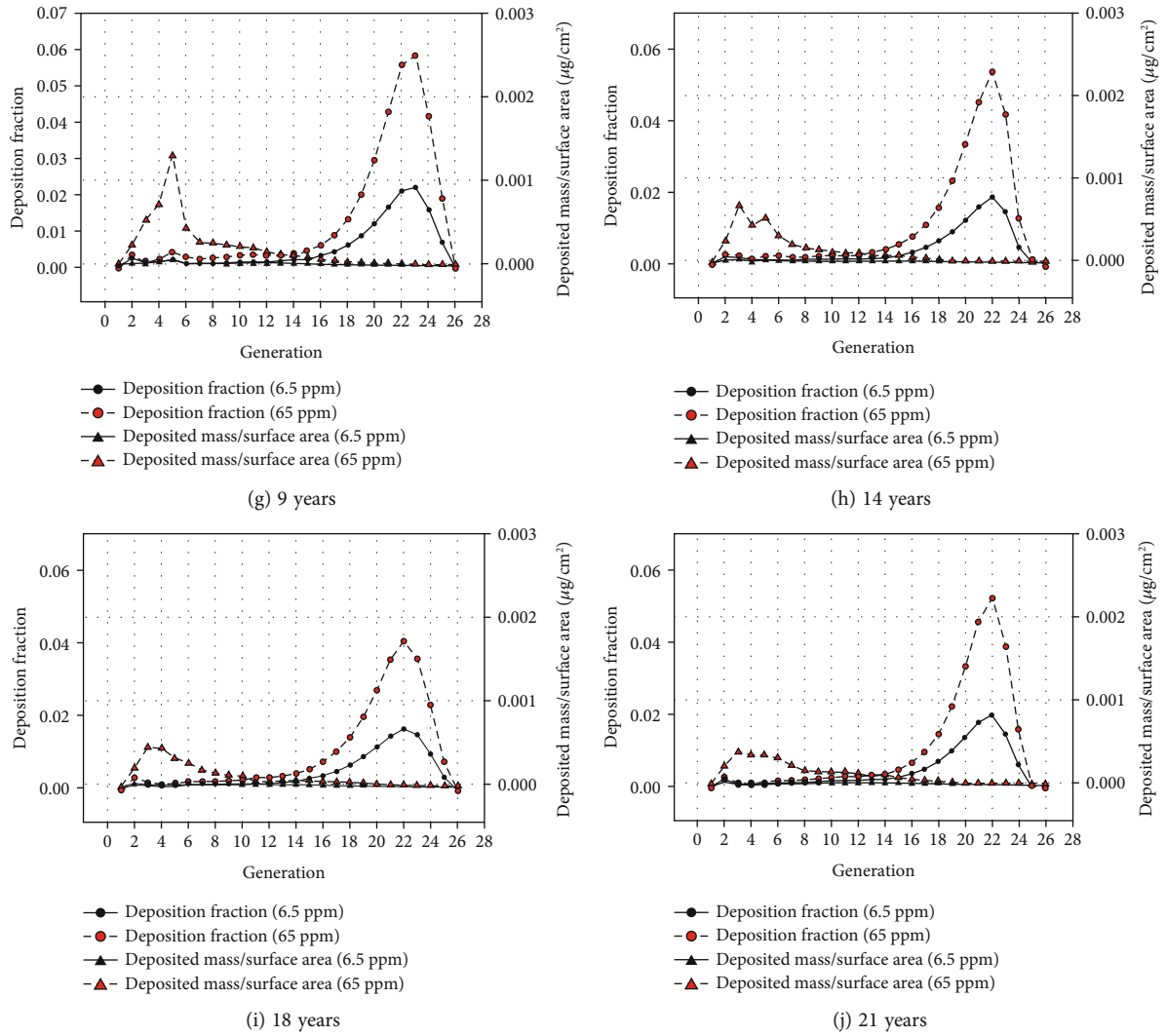



Figure 6: Deposition fraction (right $y$-axis) and deposited mass per unit surface area (left $y$-axis) at each generation of the lung according to age. $x$-axis: generation number of the respiratory tract (conducting zones (1–16) and transitional and respiratory zones (16–26)).

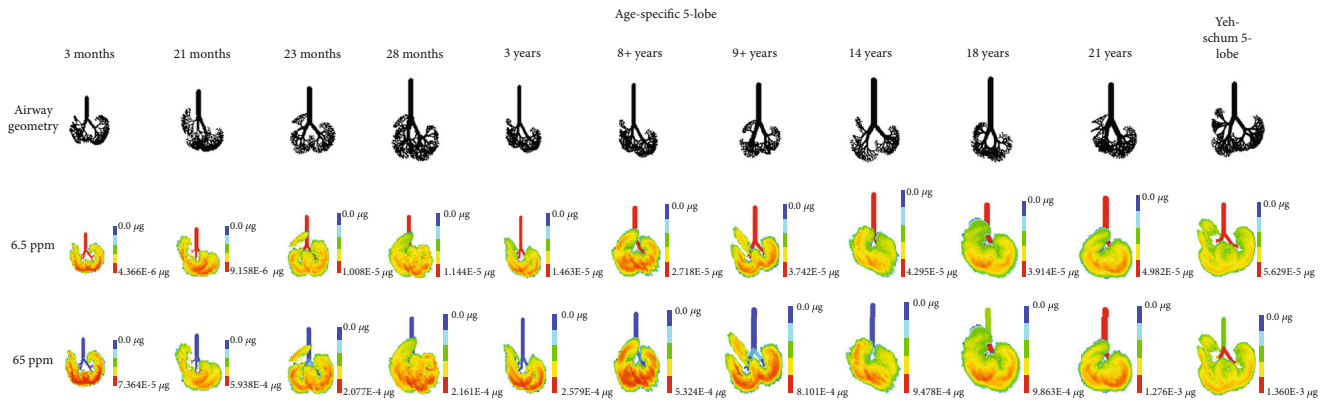



Figure 7: Lung visualization of deposited mass dose according to concentration for daily average exposure. Note that the scales differ among figures.

to number-based deposition dose estimation (Figure 1). In contrast, the mass-based deposition dose followed the order of head airway region > alveolar region > tracheobronchial region (bottom of Figure 2). Considering the deposition dose per unit body weight, children were more affected, compared with adults (Figures 1–6). In the lung, most particles were deposited in the lower part of the bronchi (i.e., the alveolar region; Figures 4(a)–4(d) and 6(a) and 6(b)).

## Data Availability

All data that support the findings of this study are available in the supporting information (see Supporting Information). The more detailed datasets of the current study are available from the corresponding author upon reasonable request.

## Disclosure

The experimental results of this manuscript are part of the first author's doctoral dissertation, but the interpretation and discussion of the results have changed a lot during the submission process to this journal. A thesis paper has previously been published[1].

## Conflicts of Interest

The authors declare they have no actual or potential competing financial interests.

## Authors' Contributions

Sunju Kim (first author) was responsible for the methodology, experiment, data analysis, and original draft preparation (https://Orcid.org/0000-0001-9997-0776). Chungsik Yoon (corresponding author) was responsible for the conceptualization, supervision, discussion, writing, reviewing, and editing (https://Orcid.org/0000-0001-7822-0079).

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## Supplementary Materials

Summary of airborne particle concentration according to PHMG solution concentration and during and after the operation of the humidifier is presented in Table S1. Exposure factors used for the ICRP and MPPD models mentioned in Methods are presented in Tables S2 and S3, respectively. Inhaled dose as a particle number mentioned in Results is presented in Table S4. Sampling diagram in the clean room during humidifier use is shown in Figure S1. Lung visualization of deposited mass dose according to concentration during sleeping is shown in Figure S2. *(Supplementary Materials)*

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