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An overlooked route of inhalation exposure to tap water constituents for children and adults: Aerosolized aqueous minerals from ultrasonic humidifiers

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ABSTRACT

Fine particulates and aerosols emitted by commonly used, room-sized ultrasonic humidifiers may pose adverse health effects to children and adults. The literature documents adverse effects for children exposed to minerals emitted from humidifiers. This study performs novel and comprehensive characterization of bivariate particle size and element concentrations of emitted airborne aerosols and particles from ultrasonic humidifiers filled with tap water, including size distribution from 0.014 to 10 μm by scanning mobility particle sizer and AeroTrak; corresponding metal and elemental concentrations as a function of particle size by inductively coupled plasma mass spectrometer; and calculations of deposition fraction in human lungs for age-specific groups using the multi-path particle dosimetry model (MPPD). Deposition fraction is the ratio of mass deposited to total mass inhaled. When filled with tap water, water evaporated from emitted aerosols to form submicron particles that became essentially "dried tap water" with median size 146 nm and mean concentration of 211 μg-total elements/m^3-air including 35 μg-calcium/m^3-air in a room of 33.5 m^3 and air exchange rate at ~0.8 hr^{-1}. Approximately 90% of emitted particles deposited in human lungs were <1 μm as shown by MPPD model. The smaller particles contained little water and higher concentration of minerals, while larger particles of >1 μm consisted of lower elemental concentrations and more water due to low evaporation. Deposition fraction in pulmonary region was ~2-fold higher, and deposited particulate mass was 3.5-fold higher for children than adults, indicating greater inhalation exposure to children compared to adults. Modeled data of total particles mass per body weight (BW) that will deposit in adult and child lungs after 8-h humidifier exposure were respectively 2.8 μg/kg-BW and 9.8 μg/kg-BW, where calcium contributes 0.4 μg/kg-BW and 1.6 μg/kg-BW. This comprehensive study of bivariate inorganic chemical composition as a function of particle size expanded, quantified, and modeled exposure for children and adults to aerosolized calcium and other inorganic constituents in water.

1. Introduction

Contaminant exposure in a single media, such as waterborne or airborne contaminants, is a focus of traditional investigations and regulations. An increasing concern area for researchers and human population is exposure to contaminants transporting from water to air, which may pose adverse health effects to humans who breathe aerosolized and vaporized aqueous chemicals. The exposure to volatile organic chemicals during showers is an acknowledged area for air-water interface exposure. VOCs from industrial chemicals (Gallagher et al., 2015), disinfection by-products (Gordon et al., 2006), and microbial metabolites (Ömür-Özbek et al., 2010) are transported from water to air when showering, and then inhaled by humans. Portable household ultrasonic humidifiers, which aerosolize water to alleviate dryness, are a less investigated inhalation exposure pathway to children and adults for chemicals in drinking water. The United States Environmental Protection Agency (USEPA, 2011) reported about 20% of portable humidifiers were ultrasonic devices, and that at least 15% of American households use

Abbreviations: CMD, count median diameter; GSD, geometric standard deviation; SMPS, scanning mobility particle sizer; ICP-MS, inductively coupled plasma mass spectrometry; MPPD, multiple-path particle dosimetry.

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ultrasonic humidifiers. Ultrasonic humidifiers constituted 34.5% of the global humidifier market in 2016 (Technavio, 2017). Baby List (2019), a registry site for expecting parents, lists humidifiers among the top items for a new baby; three of four of its top recommendations are ultrasonic versions. The site states "ultrasonic humidifiers are recommended for use around small children" and to only consider using the alternative warm mist humidifiers "if you are able to find a safe spot to keep a warm mist humidifier far away from little hands". Prior research indicated that asbestos fibers, present in naturally contaminated water, were emitted from ultrasonic humidifiers, and increased exposure time led to higher inhalation risk (Roccaro and Vagliasindi, 2018). Additionally, disinfectants, marketed specifically for humidifier use, have caused more than 100 deaths of pregnant women and children and illness in over 1000 people; positive associations existed between lung injuries and humidifier disinfectant exposure (Kim et al., 2014a; Ryu et al., 2019). Humidifier disinfectant usage was also associated with interstitial lung disease in children (Kim et al., 2014b; Yang et al., 2013), confirming that humidifier use can have adverse health effects.

Ultrasonic humidifiers are designed to emit fine water droplets. $PM_{2.5}$ and PM_{10} (particulate matter with aerodynamic diameter smaller than 2.5 μm and 10 μm, respectively) concentrations reached 6307 μg/m^3 and 7078 μg/m^3 when using 303 mg/L total dissolved solids (TDS) tap water to fill ultrasonic humidifier with a water consumption rate at 0.48 L/h in a closed bedroom of 25 m^3 and air exchange rate of 1.16 hr^{-1} (Highsmith et al., 1988). PM_{10} of 118 and 966 μg/m^3 were emitted in a closed dormitory room of 33.5 m^3 and air exchange rate of 0.87 hr^{-1}when using 75 and 510 mg/L TDS tap water to fill the humidifiers of water consumption rate at 0.21 L/h, respectively (Sain and Dietrich, 2015). Soluble minerals and insoluble metal oxide particles, when present in fill water in the humidifiers, are emitted as sub-micron, inhalable particulates (Sain et al., 2018; Yao et al., 2019). Particles <1 μm can penetrate deeper into the lower lung region and cause mild to severe inflammatory responses depending on the chemical composition. Particles in the alveolar region can transport across epithelia and enter blood and lymphatic circulations, and thus distribute throughout the body (Oberdörster et al., 2005). Toxicology of particles is determined by various factors, e.g., their shape, size, concentration, and chemical composition. Risk assessments of emitted particles from ultrasonic humidifiers and other devices generating aerosols should consider these factors.

Data are not available for the types of water that consumers actually use to fill their ultrasonic humidifiers. As it requires approximately 2.5 L of water per 8-h cycle, it is likely that consumers may use local tap water for convenience (Davis et al., 2016) even though about three decades ago the United States Environmental Protection Agency (USEPA, 1991) recommended using distilled or low mineral water. Select ultrasonic humidifiers manufacturers make recommendations of water type to use in their products. Recommended water types for the "10 Best Humidifiers to Buy in 2020, According to Experts" (Good Housekeeping, 2020) are presented in Table S1. Three manufacturers recommended "cool or cold tap water" and two of them suggested using a filter for hard water; three manufacturers recommended "water" without further specifications; and one manufacturer recommended only "distilled water". For three other models, the user manuals were not readily available on-line and the recommendation is not known. In summary, humidifier manufactures are directly recommending the use of tap water, or simply recommending water, and thus consumers are likely using tap water rather than distilled water. Globally, tap water will have variable mineral water quality as total dissolved solids is typically in the range of 50 - >500 mg/L TDS (Dietrich and Devesa, 2019). Calcium and magnesium hardness also vary (Ong et al., 2009). Interestingly, global freshwaters and their corresponding tap waters that are not treated by membrane filtration, are undergoing increased salinization leading to more minerals being present in tap water (Herbert et al., 2015; Kaushal, 2016; Kaushal et al., 2019).

Since humidifiers are often used for children, a concern is the particulate exposure these children may receive from ultrasonic humidifiers. The following epidemiology studies indicate associations between adverse health outcomes and early life exposure to non-humidifier particulate air pollution. Clark et al. (2009) revealed association between childhood asthma and PM_{10} exposure *in utero* and during first year of life. Studies indicate adverse health effects for particulate exposure during fetal and early postnatal life (Stocks and Sonnappa, 2013) and exposure to particulates in ambient air caused increased morbidity and mortality rates in compromised people (Pope et al., 2004). The International Agency for Research on Cancer (IARC, 2015) classifies outdoor air pollution and particulate matter as carcinogenic to humans (Loomis et al., 2013). $PM_{2.5}$ & PM_{10} in ambient air are regulated respectively at <35 and <150 μg/m^3 during 24-h period (USEPA, 2010).

Previous studies show lung injuries in young children (Daftary and Deterding, 2011) and mice (Umezawa et al., 2013) from exposure to ultrasonic humidifiers. In the former case, a 6-month child exposed to an ultrasonic humidifier in a closed room for ~2 h started coughing. After hospitalization, he was diagnosed with peribronchial thickening with mild hyperinflation, and symptoms of fast breathing and hypoxemia lasted for 2 weeks. Suspected white dust settling on room surfaces was sent for elemental analysis, and large quantities of calcium, magnesium, sodium, and chloride as well as small quantities of fluoride, nitrate, phosphate, sulfate, aluminum, copper, and iron, were found. These elements are commonly seen in tap water. In the latter case, high-silica (104 mg/L TDS) and tap water (73 mg/L TDS) were used to fill the ultrasonic humidifier, and mice were exposed for 7-day or 14-day periods. Particles generated with tap water and high-silica water were composed of sodium, magnesium, silica, sulfate, and calcium from fill water in the humidifier, which were typical elements in tap water as well. Particles in the experimental chamber of 0.765 m^3, water consumption rate at 60 mL/h, and AER of 11.5 m^3/h reached 580 and 460 μg/m^3 when using high-silica water and tap water, respectively. The airborne particles induced cellular response in the alveolar macrophages, but not inflammation or tissue injury in mouse lungs. The two cases involved detection of high levels of calcium, magnesium, and sodium in emitted particles, and corresponding anions, illustrating potential risks to inhalation of white dust produced from ultrasonic humidifier filled with tap water. Longer-term epidemiologic study or toxicity testing of particles emitted from humidifiers is lacking and should be addressed.

The exposure and risk assessment of inhaled particulate matter is facilitated by the Multiple-Path Particle Dosimetry model (referred to as MPPD), available from Applied Research Associates Inc. (ARA, 2020). The model became publicly deployed in 2002 and has many applications for calculating particle deposition within the human airway for 0.001–100 μm diameter particles. The model can account for individual breathing parameters and patterns for children and adults. Lyu et al. (2018) measured concentrations of quinones and metals bounded in ambient particulates, utilized MPPD model to predict their deposited mass in human respiratory tract, and estimated the extent of oxidative stress based on the deposited mass. Sarigiannis et al. (2015) estimated the inhalation risks from polycyclic aromatic hydrocarbons absorbed on ambient particulates for human child and adult, and the MPPD model showed higher normalized-to-bodyweight exposure dose to child than adult. When applied to ultrasonic humidification of a conference room, the MPPD model demonstrated that inhaled and lung-

deposited mass was greater when the fill water TDS was higher, and that both hard and soft waters influence lung-deposited mass for high TDS waters (Yao et al., 2020). MPPD is widely employed to evaluate human exposure to particulate matter (see Table S2 in Supporting Information for summary of environmental applications involving the MPPD model).

Previous research (Sain and Dietrich, 2015; Yao et al., 2019) demonstrates that, over time, the metals and inorganic elements in the humidifier reservoir increase in concentration indicating that more pure water is emitted and the metals and elements concentrate within the reservoir. This suggests that particles emitted from the humidifier do not have the same elemental concentrations as the initial fill water. This article aims to evaluate inhalation exposure and risk for particles emitted from ultrasonic humidifiers filled with tap water. The objectives of this study are: 1) investigate the relationship between metal and elemental concentrations as a function of particle sizes emitted from ultrasonic humidifiers; 2) use the MPPD model to quantify metal and elemental deposition fraction in child and adult respiratory tracts from breathing aerosolized water from ultrasonic humidifiers; 3) estimate calcium and mineral dosages for children and adults, from inhaling aerosolized tap water from ultrasonic humidifiers.

2. Materials and methods

2.1. Overview of the experimental design and calculations

As shown in Fig. 1, this study collected airborne particles generated from aerosolized water and characterized their sizes and chemical composition. From measured data, particle properties were calculated and served as inputs in the inhalation exposure model. Detailed information on the instrumentation and the model is discussed in following sections.

2.2. Aerosol sample collection

Experiments were conducted in an unoccupied dorm room during winter season when relative humidity is low and humidifiers are used in households to alleviate dryness. A commercially available portable ultrasonic humidifier with water consumption rate at 0.21 L/h and run time of about 14 h was placed at the corner of an unoccupied dorm room on a stand of 0.9 m height, and maximum output setting was chosen to represent high-humidity scenario. The dorm room is 3 m × 4.3 m x 2.6 m (L x W x H), 33.5 m^3 volume, and is not mechanically ventilated. The door and window were closed during the experiment and the air exchange rate (AER) ranged from 0.8-0.86 per hour for measurements on three different days. The humidifier was filled with 3 L of Blacksburg, VA tap water and operated for 8 h. Blacksburg tap water had a hardness of 42 mg/L as $CaCO_3$ and a TDS concentration of 75 mg/L.

A cascade impactor (particle cut-off sizes: 2.5 μm, 1.0 μm, 0.50 μm, and 0.25 μm, Sioutas Cascade Impactor, SKC Inc.), an air temperature/humidity monitor (EasyLog USB, Lascar Electronics Inc.), a scanning mobility particle sizer (SMPS, model 3080, TSI) and an optical particle counter (AeroTrak, model 9306, TSI) were placed 1.5 m away from humidifier outlet in the path of the emitted aerosols/particles (see experimental setup diagram Fig. S1 in Supporting Information), with a height of 0.64 m to represent bed height (Lyons and Oates, 1993). SMPS measures submicron particles (0.014–0.750 μm), AeroTrak measures larger particles (1–10 μm), and the impactor collects particles in 5 size bins (<0.25 μm, 0.25–0.50 μm, 0.50–1 μm, 1–2.5 μm, >2.5 μm). The particle sizers take measurements every 6 min during the 8-h humidifier operation. A summary of instrumental size ranges are listed in Table S3. Emitted airborne particles were collected on PTFE filters (25-mm filter, Cat. No. 225–3708; 37-mm, Cat. No. 225–1709. SKC Inc.) in 5 size bins: < 0.25 μm, 0.25–0.5 μm, 0.5–1 μm, 1–2.5 μm, and >2.5 μm. The sampling pump (Leland Legacy Sample Pump, Cat. No. 100–3002) was set at flow rate of 9 L/min and collected aerosols during the 8-h humidifier operation period.

For control samples, background air of experimental room was measured using SMPS and AeroTrak for 30 min before turning on the humidifier. Metals in distilled water produced aerosols in the experimental room were also sampled using the Cascade Impactor.

2.3. Measuring metals and elements by ICP-MS

Cascade Impactor filters were acid digested by submerging with 5% v/v nitric acid (LabChem, Cat. No. LC177003) and 95% pure water (Nanopure Water System, model D4744, Barnstead) in PTFE bottles

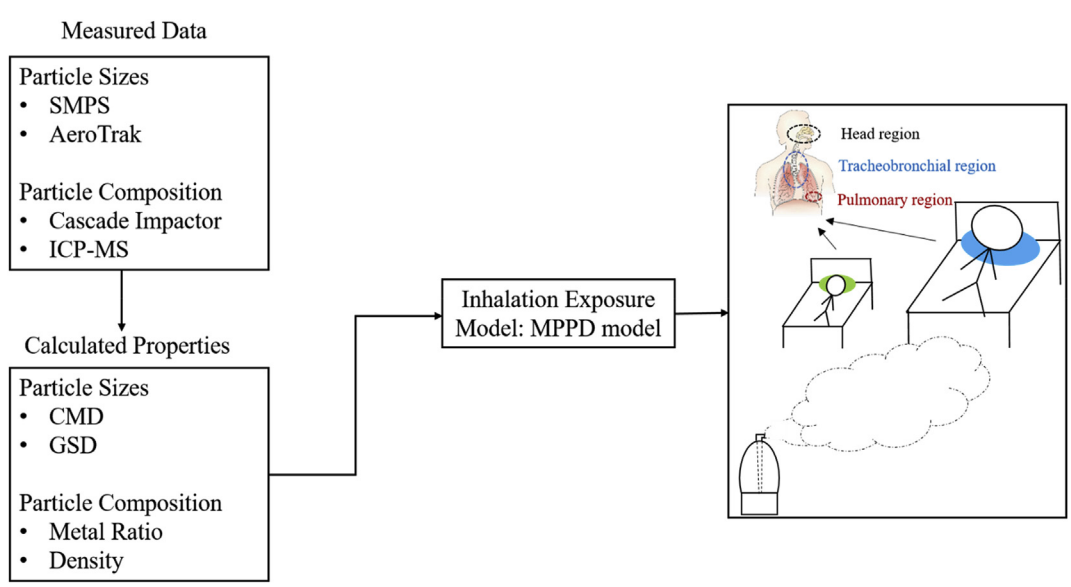


Fig. 1. Overview of methodology in this study. CMD: count median diameter, GSD: geometric standard deviation, SMPS: scanning mobility particle sizer, ICP-MS: inductively coupled plasma mass spectrometry.

overnight before inductively coupled plasma mass spectrometry (ICP-MS, Thermo Scientific X-0458) for elemental mass concentrations. Calculated airborne particle mass concentrations were corrected for filter blanks. Elements and metals were measured by ICP-MS. Elements are Na, Mg, Al, Si, P as PO_43-, S as SO_4^{2-}, Cl, K, Ca, Ti, V, Cr, Fe, Mn, Co, Ni, Cu, Zn, As, Se, Sr, Mo, Ag, Cd, Sn, Ba, Pb, and U. The term "total ICP-MS" elements combines masses of all elements and metals. Elemental detection limits by ICP-MS are listed in Table S4.

The metals recoveries for nitric acid extraction of the PTFE filters were between 80 and 120%, and within the acceptable recovery range of 75–125% (US EPA, 1996; US EPA, 2014). Specifically, the recovery for Ca was 120%, Na was 114%, K was 96%, Mg was 104%, Mn was 114%, and Pb was 80%. Overall, the metal recovery was 104%. Recoveries were determined by placing a known volume of tap water or DI water (controls) on PTFE filters, evaporating the water in a desiccator, then extracting and measuring with ICP-MS as previously described. Percent recovery calculations subtracted the metals for the DI control filters from the tap water filters.

2.3. Calculating particle size, density, concentration and elemental composition

The MPPD inhalation exposure assessment requires properties of aerosol count median diameter (CMD) and geometric standard deviation (GSD) for the various sizes of inhaled particles. Particle density is another important determinant of particle deposition fraction. These properties were calculated with equations presented in Supporting Information, Text S1 (TSI Inc, 2012).

Metal and elemental concentrations in fill water and in airborne particles (collected by bin size on filters in the cascade impactor) were measured by ICP-MS. In this study, which focused on metal exposure, metal ratio is defined as the ratio of mass of an individual metal to mass of total metals in either fill water or in airborne particles. The metal ratio in fill water was calculated by the concentration of an individual metal ion in fill water divided by the sum of concentrations of all metal ions measured in fill water. Metal ratio in air was calculated by dividing the mass of an individual metal ion collected on each impactor bin for specific particle sizes by the sum of mass of all metals in that size bin. If the metal ratio in fill water is the same as airborne particles in a certain bin size, relative metal composition can be considered identical for that defined size of particles. If the metal ratio in fill water is higher than that in a defined size airborne particle bin, the particles consist of more water than metals. This analysis is necessary to determine if the ratio and mass of metals in each particle size bins is the same or different; the results are critical to calculate the amount of metal inhaled.

2.4. Inhalation exposure assessment

Multiple-path particle dosimetry model (MPPD v3.04, ARA) is software applicable for calculating deposition of inhaled particles in respiratory tracts of human children and adults. Human airway morphometry data in different age groups, i.e. functional residual capacity (FRC) and upper respiratory tract (URT) volume, breathing frequency (BF), and tidal volume (TV, the lung volume of air displaced by a typical inhalation and exhalation), are provided in default settings or can be manually entered as modeling parameters (refer to Table S5). There are eight human exposure models in the MPPD software. For this study, the age-specific 5-lobe model was used to estimate child exposure, based on previous studies (Mortensen, 1988; Phalen et al., 1985). The Yeh-Schum 5-lobe airway model (Yeh and Schum, 1980) was chosen to estimate adult exposure. In this study, ages of 3, 21 months and 3, 8, 14, 18, and 21 years were selected. In addition, appropriate FRC (Altman and Dittmer, 1971; Dunhill, 1962; Overton and Graham, 1989; Phalen et al., 1985), head volume (Hart et al., 1963; Overton and Graham, 1989), tidal volume (Hofmann, 1982), and breathing frequency (Hofmann, 1982) default values are automatically linked with their respective ages. Body orientation of laying on the back was chosen to represent sleeping conditions. The MPPD software generated results for deposition fractions in head (oral and nasal), tracheobronchial, and pulmonary regions. Deposition fraction is the ratio of deposited mass in each region to the total mass inhaled (Anjilvel and Asgharian, 1995). Thus the denominator, e.g., total mass inhaled, accounts for losses of exhaled mass. Humans had airway morphometry data as shown in Table S5.

Experimentally-determined aerosol properties (concentration, diameter, density, and aspect ratio) were entered manually to predict particle deposition fraction in the respiratory tract. Aerosol properties, i.e., CMD, GSD, and density, were essential inputs to determine the deposition fractions in human respiratory tracts. The CMD and GSD of inhaled particles were calculated using steady-state size distribution curves from SMPS.

2.5. Statistical analysis

The calculations of airborne particles properties and graphs were performed in R Core Team (2019). A Kolmogorov-Smirnov (K–S) test on the size distribution from the beginning of humidifier operation to the end of 8 h was done to determine steady-state size distribution. A non-parametric Spearman correlation test on total particle number and mass concentrations over time was conducted to determine the association between the two parameters. Linear regression of metal ratio in airborne particles and metal ratio in fill water in ultrasonic humidifier reservoir was performed. In addition, linear regression with indicator variable analysis was used to determine significant differences between the slopes and intercepts of two linear models. Reported metal ratio and particle mass fraction were mean values from 5 replicates. An alpha value of 0.05 was used for all statistical tests.

3. Results

3.1. Particle concentrations and size distribution at steady state

Before turning on the ultrasonic humidifier, conditions in the experimental room were 24 °C, 28% relative humidity, a CMD at 38 nm, and very low particle concentrations of 4366 particles/cm^3 and 2 μg/m^3. When the humidifier was filled with distilled water, the particle concentration was 12,100 particles/cm^3, the mass concentration was 25 μg/m^3, with a CMD at 89 nm. The background indoor air and distilled water produced particles contained few metals: sodium, magnesium, potassium, and calcium, as representative tap water metals, were <2 μg/m^3 in the room (see Fig. S3 in SI). Therefore, the metals in background air were very low.

After operating the humidifier with tap water for 2 h, the room air temperature remained at approximately 24 °C during the 8-h operation period, while relative humidity increased from 28% to 45% (see Fig. S2). The relative humidity suggested rapid evaporation of emitted water droplets, as the lifetime of a 10-μm water droplet particle in air is 0.27 s under condition of 60% RH and 5 °C temperature difference between ambient air and pure water droplet particle (Holterman, 2003).

The particles reached "steady-state" in the room after 2 h' operation as the size distribution of emitted particles did not change significantly after 2 h and at 8 h (Fig. 2). Particle number concentration and mass concentration were constant approximately at 56,500 particles/cm^3 and 320 μg/m^3, reported by SMPS.

Mathematical models, as indicated in Fig. 2A and B, describe the changes of particle number and mass concentrations over humidifier operation time. The Spearman's rank correlation test showed 0.899 and 0.919 between time intervals versus particle number and mass concentrations, respectively, which suggested strong association between humidifier operation time and concentrations of emitted particles.

3.2. Size distribution of emitted particles over 8-h operation

The size distributions of emitted particles after operating the humidifier for 0.1 h, 1 h, 2 h, and at the end of 8-h operation were shown in Fig. 2C. CMD is identical to geometric mean diameter in lognormal distributions, and GSD describes the spread of a distribution. 95% of the particles will fall into the range of CMD/GSD^2 to CMD*GSD^2. During the first 6 min after turning on the humidifier, 95% of emitted particles were between 32 and 265 nm, and particles grew larger to 46–388 nm after 1 h. K–S tests indicated that the particle size distribution changed between the background to the first 6-min distribution, and that particle size distributions at the end of 1–2 h were statistically identical as that of the end of 8 h. At steady-state, indicated by the 8th hour data, 95% of particles fell into the size range of 51–424 nm. Large particles of size 1 μm, 2.5 μm, 5 μm, and 10 μm were measured by the AeroTrak and had significantly lower concentrations than the 0.014–0.750 μm particles measured by SMPS. The concentrations of larger particles did not affect the CMD and GSD as the CMD using only SMPS is 146.36 nm (GSD = 1.74), and with AeroTrak the CMD is 146.49 nm (GSD = 1.74).

3.3. Elemental metal composition of emitted particles

The approach of measuring humidifier particle constituents and masses using ICP-MS data allowed for a direct measure of the μg amounts of elements and metals from particles collected on the five Cascade Impactor filters. Thus, total ICP-MS elements are representative of, but not the same as TDS, since ICP-MS measures major anions including chloride and sulfate but cannot measure bicarbonate which is another major anion in Blacksburg tap water. Fig. 3A shows the fraction of particle mass in each of the five size bins for small diameter particles (<0.25 μm, 0.25–0.50 μm, 0.50–1 μm, 1–2.5 μm, and >2.5 μm). The result indicates that ~50% of airborne particles were smaller than 0.25 μm, ~35% were 0.25–0.50 μm, and ~10% were 0.5–1.0 μm, regardless of initial concentrations of metal concentrations in fill water. In other words, 95% of emitted airborne particles were smaller than 1 μm on mass

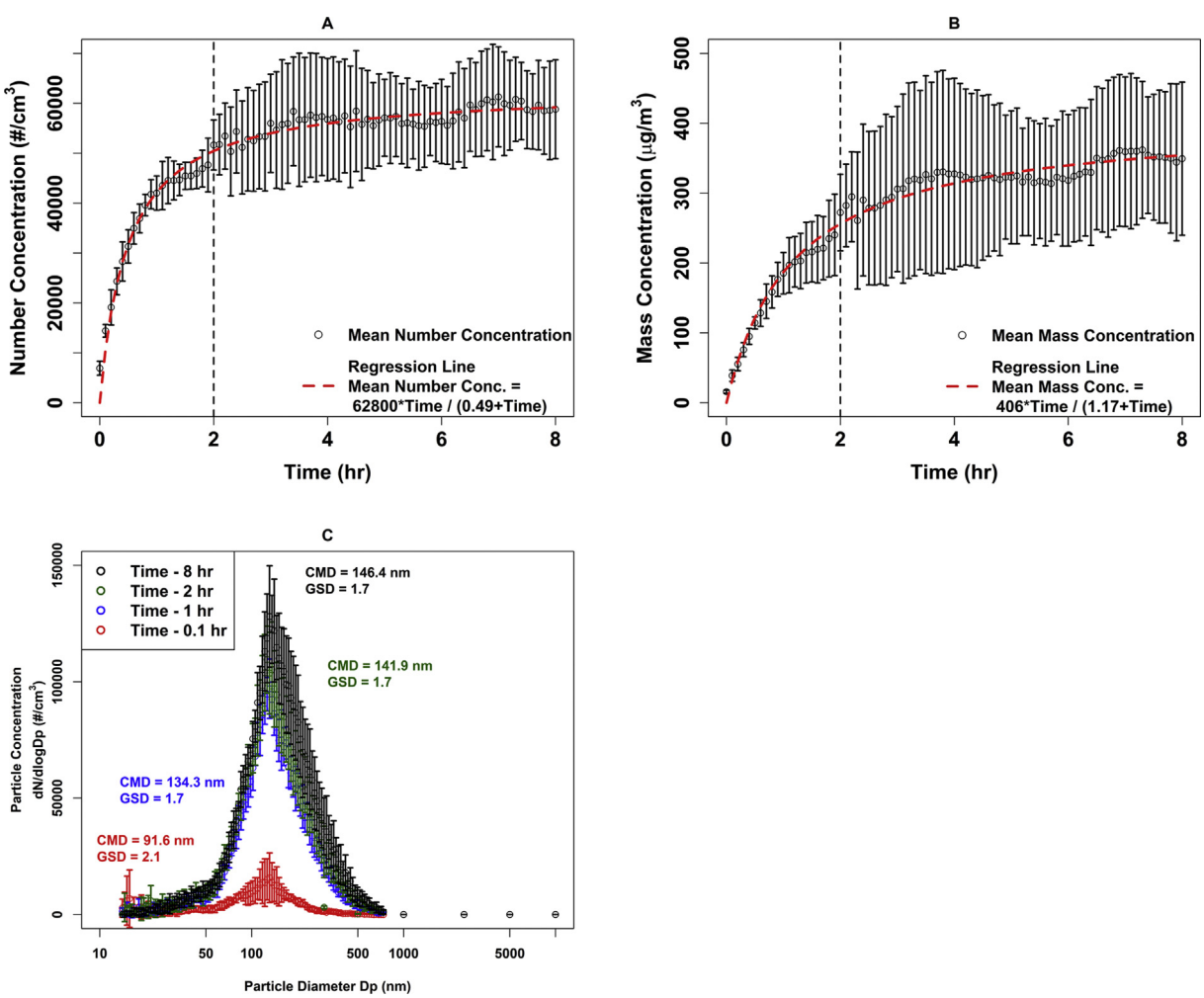


Fig. 2. (A) Particle number concentration, (B) mass concentration, and (C) and particle size distributions in experimental room during humidifier operation. In panel C, black dots indicated distribution at the end of 8th hour, green dots indicated distribution at 2 h, blue dots indicated distribution at 1 h, and red dots indicated distribution at first 6 min. CMD: count median diameter, GSD: geometric standard deviation. Error bars indicate standard deviation for all plots. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

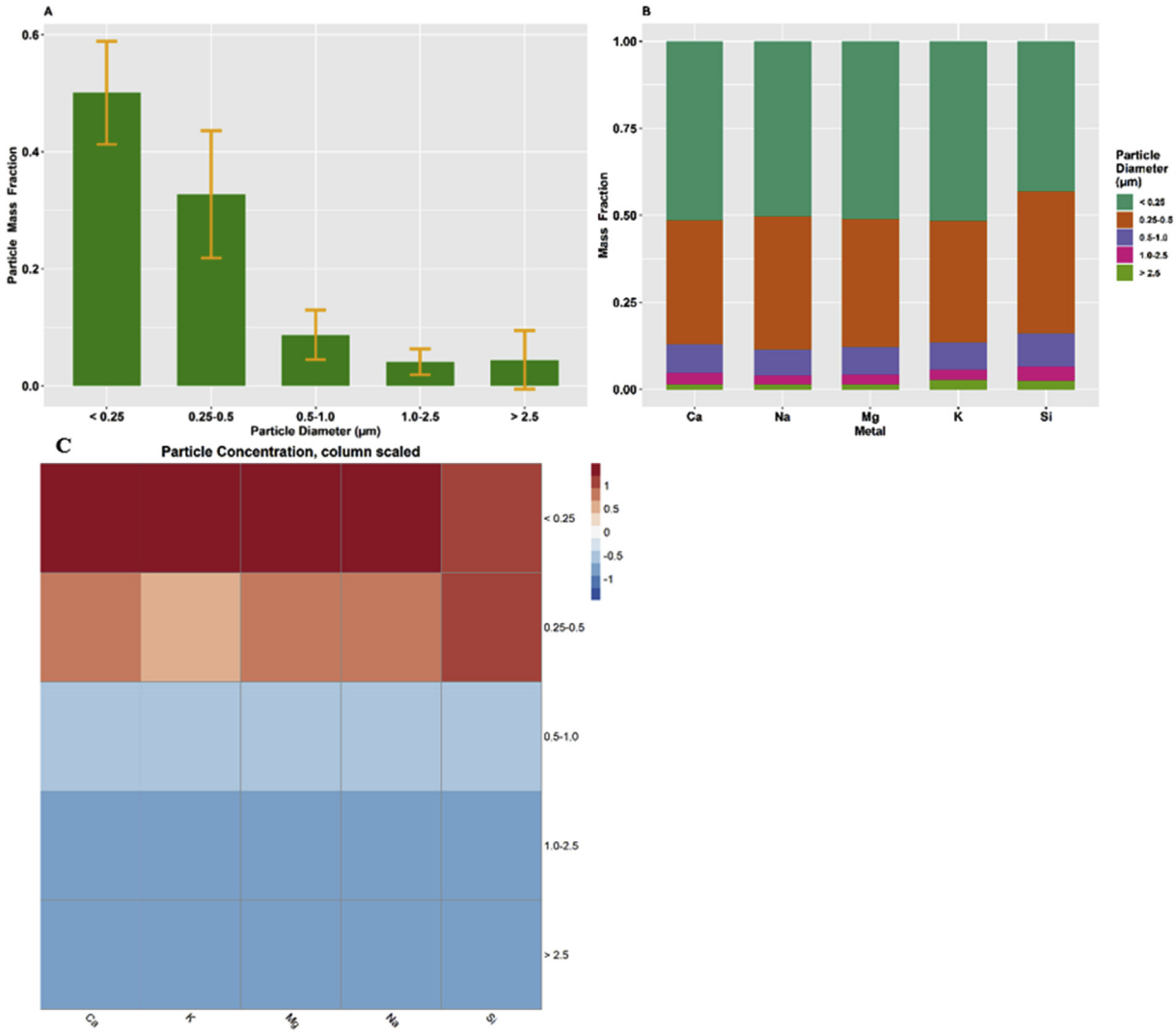


Fig. 3. (A) Particle mass fraction distribution based on particle sizes; (B) normalized mass fraction of representative metals; (C) heatmap of mean - centered concentrations (μg/m^3—air) for each element as a function of particle size. Heatmap legend values shown are standard deviations above or below the mean where white is no deviation from the mean, red represents concentrations above the mean, blue represents concentrations below the mean, and darker colors represent greater standard deviations from the mean (n = 5). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

basis. Fig. 3B demonstrates that the mass fraction distribution was comparable across the 5 particle size bins for both metals and metalloids in the fill water. Sodium, magnesium, potassium, and calcium are important metals, and Si an important metalloid, with concentrations typically in the range of 1000–10,000 ppb in fill water. As indicated by Fig. 3A and B, approximately 50% of the metal mass occurred in <0.25 μm emitted airborne particles and 35% occurred in 0.25–0.5 μm particles. Fig. 3C is a heatmap representative of relative air concentrations of the metals and Si as a function of particle size. Fig. 3C shows "relative concentration" as standard deviation from the mean, with red indicating higher than mean concentration and blue lower than mean concentration. The two smallest particle sizes, <0.25 and 0.25–0.50 μm, were highest in mass concentrations of all metals and the metalloid, and the mass concentrations of particles >1 μm were consistently low for these elements due to the presence of water in the larger particles.

The airborne particle concentration after 8 h (at steady-state) was 211 μg/m^3 based on total ICP-MS elements collected on impactor, while the total calculated mass concentration from SMPS was 320 μg/m^3. This difference may be explained through bicarbonate, which cannot be measured by ICP-MS, and constitutes about 35% of the total dissolved solids in Blackburg tap water (Sain and Dietrich, 2015; Yao et al., 2019). If bicarbonate is assumed to be 35% of TDS and total ICP-MS elements measures all anions/cations except bicarbonate, then total ICP-MS elements plus bicarbonate would be 324 μg/m^3, a value very similar to that measured by SMPS. This difference may also be explained by the increased humidity in the room during the experiment. Absolute humidity was 0.006 kg/m^3 when RH% was 28% and 0.010 kg/m^3 when 45%. Emitted particles can be considered as "wet" particles in air, containing water and metals/elements. "Wet" airborne particles were collected by the cascade impactor, and only metals/elements in the particles were measured by ICP-MS. SMPS collected "wet" airborne particles; the instrument calculated mass concentration based on assuming a density of 1 g/cm^3 and spherical shape for the particles. Therefore, SMPS may report higher mass concentration because it included both aerosolized water and all aerosolized metal/elements.

Fig. 4 corroborated Fig. 3 to demonstrate that small particles contain more metals, and the interference of background metals is negligible. This is essential information for modeling human

inhalation exposure as particle size determines deposition location and therefore metal dose. Additionally, Fig. 4 shows that the smallest particles are essentially dried tap water. The 1:1 dash line is representative of dried tap water particles in air. The corresponding metal fractions of different particle sizes in air over metal fraction in water indicated that larger airborne particles contained more water than small airborne particles, evidenced by less-sloped lines, lower concentration of metals are in air compared to water. The metal compositions of particles of <0.25 μm and of 0.25–0.50 μm were very similar to that of the tap water that filled the reservoir. Linear regression model parameters and the statistical model comparisons are as shown in Fig. 4. The model comparisons indicated the metal composition slopes for emitted particles of <0.25 μm and particles of 0.25–0.5 μm were statistically identical when using metal ratio in tap water as independent variable, but significantly different for larger size bins.

Rodes et al. (1990) predicted the count median diameter of initially formed water droplet particles by 1.6 MHz ultrasonic humidifiers was approximately 3 μm when assuming pure water surface tension and density. This suggested that large "wet" particles were emitted from ultrasonic humidifiers first, and then water evaporated forming small particles in air. The evaporation process happened rapidly when the RH% in the room was below 50%, as mentioned in the steady-state room conditions section above.

The chemical analysis of metals on impactor filters indicated that airborne particles <1 μm had more of the total mass compared to larger particles, and their metal composition was equivalent to fill water. The particle density in this study was 1.74 g/cm^3. The value was close to densities of aerosolized inorganic salts, i.e. ammonia sulfate of 1.76 g/cm^3, ammonia nitrate of 1.69 g/cm^3, and sodium chloride of 2.08 g/cm^3 calculated from a similar method (Sarangi et al., 2016).

3.4. Inhalation exposure to the emitted particles

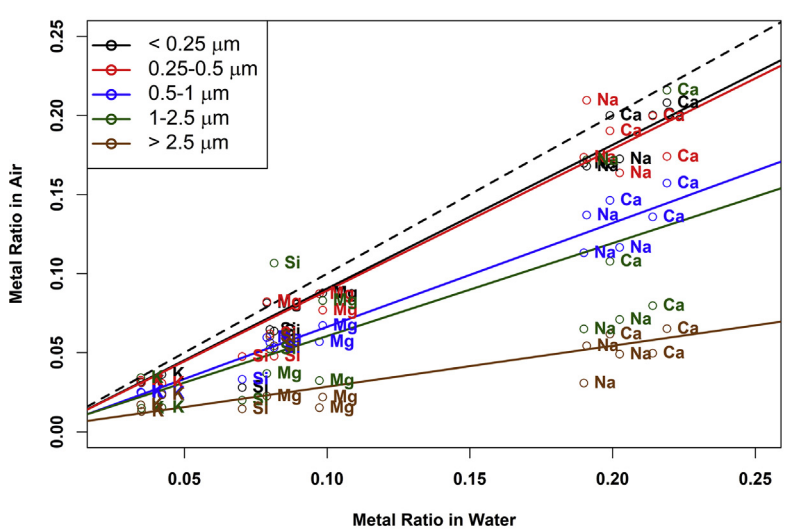
The critical aerosol properties described in previous sections are used to determine inhalation exposure by MPPD. Different age exposure models were used to calculate regional deposition fractions of inhaled particles within human child and adult respiratory tracts. Aerosol CMD was 146 nm, GSD was 1.7, density was 1.74 g/cm^3, and particles were assumed spherical.

Table 1 indicates the regional deposition in human respiratory tract using MPPD. For younger humans, more particles inhaled would deposit in the respiratory tract, especially in the pulmonary region where the inhaled particles would clear more slowly than the trachea region (Stuart, 1984). For resting adults breathing 12 breaths per minute and 625 mL per breath, predicted total deposition fraction of 0.22 was similar to other findings. When a non-resting adult has 1000 mL tidal volume and breathing frequency of 15 per minute, total deposition fraction was reported to be 0.25 for sodium chloride particles (Blanchard and Willeke, 1984); Heyder et al. (1986) found the total deposition fraction of 0.1 and 0.2 μm particles were 0.26 and 0.15, respectively.

Under the same exposure scenario, particle deposition fraction is ~2-fold higher in pulmonary region and the sum of three regions for 3-month infants, compared to >21-year adults. Mature adults experience low particle deposition in the head region (nose and mouth). Tracheobronchial deposition fraction does not change significantly over age. Particles mass deposited in the pulmonary region increase with age for humans under 21 years old, while particle deposition fraction in the pulmonary region has a descending trend when age increases. When adjusted for body weight, the deposited mass (μg/kg-body weight) has a decreasing trend when age increases. The results indicate that exposure to

Table 1
MPPD modeled regional and total deposition fraction and deposited mass unadjusted for body weight (μg) of the airborne particles emitted from humidifier for inhalation by humans in different age groups after 8-hr exposure. Deposited mass in parentheses.

Age	Deposition Fraction (Deposited Mass, μg)			
	Head	Tracheobronchial	Pulmonary	Total
3 months	0.182 (26)	0.050 (6.3)	0.235 (25.3)	0.467 (57.6)
21 months	0.198 (52)	0.051 (12)	0.215 (48)	0.464 (112)
3 years	0.21 (68)	0.041 (14)	0.178 (58)	0.43 (140)
8 years	0.213 (125)	0.044 (25)	0.23 (105)	0.486 (255)
14 years	0.155 (140)	0.046 (29)	0.171 (93)	0.372 (262)
18 years	0.064 (48)	0.048 (28)	0.176 (150)	0.287 (226)
21 years	0.063 (48)	0.046 (27)	0.185 (152)	0.295 (227)
>21 years	0.07 (55)	0.052 (39)	0.102 (77)	0.224 (171)



Size Bin	Intercept (95% CI)	Slope	R^2
< 0.25	-1.5E-4 (-1.6E-3, 1.2E-3)	0.908 *** (0.886, 0.930)	0.99
0.25-0.50	-1.8E-4 (-2E-3, 1.6E-3)	0.895 *** (0.866, 0.924)	0.98
0.5-1.0	6.8E-4 (-4.8E-4, 1.8E3)	0.657 *** (0.639, 0.675)	0.99
1.0-2.5	1.7E-3 (-2.9E-3, 6.4E-3)	0.588 *** (0.514, 0.662)	0.77
> 2.5	2.8E-3 ** (7.5E-4, 4.9E-3)	0.258 *** (0.225, 0.291)	0.77

Comparing Size Bins	Intercept difference	Slope difference
< 0.25 vs 0.25-0.50	-2.4E-5	-0.013
< 0.25 vs 0.5-1.0	-8.4E-4	-0.251 ***
< 0.25 vs 1.0-2.5	1.9E-3	-0.320 ***
< 0.25 vs > 2.5	3.0E-3 *	-0.650 ***

***: $p < 0.001$; **: $0.001 < p < 0.01$

Fig. 4. Composition of metals in fill water and in airborne particles (n = 5). Dots indicate mass ratio of individual metal to total metals in water and its corresponding metal ratio in air. Metal species is indicated by text next to corresponding dots, and are differentiated by color for various size bins. Solid lines indicate linear regression lines of mineral fraction in air over mineral fraction in water. Dash line indicates 1:1 line. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

particles emitted from ultrasonic humidifier poses greater inhalation risk to infants and young children than adults. Pulmonary deposition may impair lung development in early exposure; new alveoli develops in the first 3 years and after first 3 years the lung grows by expansion (Grigg, 2009; Stocks and Sonnappa, 2013).

3.5. Prediction of inhaled metal mass for children and adults

This study provides an approach to predict inhalation exposure from fill water quality and size distribution of emitted particles. Since calcium exposure as white dust is a concern, the predicted calcium ratios in air in different particle size bins were calculated by linear regression equations shown in Fig. 4, assuming calcium being 0.2 fraction of total elements in fill water based on ICP-MS measurements. The total elemental mass concentration in particle was measured by ICP-MS, and calcium mass concentration was predicted by multiplying measured total elements and predicted calcium ratio in air in respective size bins. Total accumulated deposited mass was generated from the MPPD model by assuming 8-h humidifier operation time. When the fill water contains detectable metal ions, using the calculated CMD and GSD, the deposited mass in adult and 3-month old child are predicted and presented in Table 2. The deposited mass indicated that both adult and child exposure doses increased with increased airborne particle mass concentrations, and children are exposed to 3.5-fold more total elements than adults when inhaled particles were normalized over body weight.

4. Discussion

This study characterized detailed size and elemental composition of airborne particles emitted to a room from an ultrasonic humidifier. The particle data were input to an established MPPD model to predict human inhalation exposure to calcium and total ICP-MS elements for children and adults. The fractional deposition of calcium and elements was calculated for the head, tracheobronchial, and pulmonary regions. The results show that for an adult, 199.6 μg, and for a 3-month old child, 58.8 μg, of metals and elements deposited in the lungs after 8-h exposure to particles emitted from an ultrasonic humidifier filled with tap water.

Ultrasonic cavitation creates air bubbles containing water vapor and impurities, such as VOCs and minerals. The mechanism may contribute to the observation that proportionally more water is emitted from the humidifier than metals or elements. As previously demonstrated by Sain and Dietrich (2015) and Yao et al. (2019), the humidifier emits aerosols with slightly lower concentrations of minerals (e.g., 85–90%) than present in the fill water. Thus, more water is emitted and the mineral concentrations increase in the humidifier reservoir over time. For smaller emitted aerosols, the water evaporates quickly, forming essentially "dried tap water" particles while the larger particles contain more water (Rodes et al., 1990).

Our measurements indicated emitted particles reached 211 μg/m^3-air averaged over 8-h operation, which was 6 times higher than regulated $PM_{2.5}$ and 1.4 times higher than regulated PM_{10} (USEPA, 2010). Studies show association between $PM_{2.5}$ and lung diseases, such as chronic obstructive pulmonary disease, cardiopulmonary diseases (e.g., ischemic heart disease), and even lung cancer (Burnett et al., 2014; Thurston et al., 2016). Both short-term (a few hours to weeks) and long-term (years) exposures to PMs are linked with increased mortality; the longer the exposure period lasts, the higher mortality rate due to increased $PM_{2.5}$ (Brook et al., 2010). In addition, residential and commercial $PM_{2.5}$ contributed to mortality of 675 thousand deaths out of 2.23 million total deaths related to anthropogenic $PM_{2.5}$ globally (Silva et al., 2016).

In the present study, the measured concentrations and the modeled deposited particle mass of total elements or calcium exposure doses generated from MPPD model can be informative for future toxicity testing, when evaluating adverse health effects of white dust emitted from ultrasonic humidifier. In addition, since humans with asthma and young children are more vulnerable to exposure of air pollution, the use of distilled water to fill ultrasonic humidifier is important especially for them (USEPA, 1991).

When looking into the metal composition in airborne particles, a few studies showed the association between inhaled metal ions bound in PMs from various sources and human diseases. Meng et al. (2013) found significant association between 17 metal ions, including calcium, bound in PMs and human cardiovascular diseases, and ion properties (e.g., ion size, solubility, oxidation potential, and ability to form covalent and ionic bonds) were identified as critical factors affecting the association. Thurston et al. (2016) analyzed the relation of specific metals in $PM_{2.5}$ and ischemic heart disease. Calcium, as representative of soil particles, had an estimated hazard ratio for ischemic disease of 1.01 (95%

Table 2
Comparison of inhaled particle mass during 8-hr exposure for adult and 3-month child.

Particle Size Range, μm [a]	Particle Size CMD, nm (GSD)	Calcium Ratio in Air in Impactor Size Bin [b]	Mass Concentration in Particle μg/m^3 [c]		Total Accumulated Deposited Mass in Lung, μg during 8-hr exposure			
					Adult, >21 y		Child, 3 months	
			Total ICP/MS Elements[d]	Ca^{2+}	Total ICP/MS Elements	Ca^{2+}	Total ICP/MS Elements	Ca^{2+}
<0.25	124.88 (1.56)	0.181 (0.202)	97.63	17.67	78	14.3	27.5	4.9
0.25–0.50	316.84 (1.20)	0.179 (0.189)	70.20	12.57	48.8	8.7	18.4	3.3
0.5–1.0	583.09 (1.11)	0.132 (0.146)	21.23	2.80	18.4	2.4	5.8	0.77
1.0–2.5	1016.80 (1.14)	0.1193 (0.124)	12.10	1.44	18.7	2.2	4.0	0.48
>2.5	5558.94 (NA[e])	0.051 (0.060)	9.78	0.50	35.7	1.8	3.1	0.26
Sum	–	–	211	35	199.6	29.4	58.8	9.7
Normalized for body weight [f]	–	–	–	–	2.8	0.4	9.8	1.6

[a] Based on Impactor Size Bin (Table S2).
[b] Assumes calcium ratio 0.2 in fill water; measured calcium ratios in air in 5 size bins are shown as values in parentheses.
[c] Assumes total concentration as 211 μg/m.^{3}.
[d] Values do not include bicarbonate which could not be measured by ICP-MS.
[e] NA because N in Eqn.2 in SI is smaller than 1.
[f] Unit in μg-chemical/kg-body weight, assume adult body weight 70 kg, and 3-month child 6 kg[4].

confidence interval 0.98–1.03) per interquartile range of 43.8 ng/m^3, while $PM_{2.5}$ was 1.03 (95% confidence interval 1.00–1.06) per interquartile range of 3134.6 ng/m^3. The lower hazard ratio of calcium versus $PM_{2.5}$ suggests potential lower risks to inhalation exposure to calcium. However, the concentration of calcium tested was extremely low (10th–90th percentile of 29.6–100.4 ng/m^3) compared to our study (35 μg/m^3). The much higher dose could lead to a greater hazard ratio for inhaling calcium-containing particles. Lyu et al. (2018) estimated the deposition fraction of aspirated particles within human respiratory tract by MPPD model and investigated their oxidative potential; results showed that inhaled water-soluble metals, bound in airborne PMs, contributed 1.2-fold greater capacity to generate oxidative stress than inhaled quinones. Epidemiological evidence suggests that children exposed to metals in dust from a mining region have a higher relative risk of respiratory disease. In an associated study, mice were exposed to PM_{10} collected from this mining region. This exposure resulted in some degree of pulmonary inflammation and lung injury in the mice due to inhaling metals in airborne particles (Zychowski et al., 2019). Collectively, metal ions bound in airborne particles pose adverse health effects to mice and humans, and the oftentimes-overlooked residential scenario could lead to unexpected risks. This study provides potential for future biological study of inhalation risk from inorganic metal-containing airborne particles emitted from ultrasonic humidifiers.

Limitations of this novel study are the lack of inclusion of other fill water qualities, for example, high hardness water and high TDS water, and exposure to anions in water such as carbonate, chloride, or sulfate. Even though the concentrations of backgrounds metals/elements were low in the experimental room, they were combined with water from the ultrasonic humidifier and included in the modeled exposures from filling the humidifier with tap water. This is realistic, as a room will have background levels of particles/metals/elements that will be combined with the humidifier-emitted particles. This study focused on the investigation of a typical tap water that is low hardness and low TDS. Therefore, the linear regression and statistical analysis may not apply to other water types that may lead to extrapolation. Retained mass within human respiratory tract is also affected by dissolution, alveolar clearance, and translocation, thus the determination of deposited mass is complicated and may not be fully explained by deposition mechanism only.

5. Conclusions

This study presents detailed particle size, concentration, composition, and exposure data when a typical tap water of 75 mg/L TDS is used to charge an ultrasonic humidifier in order to change air quality through humidification in a 33.5 m^3 room with air exchange rate of 0.8–0.86 hr^{-1}.

- Emitted ≤1.0 μm particles account for ~90% of total emitted particles and 85% were essentially "dried tap water" and <0.5 μm, while >1 μm particles comprised ~10% and contained less metals and more water.
- The concentrations of metals/elements varies based on particle size and particle water content. Nonetheless, the same relative amounts of metals/elements are present in each particle. Thus, inhalation of small particles increased mass exposure to common tap water metals (e.g., calcium, sodium, magnesium), and also associated anions.
- Average indoor air particle concentrations were 211 μg/m^3-air, based on ICP-MS metals and elements without bicarbonate, which exceed USEPA $PM_{2.5}$ and PM_{10} values for ambient air.
- The size and chemical composition characterization of airborne particles emitted from ultrasonic humidifier can be combined with an inhalation model to predict deposited particle mass in the human respiratory tract.
- Relatively higher deposition fractions of emitted particles in adult and child pulmonary region than head and tracheobronchial regions indicated increased risks to lower region respiratory injury. Greater inhalation risk is confirmed for child compared to adult.
- A precautionary measure is to use distilled water to fill the ultrasonic humidifier.

Author contributions

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Additional text on equations to calculate particle size and density, 5 tables and 3 figure and with details on: 1) table of recommended water to fill ultrasonic humidifier; 2) table of MPPD model applications in prior research; 3) table of instrumentation in this study; 4) table of metals' detection limits by ICP-MS; 5) table of airway morphometry data in this study; 6) figure of experimental room setup; 7) figure of relative humidity and temperature change in the experimental room during humidifier operation; 8) figure of background metals in the room.

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