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Determination of Intranasal Deposition of Particles in Anatomically Correct Physical Models of Children and Adults and Comparison with Previous Studies

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Physical models of the respiratory system provide a method for quantifying particle deposition in humans without exposing them to toxic agents. In this study, intranasal deposition of 0.58–10 μm particles of Arizona Test Dust was quantified in 3D-printed models of 2-, 5-, and 18-year-old humans at flow rates representing sitting-awake, light-activity, light-exercise, and heavy-exercise conditions. Intranasal particle deposition was calculated as a function of impaction parameter. Results from this study were compared with previously published results in which liquid particles were used on age-matched humans and 3D models. Similar to findings from the previous studies, results from the present study showed that impaction is the predominant deposition mechanism for dry particles in intranasal airways. In addition, results for intranasal deposition in the present study showed agreement with results obtained in the previously published studies, which validates the use of these models to conduct deposition studies.

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PREFACE

This work described in this report was started in October 2019 and completed in October 2021.

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This report has been approved for public release.

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DETERMINATION OF INTRANASAL DEPOSITION OF PARTICLES IN ANATOMICALLY CORRECT PHYSICAL MODELS OF CHILDREN AND ADULTS AND COMPARISON WITH PREVIOUS STUDIES

1. INTRODUCTION AND BACKGROUND

Particulate matter released into the ambient air from pollution sources in urban and industrial environments likely poses a significant health risk for local inhabitants (Calderon-Garciduenas et al., 1998). Studies conducted on adult subjects provide strong evidence for the carcinogenic effects of occupational inhalants in the nasal cavity and sinuses (Calderon-Garciduenas et al., 1998) and the development of olfactory dysfunction with long-term exposure to environmental pollutants (Ajmani et al., 2016). Within the general population, airborne biological particulates such as bacteria and viruses lead to infections in the intranasal and lower airways. Most people (including young children) breathe through their nose when sitting awake or during light exercise (Cheng, 2014). Thus, the intranasal region (specifically, the nasal airways and nasopharynx) is the first line of defense against inhaled particles during nose-breathing conditions: it protects the lower respiratory tract from toxic agents by filtering out most inhaled particles before they can damage the lungs (Proctor and Andersen, 1982). Understanding particle deposition within intranasal airways is important for the study of airborne hazards because the location and quantity of particle deposition affects humans' responses to hazardous aerosol exposures.

Many researchers have performed in vivo studies of intranasal liquid particle deposition in adults and children (ICRP, 1994; Becquemin et al., 1991; Kesavanathan et al., 1998; Kesavanathan and Swift, 1998; Kesavan et al., 2000; Bennett et al., 2008). Two primary challenges associated with this work are (1) in vivo particle deposition studies require approvals from institutional ethical and scientific review boards; and (2) to obtain good data, accurate breathing maneuvers must be performed by all of the research subjects. Human study approvals take time and require justification, and in some cases, they are not approved. In addition, some subjects are unable to correctly perform the required breathing maneuvers. Young children, especially, may not be able to participate in these studies, which would result in no data being obtained for that age group. The use of anatomically correct respiratory system models for particle deposition studies provides a solution to these problems.

Anatomically correct physical models that are based on stereolithography (SL) and 3D-printing technologies provide a means for quantifying particle deposition in humans without exposing subjects to potentially toxic agents or relying on their ability to perform correct breathing maneuvers. Several investigators have quantified liquid particle deposition in physical models that represent the intranasal airways of healthy infants and children (Javaheri et al., 2013; Janssens et al., 2001; Storey-Bishoff et al., 2008; Golshahi et al., 2011; Xi et al., 2012; Zhou et al., 2013, 2014). In the present study, the intranasal deposition of dry particles in vitro was evaluated using anatomically correct 3D models that were based on 2-, 5-, and 18-year-old human subjects. These results were compared with results from three previously published in vitro studies of liquid particles in which 3D replicas were used that were based on age-matched human subjects. Intranasal deposition in the 5- and 18-year-old models from the present study was also compared with results from three studies of intranasal deposition in vivo from age-matched humans.

The test subjects, equipment, and test materials used in these six studies are described herein.

Kesavanathan and Swift, 1998. This study determined the effects of particle size, flow rate, nostril shape, and nasal passage geometry on nasal particle deposition efficiency in 10 healthy, nonsmoking adults (7 males and 3 females). Study subjects were healthy Asian American and European American individuals aged 23–60 years. Subjects were exposed to a polydisperse diethylhexyl sebacate aerosol that was generated and released into a small chamber by a high-voltage electrospray. Sampling ports were used to connect a nosepiece to the aerosol chamber and a mouthpiece to a vacuum pump. Subjects inhaled deeply, closed their glottis, placed the nosepiece over their nose, and placed the mouthpiece in their mouth. The vacuum pump pulled the aerosol in through the nose and out through the mouth at three constant flow rates. Deposition was determined for 13 particle sizes that ranged from 2.1 to 6.3 μm. Tracheal deposition was not included in these measurements. An Aerodynamic Particle Sizer spectrometer (APS; TSI, Inc.; Shoreview, MN) was used to quantify the particle sizes and concentrations of aerosol that entered the nose and exited the mouth.

Storey-Bishoff et al., 2008. Particle deposition was studied in 11 infant (aged 3–18 months) nasal replicas that were constructed using rapid prototyping. Deposition in the 18-month-old (i.e., 1.5-year-old) replica was selected to compare with deposition in our 2-year-old model because it was closest in age. Nasal geometry for the 18-month-old replica was obtained from computed tomography (CT) scans of the subject in the supine position. The nasal replica included the area from the nares to the larynx. Test particles ranged in size from 0.8 to 5.3 μm, and particles passed through the replica during simulated tidal breathing (only inhalation flow was directed through the model). An electrical low-pressure impactor (ELPI) was used to measure particle counts upstream and downstream of the replica to quantify the particle deposition. A six-jet Collison nebulizer generated polydisperse aerosols of sunflower oil that ranged in size from 0.8 to 5.3 μm. A laboratory-constructed breathing machine produced a sine-wave breathing pattern.

Zhou et al., 2014. Intranasal particle deposition was evaluated in infant and child replica airways, and the results were compared with those for an adult replica. Data from the 3- and 5-year-old child and the adult replicas were selected to compare with our study results. Nasal airway replicas (including areas from the nostrils to the larynx) were developed based on CT data and were 3D-printed using rapid prototyping. Experiments were conducted with constant airflow rates that represented resting conditions. A vibrating-orifice aerosol generator produced monodisperse sodium fluorescein-tagged oleic acid aerosols that ranged in size from 2 to 28 μm. A filter was attached to each model to collect particles that were not deposited in the model. After the experiments were complete, the filters and replicas were rinsed to collect and quantify the particles.

Becquemin et al., 1991. In vivo nasal deposition of monodisperse polystyrene beads (1, 2.05, and 2.8 μm) was investigated in 12 children aged 5.5 to 11.5 years and in 8 children aged 12 to 15 years. Those results were compared with results for 10 adults. Average deposition data from the 5.5- to 11.5-year-old children and the adults were compared with data from the 5- and 18-year-old models, respectively, from the present study. Deposition was

quantified by measuring the inhaled and exhaled aerosol concentrations during nose and mouth breathing. Aerosols were created using a Tri-Jet air-compressed aerosol generator (Fogmaster; Deerfield Beach, FL), and aerosol concentrations were measured by laser velocimetry. Breathing patterns were selected to represent resting and moderate exercise conditions.

Bennett et al., 2008. Particle deposition in vivo was evaluated in 12 children (aged 6–10 years) and 11 young adults (aged 18–27 years), using 1 and 2 μm particles, during resting and mild to moderate exercise conditions. Average deposition data for these 12 children and 11 adults were compared with results from our 5- and 18-year-old models, respectively. Carnauba wax particles were produced using a monodisperse aerosol generator (known as a MAGE condensation generator). Deposition was quantified by laser photometry, which determined the inhaled and exhaled concentrations. Particle deposition was measured while subjects performed nasal and oral breathing.

Golshahi et al., 2011. Deposition of 0.5–5.3 μm sunflower oil particles was assessed in nasal airway replicas of 14 children aged 4–14 years. Those results were compared with results obtained from five adult nasal airway replicas. CT scans and rapid prototyping were used to fabricate replicas of the nasal passages. Each test replica included the region from the face to the upper trachea. To use the best age-matched data, only particle depositions from the 4-, 5-, and 6-year-old subjects and the five adults were compared with our test results. Four cyclic breathing maneuvers were simulated by a pulmonary waveform generator. Particles were generated by a Collison nebulizer, and particle size and concentration were measured by an ELPI.

Table 1 summarizes the methods used in each of these studies. Particle deposition data from these studies were compared with data obtained in the present study and are reported in the Results section.

Table 1. Method Information: Age-Matched Data from Previous and Present Studies

Author, Year	*n**	Age Range (years)	Model or In Vivo	Particle Sizes Tested (µm)	Inspiratory Flow	
					Constant or Cyclic	Rate (L/min)
Kesavanathan and Swift, 1998	10	23–60	In vivo	2.1–6.3	Constant	15, 25, 35
Storey-Bishoff et al., 2008	1	1.5	Model	0.8–5.3	Cyclic	5.5–11.2
Zhou et al., 2014	1	3	Model	2–28	Constant	7
	1	5			Constant	10, 20
	1	Adult			Constant	20
Becquemin et al., 1991	12	5.5–11.5	In vivo	1, 2.05, 2.8	Cyclic	17.04, 27.96
	10	21–54			Cyclic	27.3, 63.42 (mean inspiratory flow rates)
Bennett et al., 2008	12	6–10	In vivo	1, 2	Cyclic: nose and mouth breathing; total ventilation	6.6 to ~22
	11	18–27			Cyclic: nose and mouth breathing	7.6 to ~34
Golshahi et al., 2011	6	4–6	Model	0.5–5.3	Cyclic	4.86, 6.37, 9.20, 12.25
	5	Adult			Cyclic	5.6
Present study	1	2	Model	0.5–10	Constant	2.5, 5, 7.3, 10.2
	1	5			Constant	4, 8, 9.5, 13.3
	1	18			Constant	10, 15, 25, 35

**n*, number of study subjects.

2. METHODS

2.1 Model Production

For the present study, anatomically correct physical models of the head and intranasal airways of 2-, 5-, and 18-year-old humans were produced after CT head scans (obtained with the research subjects in the supine position) were transformed into SL format. The 2-year-old child was an African American female; the 5-year-old child was an African American male; and the 18-year-old adult was a male of unknown ethnicity. Details regarding the CT scan selection and model production are provided by Laube et al. (2015). Each completed model consisted of a soft, flexible face with closed lips and a nose with patent nostrils, nasal vestibule, nasal valve area, main nasal airway, and nasopharynx. The three models are shown in Figure 1. To simulate the mucus coating of the airway, the inside surfaces of the models were precoated with nebulized corn-oil droplets.

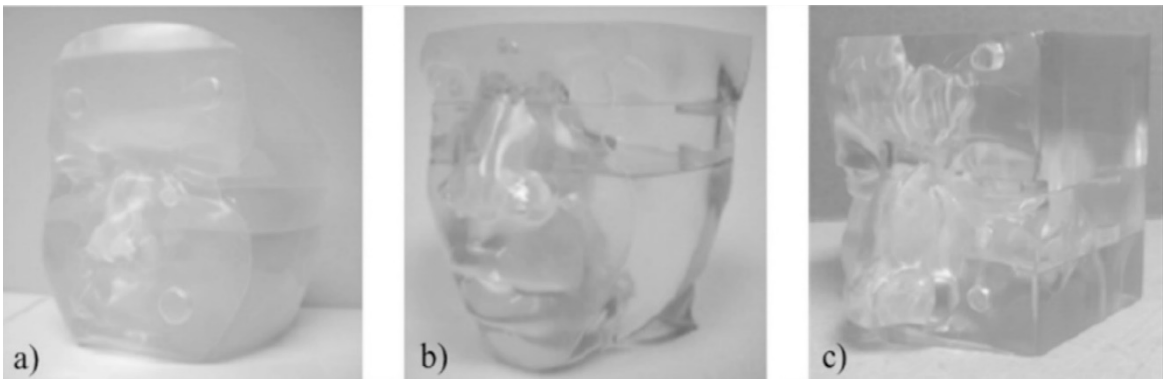

Figure 1. The three models used in this study: (a) 2-year-old African American female; (b) 5-year-old African American male; and (c) 18-year-old adult male of unknown ethnicity.

Each model was tested under flow-rate conditions that represented sitting-awake, light-activity, light-exercise, and heavy-exercise breathing conditions for 2- and 5-year-old children and an 18-year-old adult (Table 2). The sitting-awake and light-exercise flow rates were similar to those reported by the International Commission on Radiological Protection (ICRP, 1994) for all age groups. Flow rates of 15 L/min (light activity) and 35 L/min (heavy exercise) for the 18-year-old model matched the flow rates previously reported by Kesavanathan et al. (1998) in adults during nasal breathing. Flow rates for the 18-year-old model did not exceed 35 L/min for any breathing condition because higher values would have surpassed the pump capability. Flow rates of 5 L/min (light activity) and 10.2 L/min (heavy exercise) for the 2-year-old model and 8 L/min (light activity) and 13.3 L/min (heavy exercise) for the 5-year-old model represented similar increments from the sitting-awake test conditions that were used for the adult model.

Table 2. Inspiratory Flow Rates Representing Sitting-Awake, Light-Activity, Light-Exercise, and Heavy-Exercise Conditions for 2- and 5-Year-Old Children and an 18-Year-Old Adult

Model	**Inspiratory Flow Rate (L/min)**			
	Sitting Awake	**Light Activity**	**Light Exercise**	**Heavy Exercise**
2 year old	2.5	5	7.3	10.2
5 year old	4	8	9.5	13.3
18 year old	10	15	25	35

2.2 Experimental Setup

The experimental setup is shown in Figure 2. Models were individually placed in a large Plexiglas chamber (60 × 36 × 48 in.) and were connected to an APS (model 3321). All measurements were made with one APS to eliminate any sampling differences that might occur with the use of different units.

The APS pulled 1 L/min of air through its inner nozzle. Because these experiments were designed to test deposition in the model at flow rates above 1 L/min, an external vacuum pump with a flow meter was used to pull additional air through the downstream and upstream sides of the setup. The external pump was connected to the setup via three tubes (Figure 2). During exposures, the pump pulled a constant inspiratory airflow to achieve total flow rates through the downstream and upstream sides of 10, 15, 25, and 35 L/min for the 18-year-old adult; 4, 8, 9.5, and 13.3 L/min for the 5-year-old child; and 2.5, 5, 7.3, and 10.2 L/min for the 2-year-old child. These flows represented breathing rates for humans under sitting-awake, light-activity, light-exercise, and heavy-exercise conditions, respectively.

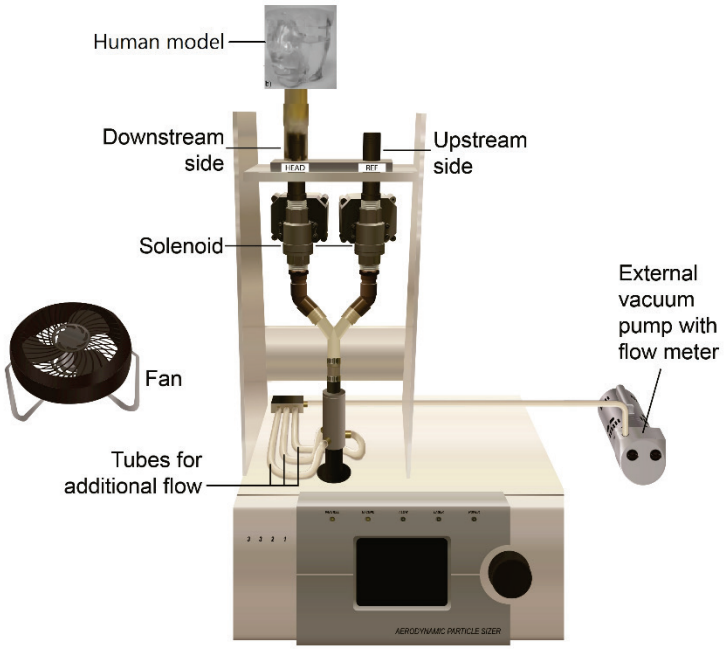

Figure 2. Experimental setup inside the test chamber (60 × 36 × 48 in.).

2.3 Mucus Simulation

Before the models were exposed to the test aerosol, an aerosol of Mazola corn oil (ACH Food Companies; Oak Brook Terrace, IL) was generated by a nebulizer and drawn through the models by a vacuum pump. The corn oil aerosol coated the inside surfaces of the model to simulate naturally occurring airway mucus.

2.4 Test Aerosol

The test aerosol was Arizona Test Dust (ATD), a solid, polydisperse aerosol that contains dry particles ranging in size from 0.54 to 9.64 µm. A two-fluid nozzle system was used to aerosolize approximately 0.06 ± 0.004 g of ATD into the chamber during each exposure. To ensure a uniform ATD concentration in the chamber, a fan mixed the air for 45 s before sampling and throughout the experiment (Figure 2). In addition, upstream and downstream particle

concentrations were measured by the APS without the model. The difference in upstream and downstream particle concentrations was less than 1% for 1–10 μm particles. This meant that particles entering the model and the upstream channel were similar in concentration. As measured by the APS, total aerosol concentration in the chamber was less than 1000 particles/cm^3. The manual for the APS indicates that at 1000 particles/cm^3, there is less than 2% coincidence for 0.5 μm particles and less than 6% coincidence for 10 μm particles.

2.5 APS Sampling

During air mixing, the APS sampled air from the upstream side for 20 s (i.e., upstream measurement no. 1). The operator then used the solenoid switches to close the upstream channel and open the downstream channel (Figure 2), and the APS sampled from the downstream side for 20 s (i.e., downstream measurement). The operator then closed the downstream channel, opened the upstream channel, and again sampled from the upstream side for 20 s (i.e., upstream measurement no. 2). Each switching procedure required 10 s. Upstream measurement no. 2 was used as the upstream measurement no. 1 for the next run. Upstream measurement nos. 1 and 2 were averaged. Each downstream measurement and the average of the two upstream measurements were recorded as a run. For each flow rate, 30 runs were completed.

2.6 Particle Deposition

Particle deposition for each particle size bin (η_i) was expressed as a percentage by dividing the downstream measurement (aerosol exiting the model) by the average of the two upstream measurements, subtracting from 1, and multiplying by 100:

$$\eta_i = \left[1 - \frac{\text{Aerosol exiting the model (downstream)}}{\text{Average upstream measurement}}\right] \times 100 \quad (1)$$

Particle deposition was plotted as a function of particle size for all models and all airflow rates. The impaction parameter was calculated as

$$\text{Impaction parameter} = d^2 Q \quad (2)$$

where d is the particle diameter, and Q is the flow rate.

2.7 Data Analysis

The percent deposition was plotted as a function of particle size for each flow rate and model. Deposition was also quantified, and results were compared as a function of impaction parameter for each model (as described by eq 2). Results from the present study were compared with previously published results, including in vivo and model data from age-matched subjects.

3. RESULTS

3.1 Particle Deposition as a Function of Particle Size, Airflow Rate, and Age

Figure 3 shows intranasal deposition in the 2-, 5-, and 18-year-old SL models as a function of particle size for airflow rates representing sitting-awake, light-activity, light-exercise, and heavy-exercise conditions. For each breathing condition, the percent deposition increased as particle size and flow rate were increased.

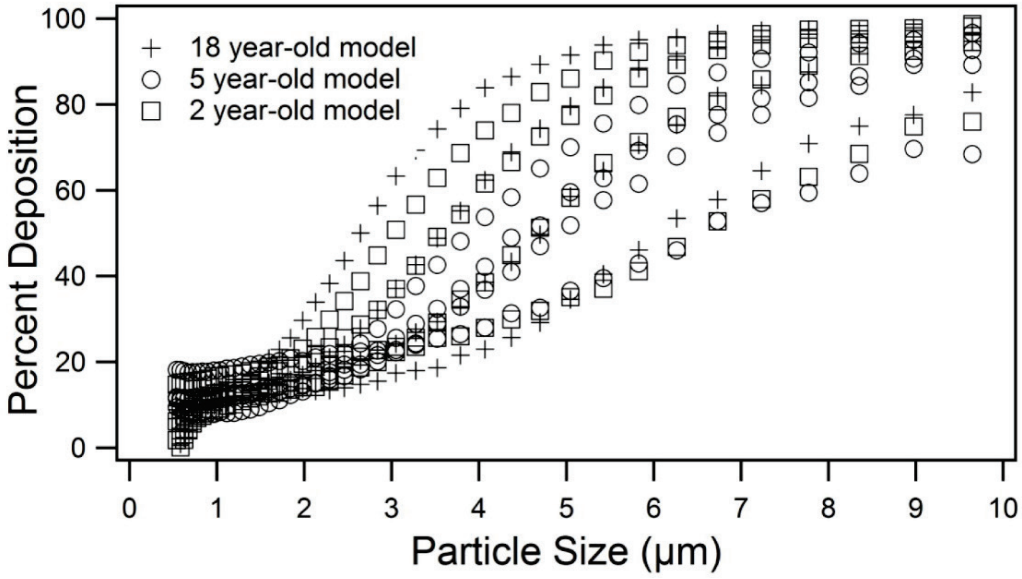

Figure 3. Percentage of intranasal deposition in 2-, 5-, and 18-year-old models.

3.2 Particle Deposition as a Function of Impaction Parameter

Figure 4 shows the intranasal deposition percentages identified for the 2-, 5-, and 18-year-old SL models for all size bins and inspiratory flow rates (shown in Table 2) plotted as a function of impaction parameter. Data that appear as disparate points in Figure 3 appear more closely associated in Figure 4, and data for each model fell on its own discrete best-fit curve. A large degree of variability still existed between the models. However, Figure 4 shows that for a given impaction parameter, intranasal deposition for the 2- and 5-year-old models was greater than it was for the 18-year-old model (Kesavan et al., 2022). In addition, particle deposition for the 2-year-old model was greater than that for the 5- and 18-year-old models (Kesavan et al., 2022).

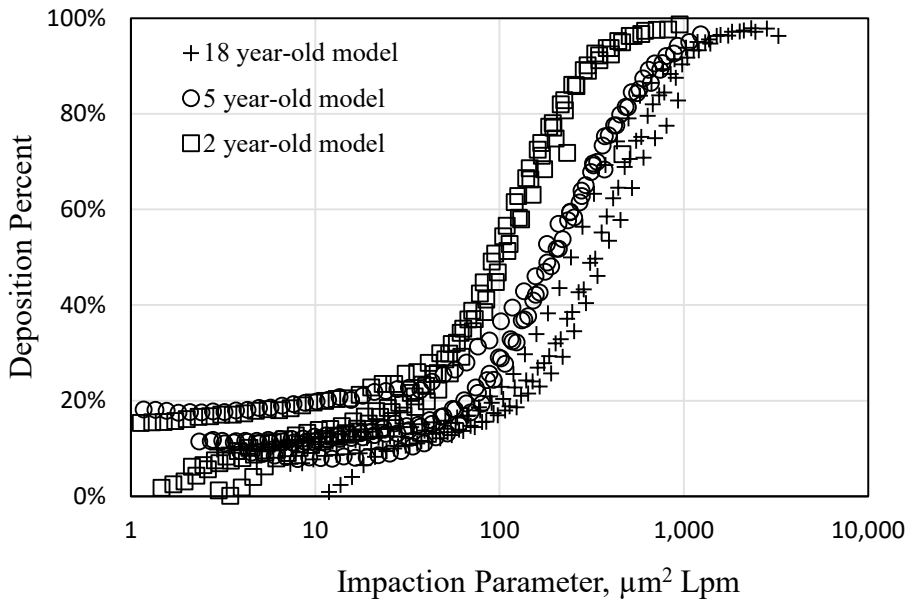

Figure 4. Percentage of intranasal deposition as a function of impaction parameter for the 2-, 5-, and 18-year-old models. Lpm, liters per minute.

3.3 Comparison of Intranasal Deposition in 2-Year-Old Model (Present Study) with Results from Previous Model Studies

As shown in Figure 5, intranasal deposition in the 2-year-old model from the present study was compared with deposition results in the 1.5-year-old model from Storey-Bishoff et al. (2008) and the 3-year-old model from Zhou et al. (2014). Deposition data from these two previously published studies tracked well with data for the 2-year-old model in the present study.

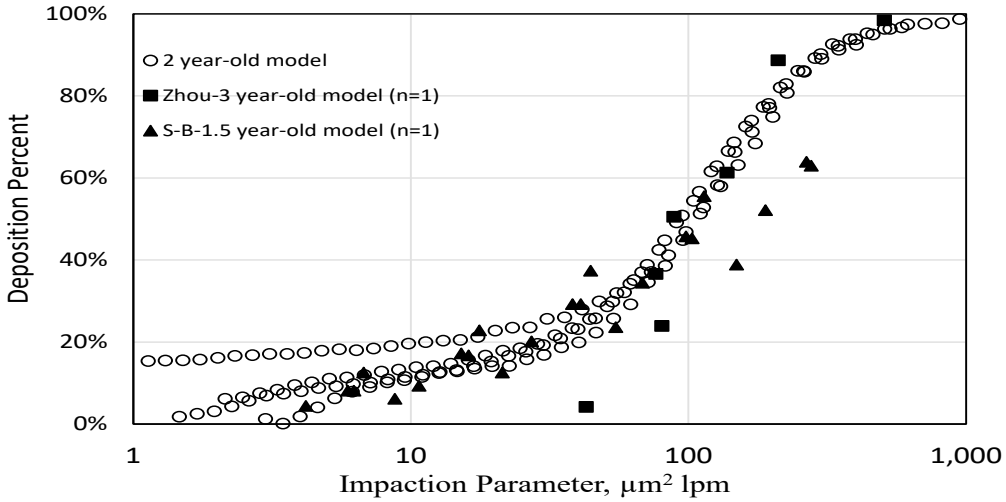

Figure 5. Percentage of intranasal deposition for the 2-year-old model in the present study compared to deposition data from Zhou et al. (2014) and Storey-Bishoff (S-B) et al. (2008).

3.4 Comparison of Intranasal Deposition in 5-Year-Old Model (Present Study) with Results from Previous In Vivo and Model Studies

Intranasal deposition in the 5-year-old model from the present study was compared with in vivo results from Becquemin et al. (1991) and Bennett et al. (2008) and with model results from Golshahi et al. (2011) and Zhou et al. (2014). For some models in the Golshahi study, deposition was similar to that for the 5-year-old model in the present study; however, deposition in the other models was significantly less (Figure 6). In the Zhou et al. (2014) study, deposition was consistently less than that obtained for the 5-year-old model in the present study (Figure 6). Differences in percent deposition for these studies could be due to intersubject variability, perhaps as a function of individual anatomical differences in intranasal airways.

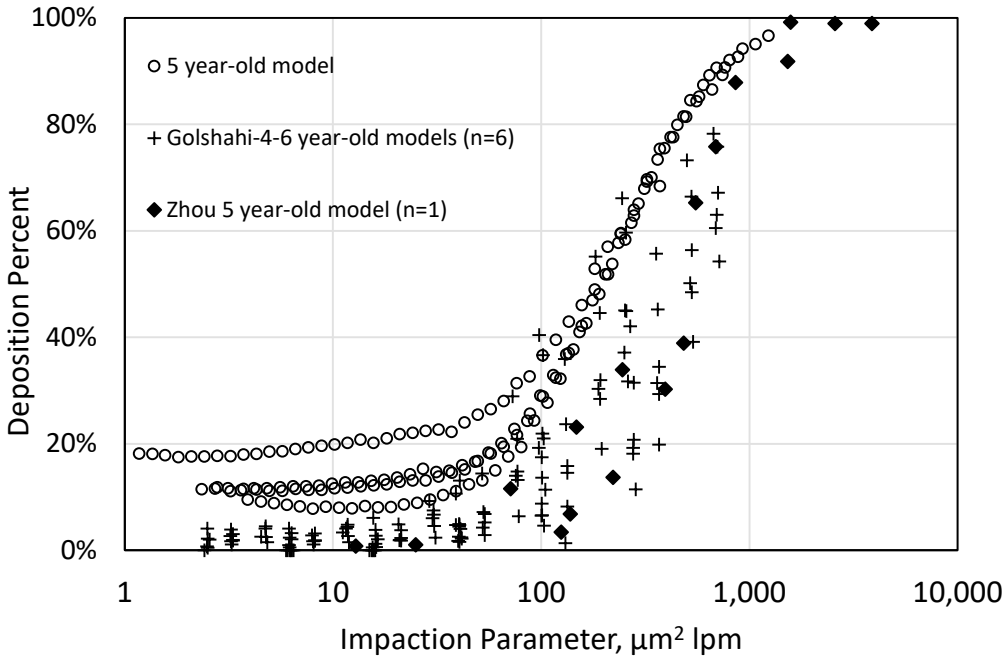

Figure 6. Percentage of intranasal deposition for the 5-year-old model in the present study compared with deposition data from Golshahi et al. (2011) and Zhou et al. (2014).

Intranasal deposition was lower in the in vivo studies of Bennett et al. (2008) and Becquemin et al. (1991) than in the 5-year-old model in the present study. This may be attributable to differences in the study subjects' age and anatomic development. The majority of subjects in the two in vivo studies were older than 5 years; subjects' ages ranged between 6 and 10 years and between 5.5 and 11.5 years in the Bennett and Becquemin studies, respectively. In those relatively older subjects, deposition appears to more closely resemble that in the 18-year-old model of the present study, as shown in Figure 7.

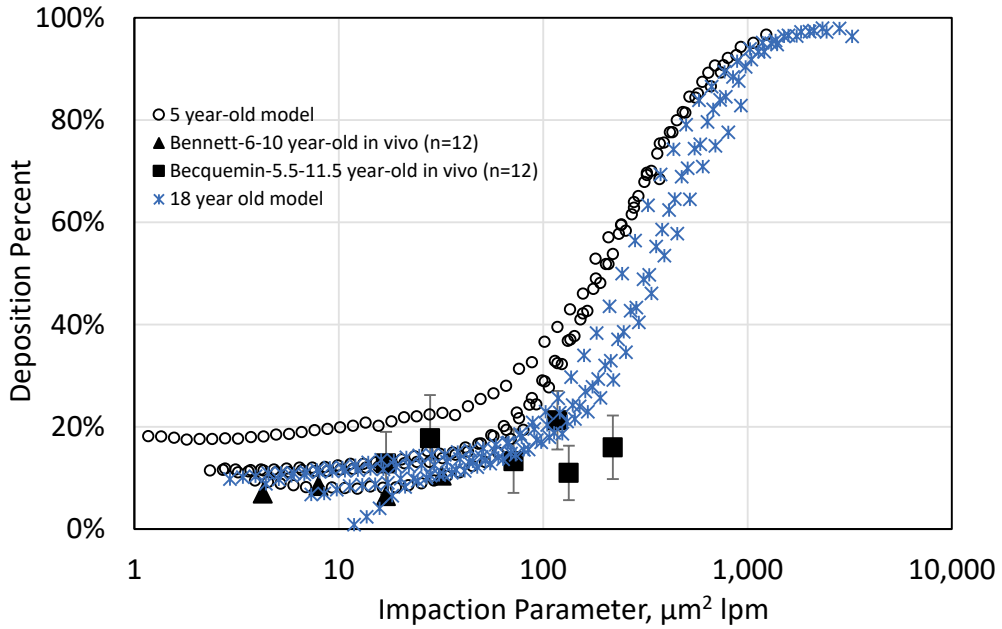

Figure 7. Percentage of intranasal deposition for the 5- and 18-year-old models in the present study compared with deposition data from Bennett et al. (2008) and Becquemin et al. (1991).

3.5 Comparison of Intranasal Deposition in 18-Year-Old Model (Present Study) with Results from Previous In Vivo and Model Studies

Intranasal deposition in the 18-year-old model from the present study was compared with that reported in in vivo studies of Becquemin et al. (1991), Bennett et al. (2008), and Kesavanathan and Swift (1998) and the model studies of Golshahi et al. (2011) and Zhou et al. (2013) (Figure 8). The majority of data from these previously published model and in vivo studies fit well with the 18-year-old model deposition data from the present study.

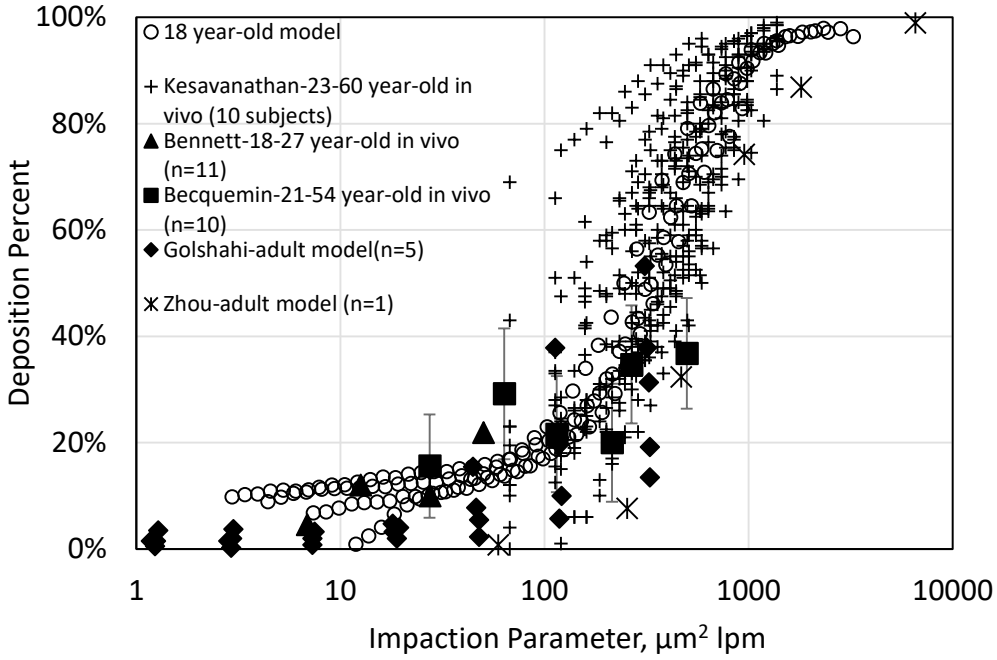

Figure 8. Percentage of intranasal deposition for the 18-year-old model in the present study compared with data from Becquemin et al. (1991), Bennett et al. (2008), Kesavanathan et al. (1998), Golshahi et al. (2011), and Zhou et al. (2013).

4. CONCLUSION

This study evaluated the intranasal deposition of dry particles ranging in size from 0.58 to 10 μm in anatomically correct SL models. The models were built based on CT scans of 2-, 5-, and 18-year-old human subjects during inspiration only at airflow rates that represented sitting-awake, light-activity, light-exercise, and heavy-exercise conditions. In general, when calculated as a function of impaction parameter, intranasal particle deposition was greatest in the 2-year-old model as compared with the 5- and 18-year-old models. Results from this study were compared with previously published results in which liquid particles were used in age-matched humans and 3D models. Similar to those previous studies, results from the present study showed that impaction is the predominant deposition mechanism for dry particles in the intranasal airways. In addition, the measurements of intranasal deposition obtained in the present study are in good agreement with results from the previously published studies, which validates the use of these models for conducting deposition studies.

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ACRONYMS AND ABBREVIATIONS

APS	Aerodynamic Particle Sizer
ATD	Arizona Test Dust
CT	computed tomography
ELPI	electrical low-pressure impactor
ICRP	International Commission on Radiological Protection
Lpm	liters per minute
SL	stereolithography

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