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Dosimetry Implications of Upper Tracheobronchial Airway Anatomy in Two Mouse Varieties

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ABSTRACT

Strain- and variety-related differences in responses of mice have been reported for a variety of inhaled particulate and gaseous materials. It is important to understand the potential contributions to such responses of differences in delivered doses to the respiratory tract as well as differences in biochemical processes. Deposition doses of inhaled particles are influenced by several factors, including airway anatomy, ventilation, and particle characteristics. Tracheobronchial airway morphometry for airway generations 1–6 of the BALB/c mouse was generated using replica lung casts prepared in situ. Measurements were performed on two groups: control and ovalbumin-sensitized male BALB/c mice. These measurements were compared with previously published airway morphometry of male $B6C3F_1$ mice. Sensitization did not significantly change measured airway dimensions in the BALB/c mouse. However, the two mouse varieties had significant differences in airway anatomy. The differences found in airway anatomy between mouse varieties correlated with differences in body length and chest circumference. Particle deposition predictions for both varieties of mice were performed for unit density spherical particles from 0.1 to 10 μm in diameter at two ventilation rates using a published aerosol dosimetry computer code. Particle deposition in the proximal tracheobronchial tree ranged up to 3 times greater for the BALB/c mouse for a 2 μm particle diameter and high ventilation rate. These differences in predicted particle deposition suggest that observed strain and variety differences in response to inhaled particulate matter may be in part due to differences in delivered doses to the respiratory tract. Anat Rec 268: 59–65, 2002.

Key words: mouse; airway morphometry; variety differences; aerosol deposition; lung casts

Laboratory mice have been used extensively in inhalation toxicology studies and there is an associated growing database on the toxicologic effects of aerosols and gases under a variety of conditions. For example, Benson et al. (1987) and Dunnick et al. (1989) used $B6C3F_1$ mice to study the toxicity of inhaled nickel subsulfide, nickel oxide, and nickel hexahydrate, and Korsak et al. (1998) used BALB/c mice to study the acute toxicity of inhaled 1-methylnapththalene and 2-methylnaphthalene. It has also been observed that $B6C3F_1$, C57B1/6, and DBA/2 mice demonstrate different induction levels of genotoxicity and hematotoxicity to chronic inhalation of benzene (Luke et al., 1988). More recently, Fernandez et al. (1999) found differences in responses of two mouse strains (BALB/c and C57BL/6) to two common inhaled spasmogens: carbachol and serotonin. Strain-related differences in response are usually assumed to be related only to differences in metabolism or tissue sensitivity. It is important to understand whether or not these differences in response are also influenced by different delivered doses to the respiratory tract, in addition to the effects of differences in biochem-

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ical processes. In addition to strain- and variety-related differences, animal models that are created by pretreatment to produce diseases may have altered dose patterns. In a recent review, the National Research Council indicated that there is a need for ascertaining whether differences in delivered doses exist between normal and compromised animals of the same strain that are used in studies of particulate air pollutants (National Research Council, 2001). When animal variety or manipulation prior to exposure could modify doses from inhaled materials, it is important to quantify the alteration in dose.

For inhaled particulate matter, airway anatomy, ventilation parameters, and particle characteristics largely determine the initial sites and efficiencies of particle deposition within the respiratory tract. Numerous mathematical models for calculating particle deposition within the respiratory tract have been developed using data representing these parameters (Findeisen, 1935; Morrow et al., 1966; Taulbee and Yu, 1975; Yeh and Schum, 1980; Heyder and Rudolf, 1984; International Commission on Radiological Protection, 1994; National Council on Radiation Protection and Measurements, 1997; Rijksinstituut Voor Volksgezondheid en Milieu, 1999a, b). Some of these models have been extensively used for risk assessment purposes. The models have been verified for simple particles (spherical, nonhygroscopic, etc.) in human clinical studies (International Commission on Radiological Protection, 1994; National Council on Radiation Protection and Measurements, 1997). Use of these dosimetry models in animal inhalation toxicology studies could provide a priori information on predicted particle deposition in various regions of the respiratory tract. Such information would aid in designing the studies and extrapolating the results to humans. Use of these dosimetry models in animal toxicology requires quantitative measurements of the airway anatomy of animals. Such measurements have been performed on a few species, including dogs, ferrets, guinea pigs, rats, and mice (Kilment et al., 1973; Raabe et al., 1976; Horsfield and Cumming, 1976; Horsfield et al., 1982; Oldham et al., 1990, 1994; Koblinger et al., 1995). Of all the strains and varieties of laboratory mice, tracheobronchial morphometry data suitable for particle deposition calculations is only available for the $B6C3F_1$ mouse (Oldham et al., 1994), and no such data have been published for lung-compromised mice.

The purposes of this study were to estimate inhaled particle doses in two types of mice and in one variety that had been pretreated to create a model for asthma. Tracheobronchial airway morphometry on the $B6C3F_1$ mouse was obtained from our published measurements made from replica casts (Oldham et al., 1994). Tracheobronchial airway morphometry on the BALB/c mouse was generated using replica lung casts and measurement techniques that matched those used in the $B6C3F_1$ mouse study; both normal and airway-sensitized BALB/c mice were available for study. As will be shown, sensitization (and subsequent aerosol challenge) did not significantly change measured airway dimensions, thus permitting the two BALB/c groups to be combined for comparison to the $B6C3F_1$ mice.

The specific objectives of this study were to: 1) determine whether there are significant differences in airway dimensions in the upper tracheobronchial tree between two different mouse varieties (B6C3F1 and BALB/c); 2) determine whether sensitization with ovalbumin altered airway dimensions in BALB/c mice; and 3) determine the potential effect of anatomical differences on the predicted initial deposition dosimetry of inhaled particulate matter. Ideally, all of the airways of the respiratory tract would be measured in a study of this type. However, practical limitations led to measuring airway lengths, diameter, branch angles, and inclination angles for only the first six generations (63 airways) of the tracheobronchial tree in six of the 20 mice used in this study.

MATERIALS AND METHODS

The 20 animals used in this study were specific pathogen-free male BALB/c mice that were 6 weeks old on delivery from Charles River (Wilmington, MA). All animals were housed in isolator cages and provided food and water ad libitum. Animals were randomly selected and placed into two groups. Group 1 was the control group. Group 2 was sensitized with an intraperitoneal (i.p.) injection of ovalbumin with alum, and 2 weeks later was challenged on 4 consecutive days with a 1-hr exposure to aerosolized ovalbumin (Hamelmann et al., 1999). The sensitized mice were involved in a large air pollution study and the investigators in that study were interested in any information concerning airway structures that could alter deposition of inhaled pollutants. The groups were of unequal body sizes since the animals in the second group were held 2 months longer after delivery from the supplier than the animals in first group. In preparation for lung casting, each group of animals was injected i.p. with a lethal dose of sodium pentobarbital (120 mg/kg) in accordance with a protocol approved by the institutional animal care and use committee. Group 2 was euthanized 24 hr after its final aerosol ovalbumin challenge. Silicone rubber (Silastic E, Dow-Corning, Midland, MI) replica lung casts

TABLE 1. Characteristics of the BALB/c mice used for airway morphometry (mean ± S.D.)

Mouse group	Age (days)	Weight (g)	Length (rump to snout) (cm)	Chest circumference at	
				Axilla (cm)	Xyphoid (cm)
Normal	67	24.4	9.5	7.3	7.6
Normal	67	25.9	9.7	7.3	7.8
Normal	67	21.2	9.3	7.3	7.5
Average (n = 3)	67 ± 0	23.8 ± 2.4	9.5 ± 0.2	7.3 ± 0	7.6 ± 0.2
Sensitized	117	26.8	10.1	6.8	8.4
Sensitized	117	26.8	10.3	6.8	7.6
Sensitized	117	26.3	10.2	7.0	7.6
Average (n = 3)	117 ± 0	26.6 ± 0.3	10.2 ± 0.1	6.9 ± 0.1	7.7 ± 0.5

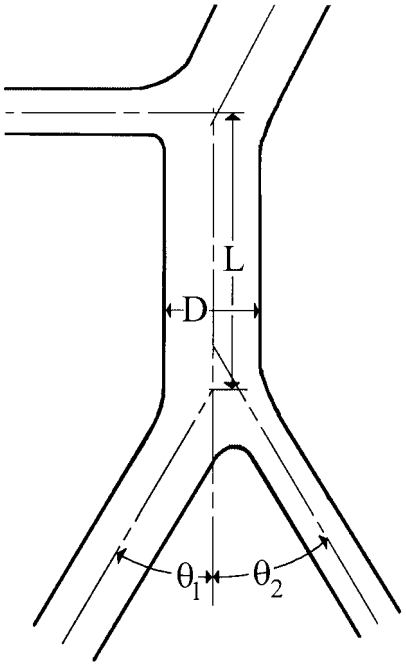

Fig. 1. An idealized airway branch defining the airway length (L), diameter (D) of the parent airway, and branch angle of the two daughter airways (θ_1 and θ_2).

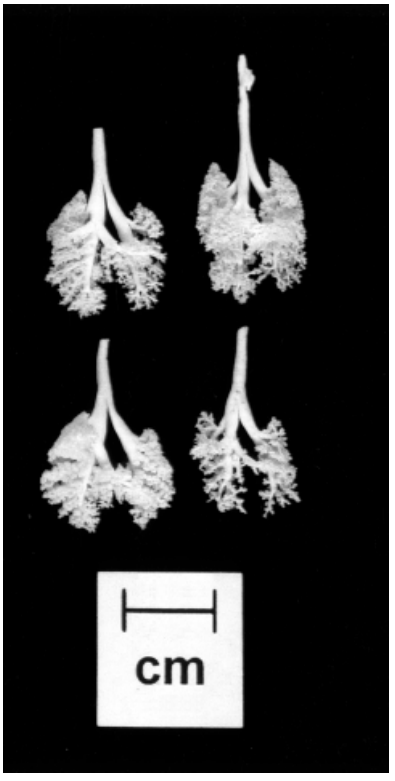

Fig. 2. Sample replica lung casts from BALB/c mice (left) and $B6C3F_1$ mice (right).

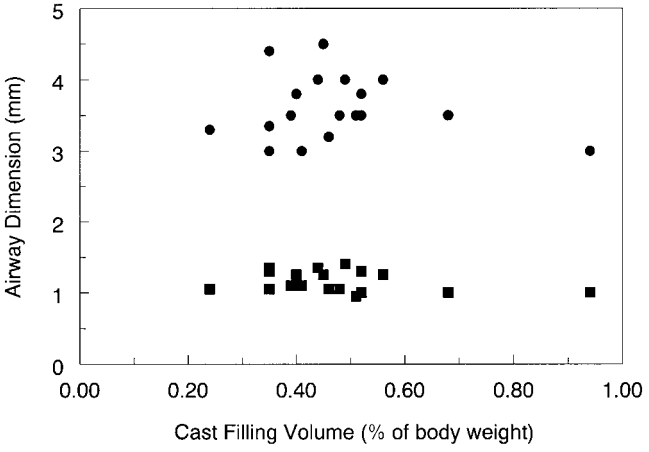

Fig. 3. Airway length (●) and diameter (■) for the right main bronchus as a function of cast filling volume expressed as a percentage of body weight. Data are from the 20 replica airway casts.

were made in situ using the saline replacement technique of Phalen et al. (1973). The technique as adapted for casting the mouse tracheobronchial tree has been published (Oldham et al., 1994). Briefly, this technique involves administration of a lethal dose of sodium pentobarbital, cannulation of the trachea between the third and fifth cartilaginous rings, ventilation of the lung with carbon dioxide for a minimum of 10 breaths at a pressure ≤ 25 cm H_2O, and filling the lung with vacuum-degassed saline (volume in ml = 0.35% of body mass in grams). These steps are necessary to remove air from the lungs. Following these preparatory procedures, Silastic E silicone rubber casting material is slowly injected at 0.15–0.2 ml/min via a syringe pump to a target volume in milliliters of 0.35% of the animal body mass in grams. This casting method produces replicas that are nearly ideal for tracheobronchial morphometry. Silastic E silicone rubber was selected because of its physical properties for cured strength, reproduction of detail, and extremely low shrinkage. After 24–30 hr of curing in situ, the lungs were removed and digested in 6–8 molar NaOH. The resulting replica casts were pH neutralized in acetic acid, washed in a detergent solution, and rinsed in distilled water. The replica lung casts were stored submerged in isopropyl alcohol in airtight glass vials.

Tracheobronchial anatomical data on the first six generations (Trachea = generation 1) were obtained from morphometric measurements of the three most complete replica lung casts from each group of animals. Table 1 shows the individual animal and group characteristics of the BALB/c mice used for morphometric measurements. A unique binary identification number was assigned to each airway (Phalen et al., 1978). The length, diameter, and branching angle were measured for each airway in generations 1–6. The inclination of the airway to the gravity force vector was measured whenever possible for each of these airways. Figure 1 shows an idealized airway segment that defines the measured airway length and diameter of a parent airway together with the branch angles of the two daughter branches. Note that airway lengths are defined such that adding the lengths along an airflow path traversing several generations yields an estimate of the

total path length. Inclination to gravity was defined for the mouse trachea as 90°. This fixed the reference orientation of the replica lung cast for determination of the each airway's inclination to gravity. The small dimensions of the lung casts necessitated use of magnifying loupes with length and angle scales of 0.1 mm and 1° resolution, respectively. For comparison purposes airway measurements were averaged by airway generation for each animal after the scheme used for humans by Weibel (1963). These average values for each airway generation for each individual animal were then averaged for each group to establish a typical path proximal tracheobronchial geometry for each group.

To calculate tracheobronchial deposition efficiencies for inhaled particles, the National Council on Radiation Protection and Measurements (1997) dosimetry model computer code was used along with two ventilation values: 25 and 50 ml/min. These values were obtained from the equation of Guyton (1947) relating ventilation to body mass. Also input into the dosimetry computer code were the airway geometry (determined in this study) and a range of unit density (1 g/cm^3) particle diameters. The two ventilation rates were used to cover the physical activity range of resting to a moderate level of activity. For a mouse variety comparison, identical deposition calculations were performed using the published airway morphometry of the B6C3F$_1$ mouse (Oldham et al., 1994) that was obtained from replica lung casts prepared and measured in the identical manner used for the BALB/c mice. The effect of nasal deposition was taken into account using the experimental data for the CF$_1$ mouse of Raabe et al. (1988) and modified by the approach of Oldham et al. (1994) for both mouse varieties. This method was necessary because predictive models for deposition of aerosol particles in the nose have not been developed. Therefore, any differences in nasal deposition were not considered.

RESULTS

A total of 20 replica lung casts were produced. Figure 2 shows sample casts from both mouse types. Although the target silicone rubber injection mass (approximated by volume) was 0.35% of body mass in grams, the actual range based upon the replica lung cast weights was 0.24–0.94% of body weight. To determine whether this variation affected airway measurements, tracheal diameters and main bronchi lengths and diameters were measured on all 20-replica lung casts. Figure 3 shows right main bronchus length and diameter plotted as a function of cast filling volume. As seen in the figure, there is no relationship between either the airway length or diameter and the cast filling volume range that occurred in this study. The same result, namely that the variation in cast filling volume did not significantly affect airway dimensions, was seen for measurements of the trachea and left main bronchus.

Figure 4 shows a comparison of the measured airway parameters between groups 1 and 2 of the BALB/c mice (panel A compares airway length, panel B compares air-

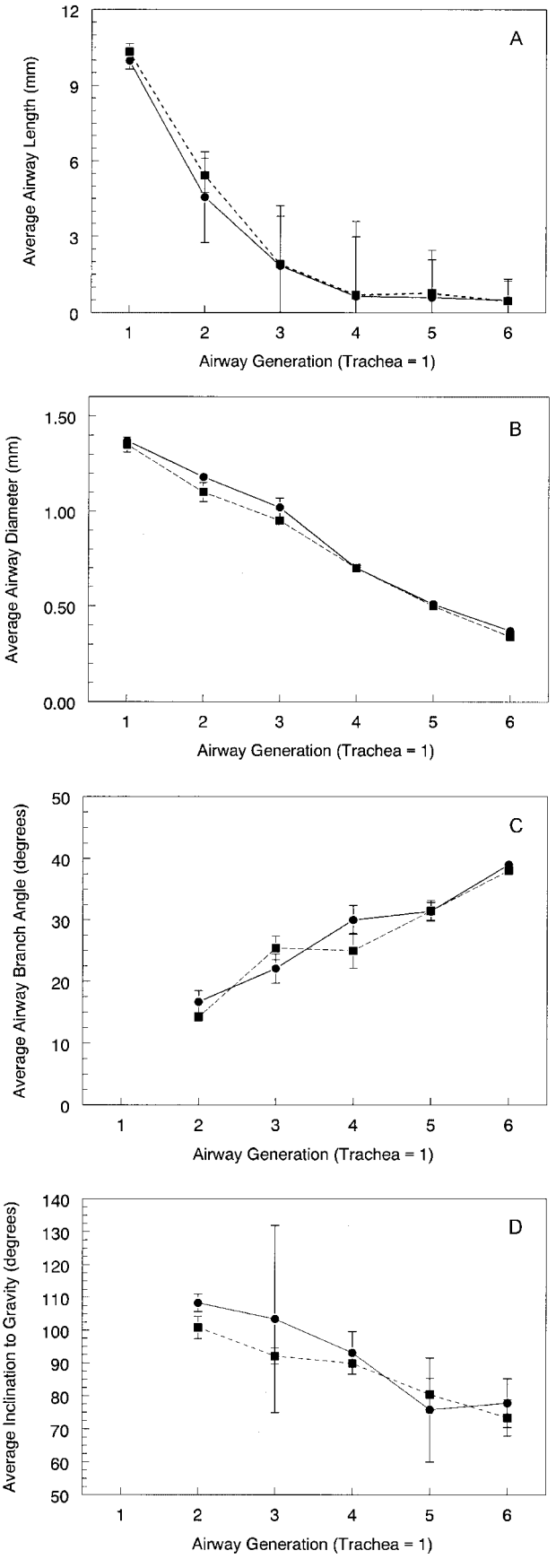

Fig. 4. Comparisons of mean airway parameters between two groups of BALB/c mice (● = group 1 and ■ = group 2) for airway generations 1–6: (**A**) airway length, (**B**) airway diameter, (**C**) branch angle, and (**D**) inclination to gravity. Error bars are standard errors.

TABLE 2. Typical path tracheobronchial geometry for generations 1–6 for the BALB/c mouse (mean ± standard error)

Generation number (trachea = 1)	Number of airways	Airway length (L) (mm)	Airway diameter (D) (mm)	Branch angle (θ) (°)	Gravity angle (ϕ) (°)
1	1	10.2 ± 0.6	1.36 ± 0	0 ± 0	90 ± 0
2	2	5 ± 0.33	1.14 ± 0.03	15 ± 1	105 ± 3
3	4	1.88 ± 0.05	0.98 ± 0.03	24 ± 2	98 ± 4
4	8	0.67 ± 0.04	0.7 ± 0.01	28 ± 2	91 ± 1
5	16	0.68 ± 0.05	0.5 ± 0.01	31 ± 1	78 ± 3
6	32	0.47 ± 0.02	0.35 ± 0.01	39 ± 1	76 ± 3

Gravity angle for the trachea was assumed to be 90° and was used as a reference for generations 2–6.

TABLE 3. Comparison of averaged group characteristics of the BALB/c and B6C3F$_1$ mice (mean ± S.D.)

Mouse type	Age (days)	Weight (g)	Length rump to snout (cm)	Chest circumference at Axilla (cm)	Chest circumference at Xyphoid (cm)
BALB/c (n = 6)	92 ± 27	25.2 ± 2.2	9.9 ± 0.4	7.1 ± 0.2	7.8 ± 0.3
B6C3F$_1$ (n = 3)	69 ± 1.7	25.8 ± 0.6	9.3 ± 0.3	5.8 ± 0.5	6.8 ± 0.2

way diameter, panel C compares branch angles, and panel D compares inclination to gravity angles). Based upon the lack of significant difference between the two groups as shown in Figure 4A–D, the data from each group were averaged by generation to form the average tracheobronchial geometry model for generations 1–6 of the BALB/c mouse (Table 2).

Prior to calculating predicted particle deposition, the mean age and body size characteristics for the BALB/c mice groups and the B6C3F$_1$ mice (from Oldham et al., 1994) were compared (Table 3). Although the mice were matched in weight, the BALB/c mice had significantly larger thorax circumferences. Figure 5 shows a comparison of the airway dimensions of the two varieties of mice (panel A compares airway length, panel B compares airway diameter, panel C compares branch angle, and panel D compares inclination to gravity angle).

Figure 6 shows the resulting predicted particle deposition efficiencies for both varieties of mice over the particle diameter range of 0.1–10 μm. Panel A shows the results for a ventilation of 50 ml/min, and panel B for a ventilation of 25 ml/min. For nearly all particle sizes the predicted deposition efficiencies are greater for the BALB/c strain.

DISCUSSION

As shown in Figure 6, there are toxicologically significant differences in predicted particle deposition between BALB/c and B6C3F$_1$ mice at equivalent ventilation levels. Most of these differences can be attributed to the difference in average airway diameters between the two strains (shown in Fig. 5B). It has been shown, by a sensitivity analysis of deposition equations used in the National Council on Radiation Protection and Measurements (1997) dosimetry code, that airway diameter is a very sensitive anatomical parameter affecting particle deposition due to the strong effect of airway diameter on airflow velocity (Phalen et al., 1990). Some of the differences in predicted deposition efficiency can also be attributed to differences in branch angles between the two types of mice for airway generations 5 and 6. These differences in branch angles apparently relate to the fact that the thoracic cavity circumference is larger for equivalent body weight, in BALB/c mice, as is seen in Table 3. Greater airway branch angles are presumed to be more efficient for filling a larger-diameter thorax.

These differences in predicted particle deposition imply that there are potentially significant differences in inhaled doses in the upper tracheobronchial tree between these two types of mice. The differences are most apparent for particles larger than about 0.4 μm in diameter, which are expected to have significant inertial impaction at airway bifurcations. Although these results suggest that inhaled particle doses are likely to be significantly different between these two mouse varieties, there are several factors that may change this conclusion when the entire respiratory tract is considered. These include possible differences in nasal deposition, tracheobronchial deposition in generation 7 through the terminal bronchiole, and pulmonary deposition. In addition, species differences that exist in the clearance rates of deposited aerosol particles (Snipes et al., 1983) may also occur in strains and varieties within a species.

Figure 4 shows that there was no difference in upper tracheobronchial anatomy between ovalbumin-sensitized and nonsensitized BALB/c mice. Since there were no morphometric differences, unless breathing parameters (frequency or tidal volume) were different between sensitized and nonsensitized BALB/c mice, no difference in delivered dose to the upper airways of sensitized BALB/c mice would be predicted in inhalation studies.

Our results may be of use in interpreting some published inhalation studies. Fernandez et al. (1999) generated a 3.1-μm-diameter aerosol of serotonin or carbachol and delivered it through a cannula into the trachea of BALB/c and C57BL/6 mice. The significant differences in response, as compared to injection of these compounds, were attributed to unspecified differences between the mouse varieties. As shown in Figure 5, for 3-μm particles there is a two- to threefold difference in predicted deposi-

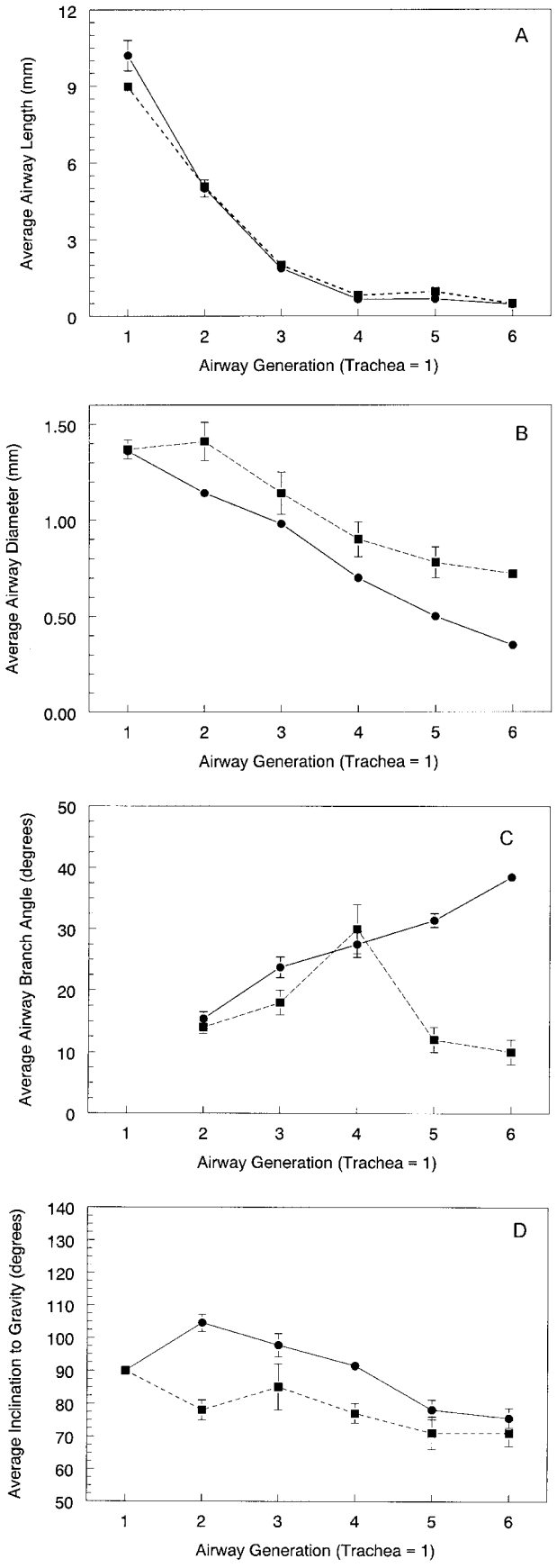

Fig. 5. Comparisons of mean airway parameters between BALB/c mice (●) and B6C3F$_1$ mice (■) for airway generations 1–6: (**A**) airway length, (**B**) airway diameter, (**C**) branch angle, and (**D**) inclination to gravity. Error bars are standard errors.

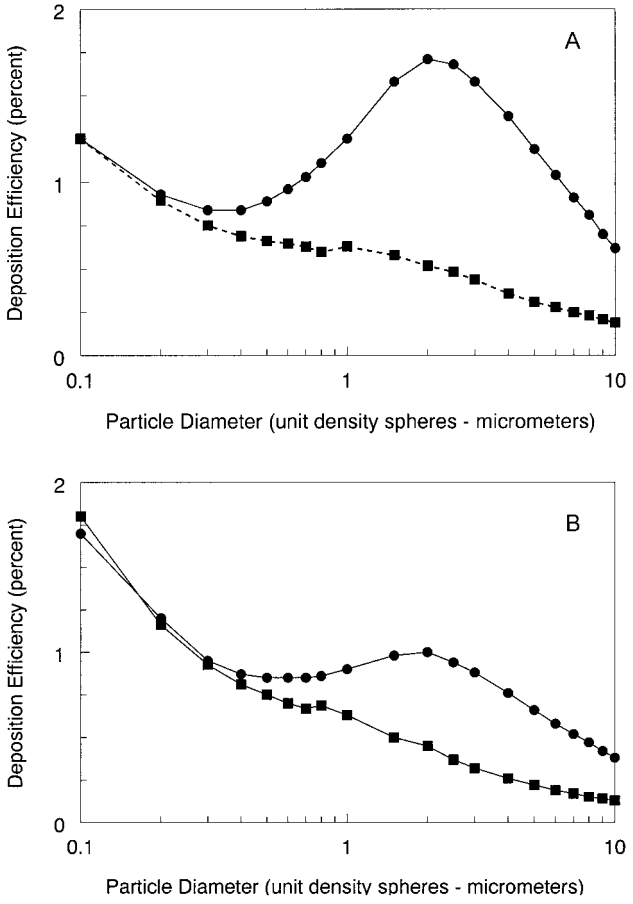

Fig. 6. Comparisons of predicted particle deposition efficiency between BALB/c mice (●) and B6C3F$_1$ mice (■) for airway generations 1–6: (**A**) deposition at 50 ml/min ventilation, and (**B**) deposition at 25 ml/min ventilation.

tion efficiency depending on the level of ventilation between the BALB/c and B6C3F$_1$ mice. Thus, some if not all of the response difference could be due to differences in the initial deposition doses of the aerosols. It is not unreasonable to think that there could be similar differences between other varieties of mice. Therefore, the differences in response that are observed in different types of mice for inhaled particulate matter may be influenced by differences in delivered doses to the respiratory tract, in addition to inherent biochemical differences. In a review of antioxidant defense mechanisms in the lungs of several species, Driscoll et al. (2002) highlighted the need for understanding interspecies differences in delivered doses. Schlesinger (1985) also highlighted the importance of species differences in aerosol deposition in interpreting inhalation studies. We would add that understanding strain-related differences in delivered doses of aerosols is also an

important aspect of inhalation toxicology study design and interpretation.

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