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## **CHAPTER 4**

# **DEPOSITION AND ABSORPTION OF TOBACCO SMOKE CONSTITUENTS**

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## Introduction

An understanding of the deposition of cigarette smoke particles in the respiratory tract is important because many of the toxic constituents of cigarette smoke are contained in the particles. The quantity retained, which constitutes the dose, is some fraction of the quantity inhaled. Measures of tobacco smoke constituents or their metabolites are also important because they reflect the absorption of tobacco smoke by the individual smoker or nonsmoker, and therefore may be more accurate markers of the actual exposure experienced by an individual. There is little experimental information describing the deposition of environmental tobacco smoke in the respiratory tract (Jarvis et al. 1983). However, cigarette smoke particles probably behave in a manner similar to other inhaled particles. In contrast, there are a number of observations of different markers in the biological fluids of smokers and nonsmokers. This review begins with a discussion of particle deposition in general and the factors that affect deposition. This understanding is then applied to the existing data on tobacco smoke deposition in the human respiratory tract. Subsequently, a variety of biologic markers of smoke absorption are examined, and the levels of these markers found in smokers and nonsmokers under a variety of circumstances are presented. Finally, an attempt is made to quantitate the exposure of nonsmokers relative to that of active smokers using levels of these biologic markers.

## Deposition

The term "deposition" refers to the transfer of a particle from inhaled air to the surface of any portion of the respiratory tract, from nose to alveolus. "Retention" is the quantity of deposited material remaining in the respiratory tract at a specified time following deposition. Retention decreases as clearance mechanisms such as mucociliary action and absorption reduce the respiratory tract burden of inhaled particles. Retention is not discussed in this review.

An aerosol is a suspension of particles in a gaseous or vapor medium; cigarette smoke is an aerosol. Aerosols are characterized by such terms as mass median diameter (MMD), the diameter below which lies one-half of the particles by mass, and count median diameter (CMD), the diameter below which lies one-half of the particles by number. Most naturally occurring aerosols have a log-normal size distribution, and the magnitude of the spread of particle size is the geometric standard deviation (GSD). Particle mass is a function of the cube of the diameter; a particle with a diameter of 0.5  $\mu\text{m}$  has one one-thousandth of the mass of a 5  $\mu\text{m}$  particle. Thus, for an aerosol with a large geometric standard deviation, the mass

median diameter may be considerably greater than the count median diameter. The smaller particles of an aerosol, despite their relatively small mass, have a large total surface area because of their great number. A monodisperse aerosol has particles of one size, with CMD equal to MMD, and a GSD of 1. For practical purposes, a GSD of 1.2 or less is accepted as monodisperse. Most naturally occurring aerosols are polydisperse, with GSDs in the 2 range. A lognormally distributed aerosol with a GSD of 2 and a CMD of 0.1 will have an MMD of 0.42. In this discussion, when size is referred to, it is the MMD unless otherwise stated. Both the total deposition and the deposition site in the respiratory tract vary substantially with particle size.

## **Size Distribution of Cigarette Smoke**

### **Mainstream Smoke**

The size distribution of cigarette smoke has been of interest to investigators for many years. The important relationship between size and respiratory tract deposition is discussed below. Most studies have been performed using mainstream smoke. Mainstream smoke is the smoke exiting from the butt of the cigarette during puff-drawing, and sidestream smoke is the smoke plume that drifts into the environment from the burning tip of a cigarette between puffs. Environmental tobacco smoke (ETS) is the ambient burden of sidestream smoke and the smoke exhaled by a smoker. Involuntary smoking is the consumption of ETS by people, either smokers or nonsmokers, from the environment. One purpose in discussing the size distribution and respiratory tract deposition of particles is to illustrate the discrepancy between the measured particle size of mainstream smoke and its measured deposition in the human respiratory tract. The deposition fraction of mainstream smoke is several times higher than would be predicted on the basis of its particulate size. The measured deposition of sidestream smoke is more in keeping with its measured size (Hiller, McCusker et al. 1982).

The standard laboratory smoke-generation technique is to force air through the cigarette as would be done by a smoker, followed by the rapid dilution of the resulting mainstream smoke so that particle size can be measured. A standard 35 cm<sup>3</sup>, 2-second puff is usually used, although actual puff volume was shown to average 45 cm<sup>3</sup> in one study (Mitchell 1962) and 56 cm<sup>3</sup> in another; for individuals, the puff volume can vary from 20 to 30 cm<sup>3</sup> up to 70 to 80 cm<sup>3</sup> (Hinds et al. 1983).

The size distribution of the diluted mainstream smoke aerosol is then measured by one of a variety of techniques such as light scattering devices, microscopic measurement, or impactor collecting

devices. Using various diluting and sizing techniques, particle size measurements of mainstream cigarette smoke have been reported from many laboratories (Table 1). One potential cause of error in measuring the size distribution of mainstream cigarette smoke is the relative insensitivity to ultrafine particles of some previously used measurement methods. More recent studies using newer measurement techniques support the suggestions by the earlier investigators (Sinclair 1950) that there is an ultrafine ( $<0.1 \mu\text{m}$ ) component to the cigarette smoke. Size characteristics have been measured by electron microscopic methods, following rapid fixation of undiluted fresh tobacco smoke, as CMD  $0.2 \mu\text{m}$  and GSD 1.5 (Keith 1982). The size distribution measured with an electrical aerosol analyzer has been reported as CMD  $0.1 \mu\text{m}$ , GSD 2.0, suggesting more ultrafine particles than previously recognized (Anderson and Hiller 1985). Smaller particles ( $<0.4 \mu\text{m}$ ) of tobacco smoke have been shown to have a chemical composition different from that of larger particles (Stöber 1984), possibly because of the large surface area of smaller particles.

Laboratory methods, such as rapid dilution, commonly used to study mainstream smoke, are highly artificial and may not accurately duplicate the generation, dilution, and inhalation of mainstream smoke by the smoker. Smoking technique and respiratory tract conditions may promote changes in particle size. Therefore, the particulate sizes in the respiratory tract may differ from the sizes measured when mainstream smoke is diluted for size analysis or when diluted sidestream smoke is inhaled by the involuntary smoker. The smoker's puff is taken as a bolus in a relatively small volume of air into the humid upper respiratory tract. Smoking techniques vary widely (Griffiths and Henningfield 1982) and have been shown to vary significantly among groups classified as healthy smokers compared with those with emphysema and also between those with emphysema and those with bronchogenic carcinoma and bronchitis (Medici et al. 1985). Some smokers hold the puff in the mouth for several seconds prior to deep inhalation. The initial puff is highly concentrated, with approximately  $10^9$  particles/cm<sup>3</sup>. At this concentration, particle coagulation can occur rapidly, causing a tenfold to a hundredfold reduction in particle number and an increase in particle size (Hinds 1982). Also, the accumulation of water in or on the particles in the high humidity of the respiratory tract can increase particle diameter (Muir 1974), and may increase the diameter as much as 30 percent (Mitchell 1962). Some evidence suggests, however, that at least for dilute cigarette smoke, hygroscopic growth occurs only under supersaturated conditions (Kousaka et al. 1982). Coagulation and water uptake by particles in the respiratory tract may considerably alter particle size distributions so that measurements under laboratory conditions probably do not

TABLE 1.—Size distribution of mainstream tobacco smoke

| Study                               | Size ( $\mu\text{m}$ ), concentration                       | Dilution        | Method  | Comment  |
|-------------------------------------|---|-----------------|---|--|
|                                     | [no. particles/cm <sup>3</sup> ]                            |                 |   |  |
| Wells and Gerke<br>(1919)           | CMD 0.27  | Not given       | Oscillation amplitude   |  |
| Sinclair<br>(1950)                  | CMD 0.0-0.3 fresh<br>CMD 0.4-0.5 aged                       |                 | Light scattering  | Aged: size increase attributed to<br>water accumulation  |
| DallaValle et al.<br>(1954)         | 0.1-0.25  | Not given       | Electrostatic separation  |  |
| Langer and Fisher<br>(1956)         | CMD 0.5 filter<br>CMD 0.6 plain<br>[2-5 x 10 <sup>8</sup> ] | 143:1           | Microscopic impinger<br>collection  | Compared with electrostatic<br>precipitation<br>GSD 1.75 |
| Keith and Derrick<br>(1960)         | CMD 0.23<br>MMD 0.45  | 295:1           | Aerosol centrifuge<br>Microscopic   | GSD 1.64<br>Calculated                                   |
| Porstendörfer and<br>Schraub (1972) | CMD 0.22<br>[5-7 x 10 <sup>8</sup> ]                        | 100,000:1       | Related rate of deposition<br>of radioactive decay<br>products onto particles to<br>particle size | Also measured deposition                                 |
| Porstendörfer<br>(1973)             | CMD 0.42<br>CMD 0.22  | 10:1<br>3,100:1 | Radon daughter attached<br>and deposited in spiral<br>centrifuge                                  |  |
| Okada and<br>Matsunuma<br>(1974)    | CMD 0.18<br>MMD 0.29  | 1,500:1         | Light scattering  | GSD 1.48   |

**TABLE 1.—Continued**

| Study                     | Size ( $\mu\text{m}$ ), concentration<br>[no. particles/ $\text{cm}^3$ ] | Dilution                      | Method  | Comment   |
|---------------------------|--|-------------------------------|---|---|
| Hinds<br>(1978)           | MMD 0.38–0.52<br>CMD 0.4<br>CMD 0.27                                     | 10:1–700:1<br>10:1<br>3,100:1 | Aerosol centrifuge  | Size distribution decreases as<br>dilution increases<br>GSD 1.3–1.5                             |
| McCusker et al.<br>(1982) | MMD 0.29–4.3<br>[ $4.2 \times 10^6$ ]                                    | 126,000:1                     | Laser doppler velocimetry   | Aerodynamic diameter GSD 1.4  |
| Chang et al.<br>(1984)    | CMD 0.24–0.26<br>[ $3.6 \times 10^6$ ]<br>MMD 5.5 secondary<br>mode      | 6:1–18:1<br><br>1–8 x $10^6$  | Electrical aerosol analyzer<br>(EAA)<br>Anderson Cascade Impactor<br>(CI) | Bimodal distribution<br>Primary mode (EAA) GSD 1.18<br>Second mode (CI) 5%–30% of<br>total mass |

NOTE: CMD = count median diameter; MMD = mass median diameter; GSD = geometric standard deviation.



**TABLE 2.—Size distribution of sidestream tobacco smoke**

| Study                            | Size ( $\mu\text{m}$ ) | Dilution         | Method   | Comment   |
|----------------------------------|------------------------|------------------|--|---|
| Keith and Derrick (1960)         | CMD 0.15               | 295:1 Centrifuge | Aerosol centrifuge   | Nature of sidestream smoke generation process makes difficult exact determination of concentration at generation and dilution |
| Porstendörfer and Schraub (1972) | CMD 0.24               | Not given        | Related rate of deposition of radioactive decay products onto particles to particle size |   |
| Hiller, McCusker et al. (1982)   | CMD 0.31               | Not given        | Laser doppler velocimetry  | GSD 1.6   |

NOTE: CMD = count median diameter; GSD = geometric standard deviation.

represent distributions found in actual mainstream smoking conditions.

### Sidestream Smoke

Sidestream smoke is generated by cigarettes burning spontaneously between puffs and is quantitatively the major contributor to ETS. Fifty-five percent of the tobacco in a cigarette is burned between puffs, forming sidestream smoke (see Chapter 3). Dilution takes place as smoke rises in the ambient air currents. This dilution with air reduces, but probably does not eliminate entirely, the coagulation that causes the particulate to increase in size, as they may in the highly concentrated state that occurs when a smoker draws a puff of mainstream smoke into the mouth and holds it briefly before inhalation. The size distribution of sidestream smoke might be expected to resemble that of diluted mainstream smoke. The results of several reports of sidestream smoke size measurements (Table 2) support this impression.

### Particle Deposition in the Respiratory Tract

#### Total Deposition

Total deposition has been studied both theoretically and experimentally. Mathematical equations can be used to predict deposition by combining mathematical models of lung anatomy with equations describing the behavior of particles in tubes. The major property to be considered is particle size and its influence on impaction, sedimentation, and diffusion. Inertial impaction is the mechanism

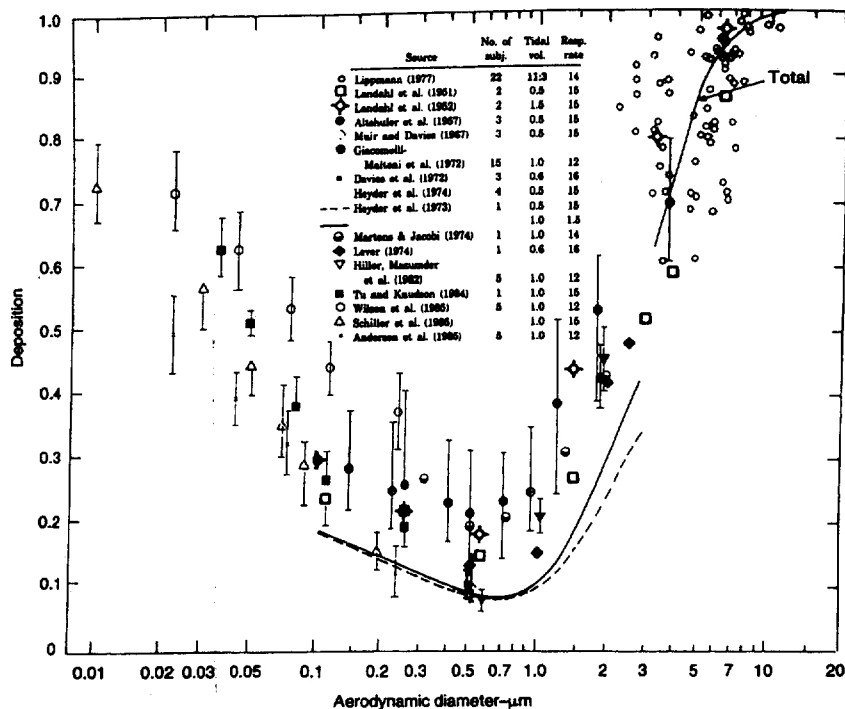
that causes particles moving in an airstream to be unable, because of excessive mass, to follow the airstream around a bend. Large particles impact at the bend in the airstream or in the lung on or near a site of airway branching. The larger the particle the greater its chance of depositing by impaction. Impaction is a relatively unimportant form of deposition for particles smaller than  $0.5 \mu\text{m}$ . The effect of gravity on suspended particles causes them to fall, a process called sedimentation, which also becomes relatively unimportant for particles less than  $0.5 \mu\text{m}$  in size. Larger particles fall faster, and for all particles, the greater the residence time (in the lung) the greater the likelihood of deposition by sedimentation. Diffusion is the net transport of particles caused by Brownian motion. It becomes increasingly important for particles less than  $0.5 \mu\text{m}$  in size (Hinds 1982). The mass median diameter of sidestream smoke is in the  $0.3$  to  $0.5 \mu\text{m}$  size range. Total deposition for inhaled particles is in the 10 to 30 percent range for  $0.5 \mu\text{m}$  sized particles.

In Figure 1, Lippmann's review (1977) of the measurements of total deposition of monodisperse aerosols in human subjects is modified to include more recent data and data on ultrafine particle deposition.

The respiratory pattern clearly affects particle deposition. Most important for all particles, including environmental tobacco smoke, is the residence time in the lung. Deposition increases with slow deep inspiration (Altshuler et al. 1957) and with breath holding (Palmes et al. 1966; Anderson and Hiller 1985). In hamsters, the deposition of  $0.38 \mu\text{m}$  particles rises in a nearly linear fashion with oxygen consumption (Harbison and Brain 1983). These data indicate that deposition of ETS during involuntary smoking increases with the increasing activity level of the exposed individual.

The presence of an electrical charge on particles may increase deposition. Mainstream smoke is highly charged (Corn 1974). The addition of either a positive charge or a negative charge to inhaled particles increases deposition in animals (Fraser 1966), and neutralization of the charge reduces deposition 21 percent in rats (Ferin et al. 1983). There is little information describing the effect of a charge on the deposition of either mainstream or sidestream smoke in human subjects.

Particle growth by water absorption may affect deposition. Mathematical models that describe the effect of humidity on particle growth indicate the potential for a considerable change in size of some particles during transit in the humid respiratory tract (Ferron 1977; Cocks and Fernando 1982; Renninger et al. 1981; Martonen and Patel 1981) and that these changes could significantly alter deposition (Ferron 1977). Growth of  $0.4$  to  $0.5 \mu\text{m}$  particles should increase their deposition fraction, but growth of a  $0.07 \mu\text{m}$  particle to  $0.1 \mu\text{m}$ , for example, would reduce its deposition (see Figure 1). Such



**Figure 1.—Total respiratory tract deposition of inhaled inert particles during oral inhalation**

NOTE: The portion of the figure from 0.01 to 0.1  $\mu\text{m}$  was added to a previously published illustration of total deposition (Lippmann 1977); sources for both are indicated. The original and the additions together encompass the complete smoke particle size range.

an effect has been shown for laboratory-generated aerosols in human subjects (Blanchard and Willeke 1983; Tu and Knudsen 1984). While hygroscopic growth has been postulated for tobacco smoke (Muir 1974), it has been demonstrated in the laboratory to occur, at least for dilute smoke, only in supersaturated conditions (Kousaka et al. 1982).

Many reports describe measured deposition of mainstream cigarette smoke in the human respiratory tract (Table 3). Although few studies of total sidestream smoke deposition are available, those few (Table 3) suggest that sidestream smoke does indeed deposit in a manner similar to that found for laboratory-designed research aerosols. The deposition fraction of mainstream smoke diluted 1:30 and inhaled by rats from chamber air containing 1.68 mg/L (assuming a rat tidal volume of 1.5 mL and a respiratory rate of 85) is

8.1 percent (Binns et al. 1978). Deposition for the sidestream smoke has been measured in mouth-breathing human volunteers at 11 percent, similar to that for similarly sized polystyrene latex spheres (Hiller, Mazumder et al. 1982). Environmental tobacco smoke exposure frequently occurs with breathing through the nose rather than through the mouth, but inert particles in the size range of ETS (0.2 to 0.4  $\mu\text{m}$ ) are not substantially reduced in number by passage through the nose. The fraction of inert 0.2  $\mu\text{m}$  particles deposited in the alveolar region of the lung is similar for mouth breathing and nasal breathing (Raabe 1984). It is possible that the charged or reactive particles of ETS may behave somewhat differently than inert particles, but it seems unlikely that nasal breathing substantially alters the deposition of the small particles of ETS in comparison with mouth breathing.

### **Regional Deposition**

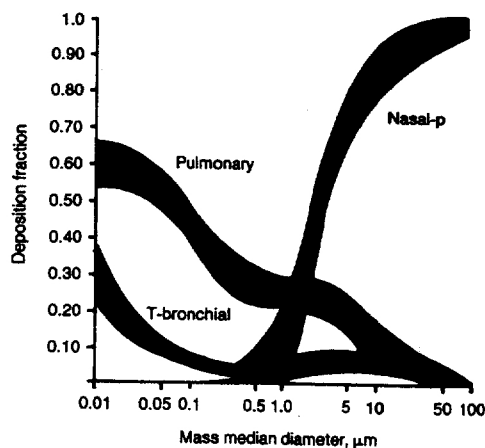
Total deposition is subdivided into the fractions depositing in the upper respiratory tract (larynx and above), the tracheobronchial region (trachea to and including terminal bronchioles), and the pulmonary region (respiratory bronchioles and beyond) (Figure 2). Deposition in these areas is referred to as regional deposition. Particle size is a major determinant of both total and regional deposition. A mathematical model prediction of regional deposition of polydisperse aerosols is shown in Figure 2 (ICRP 1966).

Experimental verification of mathematical models of regional deposition is limited. Using isotope-labeled particles, it is possible to quantitate the upper respiratory tract deposition as a fraction of total deposition. By assuming that the aerosol depositing in the tracheobronchial region will be cleared within 24 hours, it is possible to measure alveolar deposition as the fraction of the total initial deposition below the larynx that is remaining at 24 hours and tracheobronchial deposition as the difference between the initial deposition and what is remaining at 24 hours. Using this method, the deposition of 3.5  $\mu\text{m}$  particles was this: total deposition, 0.79; upper respiratory tract, 0.10; tracheobronchial region, 0.24; and pulmonary region (alveolar), 0.45 (Emmett et al. 1982). These measurements are below the estimated regional deposition for upper respiratory tract deposition and higher for the pulmonary deposition than are the measurements calculated by using the Task Group on Lung Dynamics model (ICRP 1966).

The regional deposition of mainstream cigarette smoke in smokers has also been studied. Subjects inhaled smoke from cigarettes labeled with radioactive 1-iodohexadecane (Black and Pritchard 1984; Pritchard and Black 1984). The results indicate that less than 40 percent of the particulate mass deposited in the pulmonary region, compared with an expected 90 percent deposition in the

**TABLE 3.—Respiratory tract deposition of mainstream and sidestream cigarette smoke**

| Study                          | Deposition fraction            | Puff volume (mL)             | Puff time (second) | Smoke dilution           | Respiratory pattern                             |
|--------------------------------|--------------------------------|------------------------------|--------------------|--------------------------|---|
| <b>Mainstream smoke</b>        |                                |                              |                    |                          |   |
| Baumberger (1923)              | 88%                            | Not given                    | Not given          | None                     | Inhalation                                      |
| Schmahl et al. (1954)          | 98%                            |                              |                    |                          |   |
| Polydorova (1961)              | 80%<br>(22-89 range)           |                              |                    | None                     | Usual spontaneous smoking pattern               |
| Mitchell (1962)                | 82%<br>(70-90 range)           | 45 ± 9.8 SD<br>(33-65 range) | 1.9 ± 0.6 SD       | 300:1                    | "Deep inhalation"                               |
| Dalhamn et al. (1968)          | 96% ± 3.1% SD<br>(86-99 range) | 35                           | 2                  | None                     | Pretrained standardized pattern (not described) |
| Hinds et al. (1983)            | 47%<br>(22-75 range)           | 53                           |                    | None                     | Usual spontaneous smoking pattern               |
| <b>Sidestream smoke</b>        |                                |                              |                    |                          |   |
| Binns et al. (1978)            | 8%                             | Not applicable               |                    | 30:1<br>(in chamber)     | Spontaneous (rats)                              |
| Hiller, McCusker et al. (1982) | 11%                            | Not applicable               |                    | 50-100 µg/m <sup>3</sup> | 1 L tidal volume, 12 breaths/min                |



**Figure 2.—Regional deposition of particles inhaled during nasal breathing, as predicted using the deposition model proposed by the Task Group on Lung Dynamics**

SOURCE: International Committee on Radiation Protection, Task Force on Lung Dynamics (1966).

pulmonary region for 0.5 μm particles, the size reported for cigarette smoke (Table 1). This finding further supports the concept that mainstream smoke particles increase in size in the respiratory tract by coagulation, hygroscopic growth, or both, and that this growth affects total and regional deposition. The same group studied the effect of switching the tar content of cigarettes on regional deposition. Using cigarettes with between 16 and 17 mg tar, extrathoracic deposition was found to be 14 percent of the total deposition and intrathoracic deposition to be 86 percent, with 51 percent in the tracheobronchial area and 35 percent in the pulmonary region (Pritchard and Black 1984). After switching to cigarettes with between 8 and 9 mg tar, total deposition was 74 percent of that measured from cigarettes with the higher tar content, the extrathoracic deposition was unchanged, the tracheobronchial deposition was from 34 to 42 percent, and the pulmonary deposition was 18 to 25 percent of the total mass deposited with the higher tar cigarettes. With the use of mathematical deposition modeling, the observed deposition pattern was consistent with one predicted for an aerosol with an MMD of 6.5 μm, more than 10 times greater than the MMD described for cigarette smoke (Black and Pritchard 1984).

The deposition of particles is probably not uniform within a lung region. The mass deposited in the airways, for instance, may vary

widely. Enhanced deposition at specific anatomic sites may be especially important for some inhalants. For example, the concentration of carcinogenic substances at a site may favor that site for cancer development. This may be especially important for cigarette smoke, since lung cancer may occur at sites of high deposition such as airway bifurcations. Deposition of a 0.3  $\mu\text{m}$  laboratory-generated stable aerosol has been shown to favor right upper lobe deposition, and on the basis of surface density of deposition, the lobar bronchi (Schlesinger and Lippmann 1978). The deposition per airway generation has been calculated for large particles, but has not received sufficient attention for particles in the size range of mainstream or sidestream smoke. A deposition peak has been predicted, using a lung model for the fourth airway generation (trachea is 0) for 5  $\mu\text{m}$  particles, and a peak in airway surface concentration density was predicted for 8  $\mu\text{m}$  particles at the fourth generation (Gerrity et al. 1979). Both of these deposition peaks are calculated for particles substantially larger than those of cigarette smoke.

Depositions may be quite nonuniform even within a single airway generation. An enhanced deposition at bifurcations with highly concentrated deposition on carina ridges within bifurcations has been demonstrated in a five airway generation model of the human respiratory tract for both cigarette smoke (Martonen and Lowe 1983a) and research aerosols (Martonen and Lowe 1983b).

Epidemiological studies of the pathophysiologic consequences of involuntary smoking have emphasized, among other things, an increase in the incidence of respiratory illness in children (see Chapter 2). The issue of the respiratory tract deposition of particles in children has been addressed only recently. Using morphometric measurements from casts of the lungs of children and young adults aged 11 days to 21 years, a mathematical growth model was created. Using this model and conventional methods for predicting the behavior of particles in tubes, the deposition of particles at various ages can be predicted. On the basis of these calculations, tracheobronchial depositions per kilogram of body weight for 5  $\mu\text{m}$  particles was estimated to be six times higher in the resting newborn than in a resting adult (Phalen et al. 1985). Differences are predicted also for particles the size of sidestream smoke, with tracheobronchial deposition in infancy being twofold to threefold higher in adulthood. Total deposition has also been estimated using mathematical modeling, with the total deposition estimated at approximately 15 percent at age 6 months and at 10 percent in adults (Xu and Yu 1986).

## **Respiratory Tract Dose of Environmental Tobacco Smoke**

### **Cigarette Smoke Particulate Mass Deposited**

The dose of environmental tobacco smoke to the respiratory tract is the product of the mass in inhaled air and the deposition fraction. To this point, particle size and deposition fraction, which is related to both size and respiratory pattern as well as to other less understood factors such as particle charge and hygroscopicity, have been addressed. To estimate dose, the content of smoke in inhaled air must be known, as well as the respired minute volume. Mass content in inhaled air varies widely, as does minute volume, which depends considerably on activity level. Sidestream smoke concentrations have been raised as high as  $16.5 \text{ mg/m}^3$  in experimental chambers (Hoegg 1972). High levels, 2 to  $4 \text{ mg/m}^3$ , have also been estimated using measured carbon monoxide concentrations for rooms  $140 \text{ m}^3$  in size containing 50 to 70 persons (Bridge and Corn 1972). Such levels far exceed the EPA air quality standards for total suspended particulate of  $75 \text{ } \mu\text{g/m}^3$  annual average and the  $260 \text{ } \mu\text{g/m}^3$  24-hour average in the United States and the  $250 \text{ } \mu\text{g/m}^3$  24-hour average for the United Kingdom.

Measurements of environmental smoke concentrations vary widely, depending upon the location and measurement technique (Tables 4 and 5). Levels of total suspended particulates (TSP) measured under realistic circumstances have been found to be from 20 to  $60 \text{ } \mu\text{g/m}^3$  in no-smoking areas, and can range from 100 to  $700 \text{ } \mu\text{g/m}^3$  in the presence of smokers (Repace and Lowrey 1980). These measurements include all suspended particulates, and so could include particles other than tobacco smoke. However, in a smoky indoor setting where measurements as high as  $600 \text{ } \mu\text{g/m}^3$  have been found, tobacco smoke is the major contributor to particulate mass, with the non-tobacco-smoke contribution being small and similar to that measured for nonsmoking areas, namely in the  $20 \text{ to } 60 \text{ } \mu\text{g/m}^3$  range. This concept is supported by studies in which tobacco smoke concentration in the environment was determined by measuring the nicotine content of suspended particulates. Using this technique (Hinds and First 1975), ETS levels have been estimated to be 20 to  $480 \text{ } \mu\text{g/m}^3$  in bus and airline waiting rooms and as high as  $640 \text{ } \mu\text{g/m}^3$  in cocktail lounges. These calculations of smoke concentrations were based on an average weighted nicotine fraction of 2.6 percent, an approach that may underestimate tobacco smoke particulate concentration.

The mass deposition in the respiratory tract can be estimated if the atmospheric burden of cigarette smoke particulates, minute volume, and deposition fraction is known. Assuming a smoke concentration of  $500 \text{ } \mu\text{g/m}^3$ , a minute volume of 12 liters per minute,



**TABLE 4.—Indoor concentration of total suspended particulates (TSP) measured in ordinary living or working situations**

| Study                   | Location                      | Conditions of location, occupancy, smoking (S), nonsmoking (NS) | TSP  | Background               | Comments  |
|-------------------------|-------------------------------|---|--|--------------------------|---|
|                         |                               |   | $\mu\text{m}/\text{m}^3 \bar{x} \pm \text{SD}$ | $\mu\text{m}/\text{m}^3$ |   |
| Just et al. (1972)      | Coffee shop                   | 4 locations   | 1,150  | 570 <sup>1</sup>         |   |
| Hinds and First (1975)  | Bus waiting room              | Not given   | 40<br>(16-58)                                  | Not applicable           | Suspended particulates collected on filter; nicotine content measured for calculation; TSP = nicotine/0.026     |
|                         | Restaurant                    |   | 200<br>(51-450)                                |                          |   |
|                         | Cocktail lounge               |   | 400<br>(170-640)                               |                          |   |
| Elliott and Rowe (1975) | Arena A                       | Attendance 9,600<br>Air conditioned (S)                         | 224  | 42                       | High volume sampler for suspended particulates; also measured CO at all locations and benzo[a]pyrene in arena A |
|                         |                               | Attendance 14,300<br>Air conditioned (S)                        | 481  | 42                       |   |
|                         | Arena B                       | Attendance 2,000<br>Not air conditioned (S)                     | 620  | 92                       |   |
|                         | Arena C                       | Attendance 11,000<br>Natural ventilation (NS)                   | 148  | 71                       |   |
| Cuddeback et al. (1976) | Tavern                        | 6 air changes/hr  | 0.31 $\pm$ 0.05<br>(0.23-0.34)                 |                          | 8-hr air sample collected on filter (5 $\mu\text{m}$ pore size); TSP measured gravimetrically                   |
|                         | Tavern                        | None apparent   | 0.99   |                          |   |
| Neal et al. (1978)      | Hospital intensive care units | Independent ventilation systems                                 | 30   | 68                       | Anderson personnel sampler used   |

TABLE 4.—Continued

| Study                    | Location                         | Conditions of location, occupancy, smoking (S), nonsmoking (NS)                   | TSP  | Background                              | Comments   |
|--------------------------|----------------------------------|---|--|---|--|
|                          |                                  |   | $\mu\text{m}/\text{m}^3 \times \pm\text{SD}$ | $\mu\text{m}/\text{m}^3$                |  |
| Weber and Fischer (1980) | 44 offices                       | Window ventilation; 32/44 allowed unrestricted smoking                            | 202  | Subtracted from TSP                     | TSP measured with piezoelectric balance (see above)  |
|                          |                                  | Air conditioned   | 120  | Same                                    |  |
| Repace and Lowrey (1980) | Residences                       | 5 locations, 6 measurements; 10 $\pm$ 8 persons/100 m <sup>3</sup> , all NS       | 38 $\pm$ 16                                  | Not done                                | All samples collected using piezoelectric balance with very high collection efficiency at 3.5 $\mu\text{m}$ and 10% at 4 $\mu\text{m}$ ; sample time 1-50 min, outdoors 5-15 min |
|                          | Libraries, churches, restaurants | 9 locations; 10 $\pm$ 10 persons/100 m <sup>3</sup> , all NS                      | 38 $\pm$ 16                                  | 36 $\pm$ 10 <sup>1</sup> (4 locations)  |  |
|                          | Restaurants, bars, bingo game    | 19 locations, 20 samples, 11 $\pm$ 8 persons/100 m <sup>3</sup> , all S locations | 242 $\pm$ 175 (86-697)                       | 47 $\pm$ 13 <sup>1</sup> (13 locations) |  |
|                          |                                  | 7 locations with >1 smoker/m <sup>3</sup> (mean 2.2 smokers/m <sup>3</sup> )      | 406 $\pm$ 188 (187-697)                      | 53 $\pm$ 8 <sup>1</sup>                 |  |
|                          |                                  | 18 $\pm$ 7 persons/100 m <sup>3</sup> , with 1 smoker/100 m <sup>3</sup>          |  |   |  |

TABLE 4.—Continued

| Study                     | Location            | Conditions of location,<br>occupancy, smoking (S),<br>nonsmoking (NS) | TSP  | Background                      | Comments   |
|---------------------------|---------------------|---|--|---------------------------------|--|
|                           |                     |   | $\mu\text{m}/\text{m}^3 \times \pm\text{SD}$ | $\mu\text{m}/\text{m}^3$        |  |
| Spengler et al.<br>(1981) | 35 homes            | No smokers  | $24.4 \pm 11.6^1$                            | $21.1 \pm 11.9$<br>all 55 homes | Annual mean: respirable mass<br>collected on filters after<br>removal of nonrespirable<br>fraction; 24-hr sample collected<br>every 6 days |
|                           | 15 homes            | 1 smoker  | $36.5 \pm 14.5$                              |                                 |  |
|                           | 5 homes             | 2 smokers   | $70.4 \pm 42.9$                              |                                 |  |
|                           | 1 home <sup>2</sup> | 2 smokers, tightly sealed,<br>central air conditioning                | 144  |                                 |  |

<sup>1</sup> Ambient particulate concentration at site, but outdoors.

<sup>2</sup> This home is one of the five homes above.

**TABLE 5.—Indoor concentration of total suspended particulates (TPM) generated by smoking cigarettes under laboratory conditions**

| Study                          | Test conditions   | Ventilation                      | Chamber size       | Cigarette consumption          | TPM mg/m <sup>3</sup> | Comments   |
|--------------------------------|---|----------------------------------|--------------------|--------------------------------|-----------------------|--|
| Penkala and de Oliveira (1975) | Well mixed  | None                             | 9.2 m <sup>3</sup> | 3 simultaneously, 2 q puffs    | 3.8                   |  |
| Hoegg (1972)                   | Sealed chamber; experimenter and test equipment in chamber; measured 18 min postsmoking | Portable fans circulated air     | 25 m <sup>3</sup>  | 24 simultaneously by machine   | 16.65                 | TPM measured gravimetrically after collection of suspended particulates on filters; sidestream smoke collected in chamber; mainstream smoke discharged |
|                                | Same, 150 min postsmoking   | Same                             |                    | 4 simultaneously by machine    | 1.51                  |  |
| Hugod et al. (1978)            | Sealed room   | Unventilated                     | 68 m <sup>3</sup>  | 20 simultaneously by machine   | 5.75                  | TPM measured gravimetrically from 3-hr collection on filter; mainstream smoke in chamber   |
| Cain et al. (1983)             | 4-12 occupants<br>Climate-controlled chamber  | 11 ft <sup>3</sup> /min/occupant | 11 m <sup>3</sup>  | 4/hr (by occupants)            | 0.350                 | Piezoelectric balance measured total mass over 0.01-20 μm  |
|                                |   | 68 ft <sup>3</sup> /min/occupant | 11 m <sup>3</sup>  | 4/hr (by occupants)            | 0.15                  |  |
|                                |   | 11 ft <sup>3</sup> /min/occupant | 11 m <sup>3</sup>  | 16/hr (by occupants)           | 1.25                  |  |
|                                |   | 68 ft <sup>3</sup> /min/occupant | 11 m <sup>3</sup>  | 16/hr (by occupants)           | 0.40                  |  |
| Muramatsu et al. (1983)        | Climate-controlled chamber  | 15.4 air changes/hr              | 30 m <sup>3</sup>  | 1/8 min to 60 min              | 0.19-0.26             | Piezoelectric balance  |
|                                | Climate-controlled chamber  | 15.4 air changes/hr              | 30 m <sup>3</sup>  | 3 simultaneously, then 2/8 min | 0.47-0.522            |  |

and a deposition fraction of 11 percent (Hiller, McCusker et al. 1982), mass deposition over an 8-hour work shift would be 0.317 mg.

### The Concept of "Cigarette Equivalents"

Many investigators have attempted to estimate the potential toxicity of involuntary smoking for the nonsmoker by calculating "cigarette equivalents" (C.E.). To inhale one C.E. by involuntary smoking, the involuntary smoker would inhale the same mass quantity of ETS as is inhaled from one cigarette by a mainstream smoker. This approach has led to estimates from as low as 0.001 C.E. per hour to as high as 27 C.E. per day (Hoegg 1972; Hinds and First 1975; Hugod et al. 1978; Repace and Lowrey 1980). These differences of up to three orders of magnitude seem illogical when most reports of measurements of environmental concentrations of smoke, from the most clean to the most polluted with environmental tobacco smoke, are within tenfold to fiftyfold of each other. The following discussion demonstrates why the C.E. can vary so greatly as a measure of exposure.

The calculation of C.E. is as follows:  $PMI_{(p)} = TSP \text{ (mg/m}^3\text{)} \times \dot{V}_E$ ; where  $PMI_{(p)}$  equals the particulate mass inhaled by passive smoking, TSP equals the total suspended particulate, and  $\dot{V}_E$  equals the inhaled volume.  $C.E. = PMI_{(p)}/PMI_{(ms)}$ ; where C.E. equals cigarette equivalent and  $PMI_{(ms)}$  equals the mass inhaled by (mainstream) smoking one cigarette. (This is taken to be the tar content of a cigarette as reported by the U.S. Federal Trade Commission.)

Cigarette equivalents can be calculated for any time interval chosen, i.e., per hour, per day. Although the example given is for particulate mass, C.E. can be calculated for any component of cigarette smoke, such as carbon monoxide and benzo[a]pyrene. The following calculations illustrate the different results from two different approaches to the calculation of C.E.

|              | <u>Example 1</u>        | <u>Example 2</u>       |
|--------------|-------------------------|------------------------|
| $\dot{V}_E$  | 0.36 m <sup>3</sup> /hr | 20 m <sup>3</sup> /day |
| $PMI_{(ms)}$ | 16.1 mg tar/cig         | 0.55 mg tar/cig        |
| TSP          | 40 µg/m <sup>3</sup>    | 700 µg/m <sup>3</sup>  |

#### Example 1

$$\begin{aligned}
 PMI_{(p)} &= TSP \times \dot{V}_E \\
 &= 40 \text{ µg/m}^3 \times 0.36 \text{ m}^3/\text{hr} \\
 &= 14.4 \text{ µg/hr}
 \end{aligned}$$

$$\begin{aligned}
 C.E. &= PMI_{(p)}/PMI_{(ms)} \\
 &= (0.0144 \text{ mg/hr})/(16.1 \text{ mg/cig}) \\
 &= 0.001 \text{ cig/hr}
 \end{aligned}$$

### Example 2

$$\begin{aligned} \text{PMI}_{(p)} &= \text{TSP} \times \dot{V}_E \\ &= 700 \mu\text{g}/\text{m}^3 \times 20 \text{ m}^3/\text{day} \\ &= 14,000 \mu\text{g}/\text{day} \\ \text{C.E.} &= \text{PMI}_{(p)}/\text{PMI}_{(ma)} \\ &= (14 \text{ mg}/\text{day})/(0.55 \text{ mg}/\text{cig}) \\ &= 25 \text{ cig}/\text{day} \end{aligned}$$

These calculations of C.E. approximate the approaches used in two reports—Example 1 by Hinds and First (1975) and Example 2 by Repace and Lowrey (1980)—and the results are similar. The examples are the extremes used in the two studies, and are at the extremes of commonly cited reports of C.E. Even if the TSP concentration used in the two examples were the same, the results would differ 24-fold because Example 1 is calculated per hour and Example 2 is calculated per day; 2.3-fold because of the difference in inhaled minute volume; and 29-fold because of the difference in what is considered to be a “standard” cigarette. Even using the same TSP concentration, the results would be  $1.6 \times 10^3$  different. If C.E. is to be calculated, all of the factors used in the calculation should be standardized.

The calculation of C.E. is deficient in several other ways. The deposition fraction of the total inhaled particulate mass in the respiratory tract from mainstream smoke is higher than from involuntary smoking. The deposition fraction for involuntary smoking is approximately 11 percent for mouth breathing (Hiller, Mazumder et al. 1982). The deposition from mainstream smoke has been reported to vary from 47 to 90 percent (Table 3). The cigarette equivalent calculation considers only the quantity inhaled, and if mass dose deposited is considered, one C.E. from passive smoking will cause several times less mass to be deposited than the mainstream smoke of one cigarette.

The differences in the chemical composition between sidestream smoke and mainstream smoke make the C.E. concept misleading unless C.E. is calculated for each smoke constituent. This has been accomplished (Hugod et al. 1978) using measured levels of various smoke constituents in a chamber filled with sidestream smoke. The results indicate that one C.E. for carbon monoxide could be inhaled 5.5 times faster, and for aldehyde, 2.9 times faster, than for particulate mass. Measurements of total particulate matter and benzo[a]pyrene taken in an arena with active smoking revealed a fivefold rise in TSP above background and an eighteenfold increase in benzo[a]pyrene over background. Using the measured benzo[a]pyrene concentration of  $21.7 \text{ ng}/\text{m}^3$ , an inhaled volume of  $2.4 \text{ m}^3$ , and  $8.2 \text{ ng}$  benzo[a]pyrene per cigarette, the occupant of such an environment would consume 6.4 C.E. for benzo[a]pyrene (IARC 1986, p. 87). The C.E. TSP would be 1.7. Therefore, a C.E. for the

carcinogen benzo[a]pyrene would be inhaled 3.6 times more rapidly than a C.E. for TSP (Elliott and Rowe 1975).

The wide latitude in the results of C.E. calculations demonstrates the dependence of the C.E. calculation on the numerical values of the variables chosen, and correspondingly demonstrates the marked limitations of the use of C.E. as an atmospheric measure of exposure to the agents in environmental tobacco smoke. When the quantification of an exposure is needed, it is far more precise to use terms that define the milligrams of exposure to the agent of interest per unit time. However, the term cigarette equivalent is frequently used, not simply as a measure of exposure, but as a unit of disease risk that translates the measured exposures into a risk of disease using the known dose-response relationships between the number of cigarettes smoked per day and the risk of disease. If C.E. is to be used as a unit of risk, the variables used to convert atmospheric measures into levels of risk for the active smoker need to be determined on the basis of the deposition and smoke exposure measures for the average smoker. The deposition fraction of individual smoke constituents in the population of active smokers is needed rather than the range observed in a few individuals. In addition, the actual average yield of the cigarettes smoked by the subjects in the prospective mortality studies would be needed to compare the dose-response relationships accurately. The yield using the Federal Trade Commission (FTC) method may dramatically underestimate the actual yield of a cigarette when the puff volume, rate of draw, or number of puffs is increased; therefore, calculations using the FTC numbers may be inaccurate, particularly for the low-yield cigarettes. These limitations make extrapolation from atmospheric measures to cigarette equivalent units of disease risk a complex and potentially meaningless process.

### **Markers of Absorption**

In contrast, measures of absorption of environmental tobacco smoke, particularly cotinine levels, can potentially overcome some of the limitations in translating environmental tobacco smoke exposures into expected disease risk. Urinary cotinine levels are a relatively accurate dosage measure of exposure to smoke; they have been measured in populations of smokers and nonsmokers, and are not subject to errors in estimates of the minute ventilation or yield of the average cigarette. Potential differences in the half-life of cotinine in smokers and nonsmokers, differences in the absorption of nicotine relative to other toxic agents in the smoke, and differences in the ratio of nicotine to other toxic agents in mainstream smoke and sidestream smoke remain sources of error, but the accuracy with which active smoking and involuntary smoking exposure can be