CHAPTER 4

DEPOSITION AND ABSORPTION OF TOBACCO SMOKE CONSTITUENTS

CONTENTS

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 ahsorption 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 ahsorption 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 pm has one one-thousandth of the mass of a 5 pm 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^3, 2-second puff is usually used, although actual puff volume was shown to average 45 cm^3 in one study (Mitchell 1962) and 56 cm^3 in another; for individuals, the puff volume can vary from 20 to 30 cm^3 up to 70 to 80 cm^3 (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 sizre 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.l μm) 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 μm and GSD 1.5 (Keith 1982). The size distribution measured with an electrical aerosol analyzer has been reported as CMD 0.1 μm, GSD 2.0, suggesting more ultrafine particles than previously recognized (Anderson and Hiller 1985). Smaller particles (< 0.4 μm) of tobacco smoke have been shown to have a chemical composition different from that of larger particles (Stober 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^3. 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 (μm), concentration [no. particles/cm^3]	Dilution	Method	Comment
Wells and Gerke (1919)	CMD 0.27	Not given	Oscillation amplitude	
Sinclair (1950)	CMD 0.0-0.3 fresh CMD 0.4-0.5 aged		Light scattering	Aged: size increase attributed to water accumulation
DallaValle et al. (1954)	0.1-0.25	Not given	Electrostatic separation	
Langer and Fisher (1956)	CMD 0.5 filter CMD 0.6 plain [2-5 x 10^8]	143:1	Microscopic impinger collection	Compared with electrostatic precipitation GSD 1.75
Keith and Derrick (1960)	CMD 0.23 MMD 0.45	295:1	Aerosol centrifuge Microscopic	GSD 1.64 Calculated
Poretendörfer and Schraub (1972)	CMD 0.22 [5-7 x 10^8]	100,000:1	Related rate of deposition of radioactive decay products onto particles to particle size	Also measured deposition
Porstendörfer (1973)	CMD 0.42 CMD 0.22	l0:1 3,100:l	Radon daughter attached and deposited in spiral centrifuge	
Okada and Matsunuma (1974)	CMD 0.18 MMD 0.29	1,500:1	Light scattering	GSD 1.48

TABLE l.--Continued

Study	Size (pm), concentration [no. particles/cm^3]	Dilution	Method	Comment
Hinds (1978)	MMD 0.38-0.52 CMD 0.4 CMD 0.27	10:1-700:1 10:1 3,100:l	Aerosol centrifuge	Size distribution decreases as dilution increases GSD 1.3-1.5
McCusker et al. (1982)	MMD 0.29-4.3 [4.2×10^9]	126,000:1	Laser doppler velocimetry	Aerodynamic diameter GSD 1.4
Chang et al. (1984)	CMD 0.24-0.26 [3.6×10^9] MMD 5.5 secondary mode	6:1-18:1 1-8 x 10^6	Electrical aerosol analyzer (EAA) Anderson Cascade Impactor (CI)	Bimodal distribution Primary mode (EAA) GSD 1.18 Second mode (CI) 5%-30% of 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 (μm)	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
Poretendörfer 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 air-stream around a bend. Large particles impact at the bend in the air-stream 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 µm. 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 µp 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 µm in size (Hinds 1982). The mass median diameter of sidestream smoke is in the 0.3 to 0.5 µm size range. Total deposition for inhaled particles is in the 10 to 30 percent range for 0.5 µm 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 µm 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 Pate1 1981) and that these changes could significantly alter deposition (Ferron 1977). Growth of 0.4 to 0.5 µm particles should increase their deposition fraction, but growth of a 0.07 µm particle to 0.1 µm, for example, would reduce its deposition (see Figure 1). Such

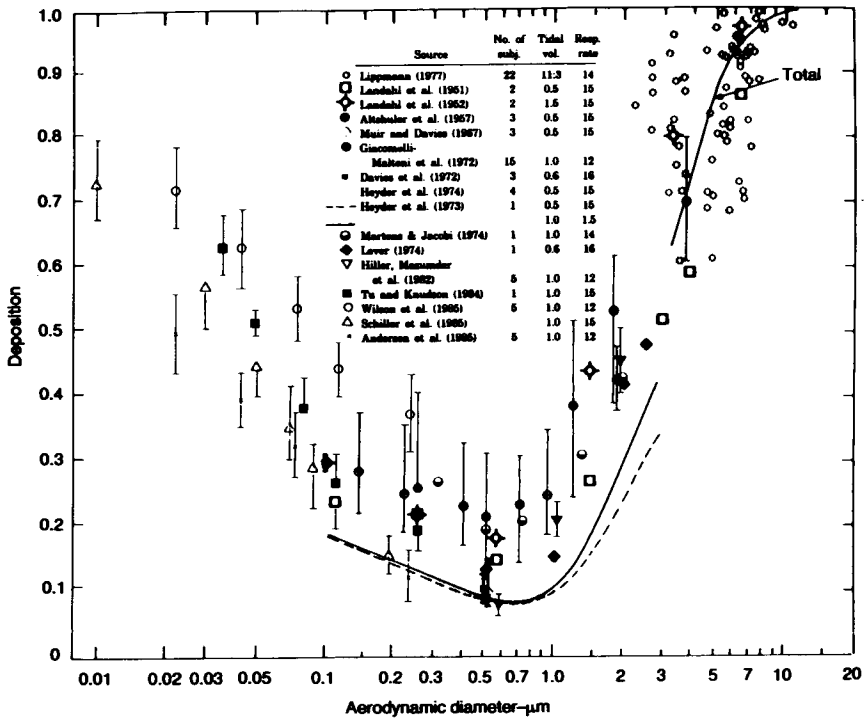

Figure 1.—Total respiratory tract deposition of inhaled inert particles during oral inhalation

NOTE: The portion of the figure from 0.01 to 0.1 μm 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 Knudson 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 μm) are not substantially reduced in number by passage through the nose. The fraction of inert 0.2 μm 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 μm 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 1986).

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

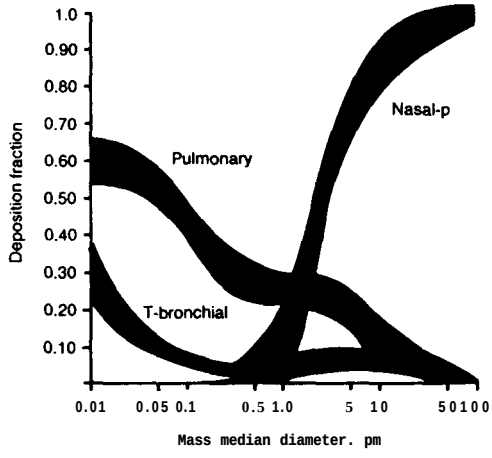

Figure 2.--Regional deposition of particles inhaled during nasal breathing, as predicted using the deposition model proposed by the Task Group on Lung Dynamics

SOURCE: International Committee on Radiation Protection, Task Force cm 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 μm 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 μm particles, and a peak in airway surface concentration density was predicted for 8 μm 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 μm 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 1936).

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 mg/m^3 in experimental chambers (Hoegg 1972). High levels, 2 to 4 mg/m^3, have also been estimated using measured carbon monoxide concentrations for rooms 140 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 $\mu g/m^3$ annual average and the 260 $\mu g/m^3$ 24-hour average in the United States and the 250 $\mu g/m^3$ 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 $\mu g/m^3$ in no-smoking areas, and can range from 100 to 700 $\mu g/m^3$ 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 $\mu g/m^3$ 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 to 60 $\mu g/m^3$ 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 $\mu g/m^3$ in bus and airline waiting rooms and as high as 640 $\mu g/m^3$ 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 $\mu g/m^3$, 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 μm/m^3 x ±SD	Background μm/m^3	Comments
Just et al. (1972)	Coffee shop	4 locations	1,150	570 [1]	
Hinds and First (1975)	Bus waiting room		40 (16-58)	Not applicable	Suspended particulates collected on filter; nicotine content measured for calculation; TSP = nicotine/0.026
	Restaurant	Not given	200 (51-450)		
	Cocktail lounge	Not given	400 (170-640)		
Elliott and Rowe (1975)	Arena A	Attendance 9,600 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 Air conditioned (S)	481	42	
	Arena B	Attendance 2,000 Not air conditioned (S)	620	92	
	Arena C	Attendance 11,000 Natural ventilation (NS)	148	71	
Cuddeback et al. (1976)	Tavern	6 air changes/hr	0.31 ± 0.05 (0.23-0.34)		8-hr air sample collected on filter (5 μm 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 μm/m³ x ±SD	Background μm/m³	Comments
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 ± 8 persons/100 m³, all NS	38 ± 16	Not done	All samples collected using piezoelectric balance with very high collection efficiency at 3.5 μm and 10% at 4 μm; sample time 1–50 min, outdoors 5–15 min
	Libraries, churches, restaurants	9 locations; 10 ± 10 persons/100 m³, all NS	38 ± 16	36 ± 10[1] (4 locations)	
	Restaurants, bars, bingo game	19 locations, 20 samples, 11 ± 8 persons/100 m³, all S locations	242 ± 175 (86–697)	47 ± 13[1] (13 locations)	
		7 locations with >1 smoker/m³ (mean 2.2 smokers/m³)	406 ± 188 (187–697)	53 ± 8[1]	
		18 ± 7 persons/100 m³, with 1 smoker/100 m³			

TABLE 4.--Continued

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

[1] Ambient particulate concentration at site, but outdoors.
[2] 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^3	Comments
Penkala and de Oliveira (1975)	Well mixed	None	9.2 m^3	3 simultaneously, 2 q puffs	3.8	
Hoegg (1972)	Sealed chamber; experimenter and test equipment in chamber; measured 18 min poetsmoking	Portable fans circulated air	25 m^3	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^3	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 Climate-controlled chamber	11 ft^3/min/occupant	11 m^3	4/hr (by occupants)	0.350	Piezoelectric balance measured total mass over 0.01-20 pm
		68 ft^3/min/occupant	11 m3	4/hr (by occupants)	0.15	
		11 ft^3/min/occupant	11 m^3	16/hr (by occupants)	1.25	
		68 ft^3/min/cccupant	11 m^3	16/hr (by occupants)	0.40	
Muramatsu et al. (1983)	Climate-controlled chamber	15.4 air changes/hr	30 m^3	1/8 min to 60 min	0.19-0.26	Piezoelectric balance
	Climate-controlled chamber	15.4 air changes/hr	30 m^3	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 (mg/m^3) x V_E; where $PMI_{(p)}$ equals the particulate mass inhaled by passive smoking, TSP equals the total suspended particulate, and 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.

	Example 1	Example 2
$\dot{V}_E$	0.36 m^3/hr	20 m^3/day
$PMI_{(ms)}$	16.1 mg tar/cig	0.55 mg tar/cig
TSP	40 $\mu g/m^3$	700 $\mu g/m^3$

Example 1

$$PMI_{(p)} = TSP \times \dot{V}_E$$
$$= 40\ \mu g/m^3 \times 0.36\ m^3/hr$$
$$= 14.4\ \mu g/hr$$

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

Example 2

$PMI_{(p)}$ = TSP x $\dot{V}_E$
= 700 $\mu g/m^3$ x 20 m^3/day
= 14,000 μg/day

C.E. = $PMI_{(p)}/PMI_{(ms)}$
= (14 mg/day)/(0.55 mg/cig)
= 25 cig/day

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 1.6×10^3 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 ng/m^3, an inhaled volume of 2.4 m^3, and 8.2 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

compared is almost certainly substantially greater with measures of absorption than with atmospheric measures.

Tobacco smoke contains many substances, but only a few have been measured in human biological fluids. Of the gaseous components, markers include carbon monoxide and thiocyanate. The latter is not a gas but a metabolite of gaseous hydrogen cyanide. Concentrations of nicotine and its metabolite cotinine are markers of nicotine uptake. In mainstream smoke, nicotine uptake reflects exposure to particulates. In environmental tobacco smoke, nicotine becomes vaporized and therefore reflects gas phase exposure (Eudy et al. 1985). Quantitating tar consumption is more difficult; urinary mutagenic activity has been used as an indirect marker.

The relative exposures of nonsmokers to various tobacco smoke constituents differs from that of smokers. Assuming that exposure to a single tobacco smoke constituent accurately quantifies the exposure of both smokers and nonsmokers to other constituents is inaccurate because mainstream smoke and environmental tobacco smoke differ in composition (see Chapter 3).

To understand the usefulness and limitations of various biochemical markers, it is important to appreciate the factors that influence their absorption by the body and their disposition kinetics within it.

Carbon Monoxide

Carbon monoxide is absorbed in the lungs, where it diffuses across the alveolar membrane (Lawther 1975; Stewart 1975). It is not appreciably absorbed across mucous membranes or bronchioles. Within the body, carbon monoxide binds, as does oxygen, to hemoglobin, where it can be measured as carboxyhemoglobin. Carbon monoxide may also be bound to myoglobin and to the cytochrome enzyme system, although quantitative details of binding to the latter sites are not available. Carbon monoxide is eliminated primarily by respiration. The amount of ventilation influences the rate of elimination. Thus, the half-life of carbon monoxide during exercise may be less than 1 hour, whereas during sleep it may be greater than 8 hours (Castleden and Cole 1974). At rest, the half-life is 3 to 4 hours.

The disposition kinetics of carbon monoxide explain the temporal variation of carbon monoxide concentration in active smokers during a day of regular smoking. With a half-life averaging 3 hours and a reasonably constant dosing (that is, a regular smoking rate), carbon monoxide levels will plateau after 9 to 12 hours of cigarette smoking. This has been observed in studies of circadian variation of carbon monoxide concentrations in cigarette smokers (Benowitz, Kuyt et al. 1982). Smoking is not a constant exposure source, but results in pulsed dosing. There is a small increment in carboxyhemoglobin level immediately after smoking a single cigarette, which then

declines until the next cigarette is smoked. But after several hours of smoking, the magnitude of rise and fall is small compared with the trough values. For this reason, carboxyhemoglobin levels at the end of a day of smoking are satisfactory indicators of carbon monoxide exposure during that day.

Carbon monoxide exposure may be more constant during environmental tobacco smoke exposure than during active smoking. The major limitation in using carbon monoxide as a means of measuring involuntary smoke exposure is its lack of specificity. Endogenous carbon monoxide generation from the metabolism of hemoglobin results in a low level of carboxyhemoglobin (up to 1 percent) (Lawther 1975; Stewart 1975). Carbon monoxide is generated by any source of combustion, including gas stoves, machinery, and automobile exhaust. Thus, nonsmokers in a community with moderate home and industrial carbon monoxide sources may have carboxyhemoglobin levels of 2 or 3 percent (Woebkenberg et al. 1981). A carbon monoxide level of 10 in room air results in an increment of 0.4 and 1.4 percent carboxyhemoglobin at 1 and 8 hours of exposure time, respectively (Lawther 1975, Stewart 1975). Thus, small increments of carbon monoxide due to environmental tobacco smoke may be indistinguishable from that due to endogenous and non-tobacco relatedsources.

Measurement of carbon monoxide is straightforward and inexpensive. Alveolar carbon monoxide pressures are proportional to the concentration of carboxyhemoglobin in blood; therefore, end-tidal carbon monoxide tension accurately reflects blood carboxyhemoglobin (Jarvis and Russell 1980). Expired carbon monoxide can be measured using an instrument (Ecolyzer) that measures the rate of conversion of carbon monoxide to carbon dioxide as it passes over a catalytically active electrode. Blood carboxyhemoglobin can be measured directly and quickly using a differential spectrophotometer.

Thiocyanate

Hydrogen cyanide is metabolized by the liver to thiocyanate. In addition to tobacco smoke, certain foods, particularly leafy vegetables and some nuts, are sources of cyanide. Cyanide is also present in beer.

Thiocyanate is distributed in extracellular fluid and is eliminated slowly by the kidneys. The half-life of thiocyanate is long, about 7 to 14 days. Thiocyanate is also secreted into saliva, with salivary levels about 10 tunes that of plasma levels (Haley et al. 1933). The long half-life of thiocyanate means that there is little fluctuation in plasma thiocyanate concentrations during a day or from day to day. Thus, the time of sampling is not critical. On the other hand, a given level of thiocyanate reflects exposure to hydrogen cyanide over

several weeks preceding the time of sampling. When a smoker stops smoking, it takes an estimated 3 to 6 weeks for thiocyanate levels to reach that individual's nonsmoking level.

Because of the presence of cyanide in foods, thiocyanate is not specific for exposure to cigarette smoke. Although active smokers have plasma levels of thiocyanate two to four times those of nonsmokers (Vogt et al. 1979, Jacob et al. 1981), light smokers or involuntary smokers may have little or no elevation of thiocyanate. When thousands of subjects are studied involuntary smokers have been found to have slightly higher thiocyanate levels than those without exposure (Friedman et al. 1983). Other studies of smaller numbers of subjects have shown no difference in thiocyanate level between exposed or nonexposed nonsmokers (Jarvis et al. 1984).

Serum or plasma thiocyanate levels can be measured using spectrophotometric methods or, alternatively, gas chromatography.

Nicotine

Nicotine is absorbed through the mucous membranes of the mouth and bronchial tree as well as across the alveolar capillary membrane. The extent of mucosal absorption varies with the pH of the smoke, such that nicotine is absorbed in the mouth from alkaline (cigar) smoke or buffered chewing gum, but very little is absorbed from acidic (cigarette) mainstream smoke (Armitage and Turner 1970). With aging, environmental tobacco smoke becomes less acidic; pH may rise to 7.5, and buccal or nasal absorption of nicotine by the nonsmoker could occur (see Chapter 3).

Nicotine is distributed rapidly to body tissues and is rapidly and extensively metabolized by the liver. Urinary excretion of unmetabolized nicotine is responsible for from 2 to 25 percent of total nicotine elimination in alkaline and acid urine, respectively; nicotine excretion also varies with urine flow (Rosenberg et al. 1980). Exposure to environmental tobacco smoke, active smoking, and use of smokeless tobacco markedly elevate salivary nicotine transiently out of proportion to serum and urinary levels (Hoffmann et al. 1984). Nicotine is present in breast milk (Luck and Nau 1985), and the concentration in the milk is almost three times the serum concentration in the mother (Luck and Nau 1984).

The rate of nicotine metabolism varies considerably, as much as fourfold among smokers (Benowitz, Jacob et al. 1982). There is evidence that nicotine is metabolized less rapidly by nonsmokers than by smokers (Kyerematen et al. 1982). A given level of nicotine in the body reflects the balance between nicotine absorption and the metabolism and excretion rates. Thus, in comparing two persons with the same average blood concentration of nicotine, a rapid metabolizer may be absorbing up to four times as much nicotine as a slow metabolizer. To determine daily uptake of nicotine directly,

both the nicotine blood concentrations and the rates of metabolism and excretion must be known. These variables can be measured in experimental studies (Benowitz and Jacob 1984, Feyerabend et al. 1985), but are not feasible for large-scale epidemiologic studies.

The time course of the decline of blood concentrations of nicotine is multiexponential. Following the smoking of a single cigarette or an intravenous injection of nicotine, blood concentrations of nicotine decline rapidly owing to tissue uptake, with a half-life of 5 to 10 minutes. If concentrations are followed over a longer period of time or if multiple doses are consumed so that the tissues are saturated, a longer elimination half-life of about 2 hours becomes apparent (Benowitz, Jacob et al. 1982; Feyerabend et al. 1985). Because of the rapid and extensive distribution in the tissues, there is considerable fluctuation in nicotine levels in cigarette smokers during and after smoking. As predicted by the 2-hour half-life, nicotine blood concentrations increase progressively and plateau after 6 to 8 hours of regular smoking (Benowitz, Kuyt et al. 1982). Nicotine concentrations have been sampled in the afternoon in studies of nicotine uptake during active cigarette smoking (Benowitz and Jacob 1984, and similar timing might be appropriate in assessing the plateau levels that result from continuous ETS exposure, such as during a workday.

Russell and colleagues (1985) quantitated nicotine exposure by comparing blood nicotine concentrations during intravenous infusions (0.5 to 1.0 mg over 60 minutes) in nonsmokers to the blood nicotine concentrations in nonsmokers exposed to environmental tobacco smoke. The data suggest that nicotine uptake in a smoky bar in *2 hours* averaged 0.20 mg per hour.

The presence of nicotine in biologic fluids is highly specific for tobacco or tobacco smoke exposure. Nicotine concentration is sensitive to recent exposure because of nicotine's relatively rapid and extensive tissue distribution and its rapid metabolism. Urinary nicotine concentration has been examined in a number of studies of environmental tobacco smoke exposure. Although influenced by urine pH and flow rate, the excretion rate of nicotine in the urine reflects the concentration of nicotine in the blood over the time period of urine sampling. In other words, nicotine excretion in a timed urine collection is an integrated measure of the body's exposure to nicotine during that time. When timed urine collections are not available, nicotine excretion is commonly expressed as a ratio of urinary nicotine to urinary creatinine, which is excreted at a relatively constant rate throughout the day. Urinary nicotine excretion is highly sensitive to environmental tobacco smoke exposure (Hoffmann et al. 1984; Russell and Feyerabend 1975). Saliva levels of nicotine rise rapidly during exposure to sidestream smoke and fall rapidly after exposure has ended (Hoffmann et al. 1984).

Presumably, this time course reflects local mouth contamination, followed by absorption or the swallowing of nicotine.

Blood, urine, or saliva concentrations of nicotine can be measured by gas chromatography, radioimmunoassay, or high pressure liquid chromatography. Sample preparation is problematic in that contamination of samples with even small amounts of tobacco smoke can substantially elevate the normally low concentrations of nicotine in the blood. Thus, careful precautions against contamination during sample collection and processing for analysis are essential. Because the concentrations are so low, the measurement of nicotine in blood has been difficult for many laboratories in the past, but with currently available assays, it is feasible for large-scale epidemiologic studies.

Cotinine

Cotinine, the major metabolite of nicotine, is distributed to body tissues to a much lesser extent than nicotine. Cotinine is eliminated primarily by metabolism, with 15 to 20 percent excreted unchanged in the urine (Benowitz et al. 1983). Urinary pH does affect the renal elimination of cotinine, but the effect is not as great as for nicotine. Since renal clearance of cotinine is much less variable than that of nicotine, urinary cotinine levels reflect blood cotinine levels better than urinary nicotine levels reflect blood nicotine levels. Plasma, urine, and saliva cotinine concentrations correlate strongly with one another (Haley et al. 1983; Jarvis et al. 1984).

The elimination half-life for cotinine averages 20 hours (range, 10 to 37 hours) (Benowitz et al. 1983). Because of the relatively long half-life of cotinine, blood concentrations are relatively stable throughout the day for the active smoker, reaching a maximum near the end of the day. Because each cigarette adds relatively little to the overall cotinine level, sampling time with respect to smoking is not critical. Assuming that smoke exposure occurs throughout the day, a midafternoon or late afternoon level reflects the average cotinine concentration.

The specificity of cotinine as a marker for cigarette smoking is excellent. Because of its long half-life and its high specificity, cotinine measurements have become the most widely accepted method for assessing the uptake of nicotine from tobacco, for both active and involuntary smoking.

Cotinine levels can be used to generate quantitative estimates of nicotine absorption. Galeazzi and colleagues (1985) defined a linear relationship between nicotine uptake and plasma cotinine levels in six healthy volunteers who received several i.v. doses of nicotine ($\leq$ 480 µg/day) for 4 days. The ability to extrapolate from this model to levels in nonsmokers is limited, however, because the elimination half-life of cotinine may be shorter in smokers than in

nonsmokers, as is the elimination half-life of nicotine (Kyerematen et al. 1982).

Cotinine can be assayed by radioimmunoassay, gas chromatography, and high pressure liquid chromatography.

Urinary Mutagenicity

Tobacco smoke condensate is strongly mutagenic in bacterial test systems (Ames test) (Kier et al. 1974). A number of compounds, including polycyclic aromatic hydrocarbons, contribute to this mutagenicity. The urine of cigarette smokers has been found to be mutagenic, and the number of bacterial revertants per test plate is related to the number of cigarettes smoked per day (Yamasaki and Ames 1977). Urinary mutagenicity disappears within 24 hours after smoking the last cigarette (Kado et al. 1985).

For several reasons, the measurement of mutagenic activity of the urine is not a good quantitative measure of tar absorption. Individuals metabolize polycyclic aromatic hydrocarbons and other mutagenic substances differently. Only a small percentage of what is absorbed is excreted in the urine as mutagenic chemicals. The bacterial system is differentially sensitive to different mutagenic compounds. The urine of smokers presumably contains a mixture of many mutagenic compounds. In addition, the test lacks specificity, in that other environmental exposures result in urinary mutagenicity. The test may also be insensitive to very low exposures such as involuntary smoking. However, one study, by Bos and colleagues (1983), indicated slightly increased mutagenic activity in the urine of nonsmokers following tobacco smoke exposure.

The presence of benzo[a]pyrene and 4-amino biphenyl covalently bound to DNA and hemoglobin in smokers (Tannenbaum et al., in press) suggests other potential measures of carcinogenic exposure. Whether such measures will be sensitive to ETS exposure is unknown. The development of specific chemical assays for human exposure to components of cigarette tar remains an important research goal.

Populations in Which Exposure Has Been Demonstrated

Absorption of tobacco smoke components by nonsmokers has been demonstrated in experimental and natural exposure conditions.

Experimental Studies

Nonsmokers have been studied after exposures in tobacco-smoke filled rooms. The smoke may be generated by a cigarette smoking machine or by active smokers placed in the room by the investigator, or the location may be a predictably smoke-filled environment such as a bar. The level of environmental smoke has most often been

quantitated by measuring ambient carbon monoxide concentrations. In nonsmokers exposed for 1 hour in a test room with a carbon monoxide level of 38 ppm, carboxyhemoglobin levels increased by 1 percent and urinary nicotine increased about eightfold (Russell and Feyerabend 1975). Seven subjects in a similar study sat for 2 hours in a public house (bar) with a carbon monoxide level of 13 ppm; their expired carbon monoxide increased twofold and their urinary nicotine excretion increased ninefold (Jarvis et al. 1983). In a study exposing eight nonsmokers to a smoke-filled room for 6 hours, a small increase in urinary mutagenic activity was measured (Bos et al. 1983).

Nonexperimental Exposures

Exposure studies performed in real-life situations have compared biochemical markers of tobacco smoke exposure in different individuals with different self-reported exposures to tobacco smoke. Absorption of nicotine (indicated by urinary cotinine levels) was found to be increased in adult nonsmokers if the spouse was a smoker (Wald and Ritchie 1984). In another study (Matsukura et al. 1984), urinary cotinine levels in nonsmokers were increased in proportion to the presence of smokers and the number of cigarettes smoked at home and the presence and number of smokers at work. Blood and urinary nicotine levels were increased after occupational exposure to ETS such as a transoceanic flight by commercial airline flight attendants (Foliart et al. 1983). Nicotine absorption, documented by increased salivary cotinine concentration, has been shown in schoolchildren in relationship to the smoking habits of the parents (Jarvis et al. 1985), and using plasma, urinary, and saliva measures, in infants in relation to the smoking habits of the mother (Greenberg et al. 1984; Luck and Nau 1985; Pattishall et al. 1985).

Quantification of Absorption

Evidence of Absorption in Different Populations

One questionnaire survey indicated that 63 percent of individuals report exposure to some tobacco smoke (Friedman et al. 1983). Thirty-four percent were exposed for 10 hours and 16 percent for 40 or more hours per week. The distribution of cotinine levels in a few populations has been reported. In men attending a medical screening examination, there was a tenfold difference in mean urinary cotinine in nonsmokers with heavy exposure (20 to 80 hours per week) compared with those who reported no ETS exposure (Wald et al. 1984). The median and 90th percentile urinary cotinine concentrations for all nonsmokers who reported exposure to other people's smoke were 6.0 and 22.0 ng/mL, respectively, compared with a median of 1645 ng/mL for active smokers. In 569 nons-moking

schoolchildren, salivary cotinine concentrations were widely distributed. Values were strongly influenced by parental smoking habits (Jarvis et al. 1985). The median and 25 to 75 percent ranges (in ng/mL) were 0.20 (0-0.5), 1.0 (0.4-1.8), 1.35 (0.7-2.7), and 2.7 (1.5-4.4) for children whose parents did not smoke or whose father only, mother only, or both parents smoked, respectively.

Quantification of Exposure

Expired carbon monoxide, carboxyhemoglobin, plasma thiocyanate, plasma or urinary nicotine, and plasma, urinary, or salivary cotinine have been used to evaluate exposure to ETS. However, successful attempts to quantify the degree of exposure have been limited largely to measurements of nicotine and cotinine. Expired carbon monoxide and carboxyhemoglobin have been found to be increased up to twofold after experimental or natural exposures (Russell et al. 1973), ‘but not in more casually exposed subjects. Thiocyanate was slightly increased in one very large study of heavily exposed individuals (Friedman et al. 1983), but most studies report no differences as a function of involuntary smoking exposure. The most useful measures appear to be nicotine and cotinine. The data on nicotine and cotinine measurements are presented in Tables 6 and 7 and suggest the following:

(1) Both nicotine and cotinine are sensitive measures of environmental tobacco smoke exposure. Levels in body fluids may be elevated 10 or more times in the most heavily exposed groups compared with the least exposed groups.

(2) The time course of change in the levels of biochemical markers depends on which marker is selected and which fluid is sampled. There is a lag between peak blood levels of nicotine and peak blood levels of cotinine, owing to the time required for metabolism (Hoffmann et al. 1984). Salivary levels of nicotine, because of the local deposition of smoke in the nose and mouth, peak early and decline rapidly.

(3) With nicotine, salivary levels increase considerably after environmental tobacco smoke exposure, but decline rapidly following the end of exposure. Blood nicotine levels are too low to be very useful in quantitating environmental nicotine exposure. Urinary nicotine is a sensitive indicator of passive smoke exposure, but because of its relatively short half-life, urinary nicotine levels decline within several hours of the time of exposure.

(4) Cotinine levels are less susceptible than nicotine to transient fluctuations in smoke exposure. Blood or plasma, urine, and saliva concentrations correlate strongly with one another. Because of the stability of cotinine levels measured at different times during an exposure and the availability of noninvasive (i.e., urine or saliva)

TABLE 6.—Nicotine measures in nonsmokers with environmental tobacco smoke (ETS) exposure and comparisons with active smoking

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration and range					
				Plasma nicotine (ng/mL)		Urine nicotine (ng/mL)		Saliva nicotine (ng/mL)	
				Before	After	Before	After	Before	After
Russell and Feyerabend (1975)	12	NS	78 min in smoke-filled room	0.73	0.90	—	80 (13–208)	—	—
	14	NS	Hospital	—	—	—	12.4 (0.8–64.3)	—	—
	13	NS	employees	—	—		8.9 (0–26)	—	—
	18	S	Average 24 cigs/day	—	—	—	1236 (104–2733)	—	—
Feyerabend et al. (1982)	26	NS	No S exposure	—	—	—	7.5	—	5.9
	30	NS	Work exposure	—	—	—	21.6	—	10.1
	8	S	Noninhalers	—	—	—	397	—	152
	15	S	Slight inhalers	—	—	—	1261	—	421
	32	S	Medium inhalers	—	—	—	1349	—	454
	27	S	Deep inhalers	—	—	—	1527	—	905
Foliart et al. (1983)	6	NS	Flight attendants	1.6 (0.8–2.7)	3.2 (1.6–4.5)	—	15.2 (8.3–34.4)	—	—
Jarvis et al. (1983)	7	NS	Before, 11:30 a.m. After, public house x 2 hr	0.8	2.5	10.5	92.6	1.9	43.6
Hoffmann et al. (1984)	10	NS	Experimental chamber						
			2 cigs burned	1.1	1.1	24[1]	51[1]	8	427
			3 cigs burned	ND	1.3	20	94	1	893
			4 cigs burned	0.2	0.5	17	100	3	730

TABLE 6.--Continued

Study	Number of subjects	smoking status	Exposure level	Mean or median concentration and range					
				Plasma nicotine (ng/mL)		Urine nicotine (ng/mL)		saliva nicotine (ng/mL)	
				Before	After	Before	After	Before	After
Jarvis et al.			Hospital clinic patients						
(1984)	46	NS	No exposure	-	1.0	-	3.9	-	3.8
	27	NS	Little exposure	-	0.8		12.2	-	4.8
	20	NS	Some exposure	-	0.7	-	11.9	-	4.4
	7	NS	Lot of exposure	-	0.9	-	12.2	-	12.1
	94	S		-	14.8	-	1750	-	672
Greenberg	32	NS	Infants, mother S	-	-	-	53[1] (0-370)		12.7 (0-166)
et al. (1984)	19	NS	Infant, mother NS	-	-	-	0 (0-59)		0 (0-17)
Luck and Nau	10	NS, neonates	No exposure	-		-	0[1] (0-14)	-	-
(1985)	10	NS, neonates	Nursed by S mother; no ETS exposure	-		-	14 (5-110)	-	-
	10	NS, infants	S mother, not nursed	-	-	-	35 (4-218)	-	-
	9	NS, infants	Nursed by S mother; ETS exposure	-		-	12 (3-42)	-	-

[1] ng/mg creatinine.

TABLE 7.--Cotinine measures in nonsmokers with environmental smoke exposure and comparisons with active smoking

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration and range					
				Plasma cotinine (ng/mL)		Urine cotinine (ng/mL)		Saliva cotinine (ng/mL)	
				Before	After	Before	After	Before	After
Jarvis et al. (1983)	7	NS	Before, 11:30 a.m. After, public house x 2 hr	1.1	7.3	4.8	12.9	1.6	8.0
Jarvis et al. (1984)			Hospital clinic patients						
	46	NS	No exposure	-	0.8	-	1.5	-	0.7
	27	NS	Little exposure	-	1.8	-	6.5	-	2.2
	20	NS	Some exposure	-	2.5	-	8.6	-	2.8
	7	NS	Lot of exposure	-	1.8	-	9.4	-	2.6
	94	S		-	275	-	1391	-	310
Hoffmann et al. (1984)	10	NS	Experimental chamber						
			2 cigs burned	1.7	2.6 (peak	14	21	1.2	2.3
			3 cigs burned	1.0	3.0 change)	14	38	1.7	2.5
			4 cigs burned	0.9	3.3	14	55	1.0	1.4
Wald and Ritchie (1984)	101	NS	Wife abstinent	-	-	8.5 (median 6.0)			
	20	NS	Wife smoker	-	-	25.2 (median 9.0)			

TABLE 7.—Continued

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration and range					
				Plasma cotinine (ng/mL)		Urine cotinine (ng/mL)		Saliva cotinine (ng/mL)	
				Before	After	Before	After	Before	After
Wald			Med screening clinic patients						
et al.	221	NS	Research colleagues			—	11.2		
(1984)	43	NS	0–1.5 hr ETS exposure/wk			—	2.8		
	47	NS	1.5–4.5 hr ETS exposure/wk			—	3.4		
	43	NS	4.5–8.6 hr ETS exposure/wk			—	5.3		
	43	NS	8.6–20 hr ETS exposure/wk			—	14.7		
	45	NS	20–80 hr ETS exposure/wk			—	29.6		
	131	S	Cigarettes			—	1645 (537–3326)		
	59	S	Cigars			—	396 (61–2138)		
	42	S	Pipes			—	1920 (1008–4569)		
Matsukura	200	NS	No home exposure			—	510[1]		
et al.	272	NS	All home exposure			—	790		
(1984)			Home exposure:						
	25	NS	1–9 cig/day			—	310		
	57	NS	10–19 cig/day			—	420		
	99	NS	20–29 cig/day			—	870		
	38	NS	30–39 cig/day			—	1030		
	28	NS	>40 cig/day			—	1560		
	472	NS	All			—	680		
	392	S	All			—	8520		
	76	NS	No workplace exposure			—	220		
	201	NS	Workplace exposure			—	720		

TABLE 7.--Continued

Study	Number of subjects	Smoking statue	Exposure level	Mean or median concentration end range					
				Plasma cotinine (ng/mL)		Urine cotinine (ng/mL)		Saliva cotinine (ng/mL)	
				Before	After	Before	After	Before	After
Greenberg et al. (1984)	32	NS, infants	S mother			-	351 (41-1885)		9 (0-25)
	19		NS mother			-	4 (0-125)	-	0 (0-3)
Jarvis et al. (1985)			Children aged 11-16						
	269	NS	Neither parent SM						0.4 (median 0.2)
	96	NS	SM father						1.3 (1.0)
	76	NS	SM mother					-	2.0 (1.7)
	128	NS	Both parents SM					-	3.4 (2.4)
Luck and Nau (1985)	10	NS, neonates	No exposure			-	0[1] (0-56)		-
	19	NS, neonates	Nursed by S mother; no ETS exposure		-	-	100 (10-555)		-
	10	NS, infants	S mother, not nursed			-	327 (117-780)	-	-
	9	NS, infants	S mother, nursed, ETS exposure			-	550 (225-870)	-	-
				Serum cotinine (ng/mL)					
Pattishall et al. (1985)	20	NS, children	Smokers in home		4.1	-	-	-	-
	18	NS, children	No smokers in home	-	1.0	-	-	-	-

TABLE 7.--Continued

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration end range					
				Plasma cotinine (ng/mL)		Urine cotinine (ng/mL)		Saliva cotinine (ng/mL)	
				Before	After	Before	After	Before	After
Coultas et al. (1986)	68	NS aged <5	No smokers in home	-	-	-	-	-	0, 1.7[2]
	41	NS aged <5	1 smoker in home	-		-	-	-	3.8, 4.1
	21	NS aged <5	2 or more smokers in home	-	-	-	-	-	5.4, 5.6
	200	NS aged 6-17	No smokers in home	-	-	-	-	-	0, 1.3
	96	NS aged 6-17	1 smoker in home	-		-	-	-	1.8, 2.4
	25	NS aged 6-17	2 or more smokers in home	-		-	-	-	5.3, 5.6
	316	NS aged >17	No smokers in home	-		-	-	-	0, 1.5
	60	NS aged >17	1 smoker in home	-	-	-	-	-	0.6, 2.8
	12	NS aged >17	2 or more smokers in home	-	-	-	-	-	0, 3.7

[1]ng/mg creatinine.
[2]median, mean.

measurements, cotinine appears to be the short-term marker of choice for epidemiological studies.

(5) Mean levels of urinary nicotine and of cotinine in body fluids increase with an increasing self-reported ETS exposure and with an increasing number of cigarettes smoked per day. There is considerable variability in levels among individuals at any given level of self-reported exposure.

Comparison of Absorption From Environmental Tobacco Smoke and From Active Smoking

Epidemiologic studies show a dose-response relationship between number of cigarettes smoked and lung cancer, coronary artery disease, and other smoking-related diseases. Assuming that dose-response relationships hold at the lower dose end of the exposure-response curve, risks for nonsmokers can be estimated by using measures of absorption of tobacco smoke constituents to compare the relative exposures of active smokers and involuntary smokers.

As discussed previously, measures of nicotine uptake (i.e., nicotine or cotinine) are the most specific markers for ETS exposure and provide the best quantitative estimates of the dose of exposure. Although the ratio of nicotine to other tobacco smoke constituents differs in mainstream smoke and sidestream smoke, nicotine uptake may still be a valid marker of total ETS exposure. Nicotine uptake in nonsmokers can be estimated in several ways.

Russell and colleagues (1985) infused nicotine intravenously to nonsmokers and compared resultant plasma and urine nicotine levels with those observed in nonsmokers with ETS exposure. An infusion of 1 mg nicotine over 60 minutes resulted in an average plasma nicotine concentration of 6.6 ng/mL and an average urinary nicotine concentration of 224 ng/mL. Using these data in combination with measured plasma and urinary nicotine levels in nonsmokers after 2 hours in a smoky bar, nicotine uptake was estimated as 0.22 mg per hour. Since the average nicotine uptake per cigarette is 1.0 mg (Benowitz and Jacob 1984; Feyerabend et al. 1985), 0.22 mg of nicotine is equivalent to smoking about one-fifth of a cigarette per hour. In making these calculations, it is assumed that the disposition kinetics of inhaled and intravenous nicotine are similar and that the rate of nicotine exposure from ETS is constant.

Steady state blood cotinine concentrations can also be used to estimate nicotine uptake. Galeazzi and colleagues (1985) measured cotinine levels in smokers receiving various doses of intravenous nicotine, simulating cigarette smoking, for 4 days. They described the relationship: [steady state plasma cotinine concentration] (ng/mL) = (0.783) x [daily nicotine uptake] (μg/kg/day). With such data, a 70 kg nonsmoker with a plasma cotinine concentration of 2.5 ng/mL would have an estimated uptake of 3.2 μg nicotine/kg/day, or

0.22 mg nicotine/day, equivalent to one-fifth of a cigarette. This approach assumes that the half-life for cotinine and nicotine eliminations is similar in smokers and nonsmokers, an assumption that may not be correct (Kyerematen et al. 1982).

A third approach is to compare cotinine levels in nonsmokers with those in smokers. Jarvis and colleagues (1984) measured plasma, saliva, and urine nicotine and cotinine levels in 100 nonsmokers selected from outpatient medical clinics and in 94 smokers. Ratios of average values for nonsmokers compared with smokers were as follows: plasma cotinine, 0.5 percent; saliva cotinine, 0.5 percent; urine cotinine, 0.4 percent; urine nicotine, 0.5 percent; and saliva nicotine, 0.7 percent. These data suggest that, on average, nonsmokers absorb 0.5 percent of the amount of nicotine absorbed by smokers. Assuming that the average smoker consumes 30 mg nicotine per day (Benowits and Jacob 1984), this ratio predicts an exposure of 0.15 mg nicotine, or one-sixth of a cigarette per day. The most heavily exposed group of nonsmokers had levels almost twice the overall mean for nonsmokers, indicating that their exposure was equivalent to one-fourth of a cigarette per day. Most studies (see Tables 6 and 7) report similar ratios when comparing nonsmokers with smokers. The exception is Matsukura and colleagues (1984), who reported urine cotinine ratios of nonsmokers to smokers of 6 percent. The reason for such high values in this one study is unknown

Personal air monitoring data for nicotine exposure can also be used to estimate nicotine uptake. For example, Muramatsu and colleagues (1984) used a pocketable personal air monitor to study environmental nicotine exposures in various living environments. They reported air levels of from 2 to 48 µg nicotine/m^3. Assuming that respiration is 0.48 m^3 per hour and exposure is for 8 hours per day, nicotine uptake is estimated to range from 8 to 320 µg per day. The average values are consistent with other estimates of one-sixth to one-third cigarette equivalents per day in general populations of nonsmokers exposed to ETS.

As noted before, these estimates must be interpreted with caution. Relative absorption of nicotine in smokers and nonsmokers may substantially underestimate exposure to other components of ETS.

Conclusions

1. Absorption of tobacco-specific smoke constituents (i.e., nicotine) from environmental tobacco smoke exposures has been documented in a number of samples of the general population of developed countries, suggesting that measurable exposure to environmental tobacco smoke is common.

2. Mean levels of nicotine and cotinine in body fluids increase with self-reported ETS exposure.
3. Because of the stability of cotinine levels measured at different times during exposure and the availability of noninvasive sampling techniques, cotinine appears to be the short-term marker of choice in epidemiological studies.
4. Both mathematical modeling techniques and experimental data suggest that 10 to 20 percent of the particulate fraction of sidestream smoke would be deposited in the airway.
5. The development of specific chemical assays for human exposure to the components of cigarette tar is an important research goal.

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