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-related sources.

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 times that of plasma levels (Haley et al. 1983). 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/kg/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

nsmokers, 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 nonsmoking

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. (1984)			Hospital clinic patients						
	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 et al. (1984)	32	NS	Infants, mother S	—	—	—	53[1] (0–370)	—	12.7 (0–166)
	19	NS	Infant, mother NS	—	—	—	0 (0–59)	—	0 (0–17)
Luck and Nau (1985)	10	NS, neonates	No exposure	—	—	—	0[1] (0–14)	—	—
	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	1.5	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 5.0)			
	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 et al. (1984)			Med screening clinic patients			—	11.2		
	221	NS	Research colleagues			—	2.8		
	43	NS	0–1.5 hr ETS exposure/wk			—	3.4		
	47	NS	1.5–4.5 hr ETS exposure/wk			—	5.3		
	43	NS	4.5–8.6 hr ETS exposure/wk			—	14.7		
	43	NS	8.6–20 hr ETS exposure/wk			—	29.6		
	45	NS	20–80 hr ETS exposure/wk			—	1645 (537–3326)		
	131	S	Cigarettes			—	396 (61–2138)		
	59	S	Cigars			—	1920 (1008–4569)		
	42	S	Pipes						
Matsukura et al. (1984)	200	NS	No home exposure			—	510[1]		
	272	NS	All home exposure			—	790		
			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 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
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 and 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[a]
	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.

[a] 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 (Benowitz 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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CHAPTER 5

TOXICITY, ACUTE IRRITANT EFFECTS, AND CARCINOGENICITY OF ENVIRONMENTAL TOBACCO SMOKE