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Contribution of Passive Smoking to Respiratory Cancer

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This article reviews data from experimental and epidemiologic studies on passive smoking and makes 12 recommendations for further study. The physicochemical nature of passive smoke, the smoke inhaled by nonsmokers, differs significantly from the mainstream smoke inhaled by the active smoker. At present, measurement of urinary cotinine appears to be the best method of assessing exposures to passive smoking. Data indicate that the greater number of lung cancers in nonsmoking women is probably related to environmental tobacco smoke. Exposures in utero and very early in life to passive smoking may be important in relationship to the subsequent development of cancer and need further consideration. The short-term effects of environmental tobacco smoke on the cardiovascular system, especially among high-risk individuals, may be of greater concern than that of cancer and requires further study. Further study of increased risks of lung cancers in relation to environmental tobacco smoke exposure requires larger collaborative studies to identify lung cancer cases among nonsmokers, better delineation of pathology, and more careful selection of controls. In addition, studies of epithelial cells or specific cytology should be undertaken to determine evidence of cellular changes in relation to environmental tobacco smoke exposure. Animal inhalation studies with passive smoke should be initiated with respect to transplacental carcinogenesis, the relationship of sidestream smoke exposure with lung cancer, the induction of tumors in the respiratory tract and other organs, and the differences in the physicochemical natures of sidestream and mainstream smoke.

Tobacco smoke affects not only people who smoke but also nonsmokers who are exposed to the environmental pollutants that are generated when tobacco products are burned. Sidestream smoke (SS), which is emitted from the tobacco products during puff intervals, constitutes the major source of such pollutants. Some of the mainstream smoke (MS) which escapes into the environment from the mouthpiece of the cigarette, cigar, or pipe after drawing a puff and that portion of the smoke exhaled by the smoker are further contributors to indoor air pollution. The exposure of nonsmokers to environmental tobacco smoke pollutants is also known as "passive smoking."

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Sidestream Smoke

The composition of SS differs significantly from that of MS. The SS generated between puff-drawing originates from a hydrogen-enriched, strongly reducing atmosphere. It contains, therefore, more combustion products than MS formed as a result of oxygen deficiency and thermal cracking. In addition, SS formation involves generation of larger quantities of reaction products of nitrates.

Table 1 compares MS and SS from an 85-mm nonfilter cigarette (*1*). These two tobacco combustion products are generated at distinctly different temperatures, and particle sizes in MS (0.1–1.0μm) are about 10 times those in SS (0.01–0.1μm). This suggests that, upon inhalation, SS particles reach the more distant alveolar spaces of the lung to a greater extent than do the MS particles (*2*). Above pH 6, increasing amounts of unprotonated nicotine are present in the smoke. Therefore, SS (pH 6.4–6.6) contains more free nicotine in the gas phase than MS (*3*).

About 300 to 400 of the more than 3800 individual compounds identified in tobacco smoke have been quantitatively determined in both MS and SS. Ratios >1.0

Table 1. Comparisons of mainstream (MS) and sidestream (SS) smoke of cigarettes (physicochemical data).[a]

	MS	SS
Parameters		
Peak temperature during formation, °C	≈900	≈600
pH (total aerosol)[b]	6.0–6.2	6.4–6.6
Particle size, μm	0.1–1.0	0.01–0.1
Median diameter, μm	0.4	
Smoke dilution (vol. %)[c]		
Carbon monoxide	3–5	≈1
Carbon dioxide	8–11	≈2
Oxygen	12–16	16–20
Hydrogen	15–3	≈0.5

[a] From Hoffmann et al. (*12*) by permission.
[b] For 85 mm nonfilter cigarette.
[c] At 10 mm distance from the burning coal.

in Table 2 (*4*) show that more of a given compound is released into SS than into MS. However, it must be realized that, in general, exposure to SS occurs after considerable air dilution, while the MS of cigarettes is inhaled without major dilution.

The first part of Table 2 focuses on a comparison of a few volatile compounds in MS and SS. On the basis of the amount of tobacco burned during the smouldering of a cigarette without filter tip, SS to MS ratios should be between 1.3 to 1.7. This calculation is based on the assumption that the combustion processes during both phases of smoke generation are comparable. However, this is not the case, as indicated by the higher SS values for CO (2.5–4.7), CO_2 (8–11), acrolein (8–15), and benzene (10), and for the pyrolysis products of nicotine: pyridine (6.5–20), 3-methylpyridine (3–13), and 3-vinylpyridine (20–40). The lower SS value for hydrogen cyanide (0.1–0.25) also indicates that the generation of MS and SS is governed by different combustion processes. The higher SS yields of the reduction products of nitrate such as nitrogen oxide (4–10), ammonia (40–170), methylamine (4.2–6.4), and especially the highly carcinogenic *N*-nitrosodimethylamine (20–100) and *N*-nitrosopyrrolidine (6–30) suggest higher toxicity and carcinogenicity for undiluted SS than for MS.

Similarly, compared to MS, the particulate phase of undiluted SS contains significantly higher amounts of carcinogenic amines (2-toluidine, 2-naphthylamine, 4-aminobiphenyl), carcinogenic hydrocarbons (benz[a]anthracene, benzo[a]pyrene), and metals (cadmium, nickel, zinc).

Finally, it must be emphasized that the data in Table 2 are derived from analyses carried out under standardized laboratory conditions that may not fully reflect the conditions prevailing in environmental settings, which are influenced by such variables as puff-drawing of the cigarette, room temperature, degree of ventilation, and a number of other factors. Another important point is that MS emissions are significantly affected by filtration, while SS emissions are practically unchanged by the presence and nature of the filter tip of a cigarette.

Table 2. Distribution of compounds in cigarette mainstream smoke (MS) and sidestream smoke (SS) for nonfilter cigarettes.[a]

	MS	Unit	SS/MS
Vapor phase			
Carbon monoxide	10–23	mg	2.5–4.7
Carbon dioxide	20–40	mg	8–11
Carbonyl sulfide	18–42	μg	0.03–0.13
Benzene	12–48	μg	10
Toluene	160	μg	6
Formaldehyde	70–100	μg	0.1–≈50
Acrolein	60–100	μg	8–15
Acetone	100–250	μg	2–5
Pyridine	16–40	μg	6.5–20
3-Methylpyridine	12–36	μg	3–13
3-Vinylpyridine	11–30	μg	20–40
Hydrogen cyanide	400–500	μg	0.1–0.25
Hydrazine	32	ng	3
Ammonia	50–130	μg	40–170
Methylamine	11.5–28.7	μg	4.2–6.4
Dimethylamine	7.8–10	μg	3.7–5.1
Nitrogen oxide	100–600	μg	4–10
N-Nitrosodimethylamine	10–40	ng	20–100
N-Nitrosopyrrolidine	6–30	ng	6–30
Formic acid	210–490	μg	1.4–1.6
Acetic acid	330–810	μg	1.9–3.6
Particulate phase			
Particulate matter	15–40	mg	1.3–1.9
Nicotine	1–2.5	mg	2.6–3.3
Anatabine	2–20	μg	<0.1–0.5
Phenol	60–140	μg	1.6–3.0
Catechol	100–360	μg	0.6–0.9
Hydroquinone	110–300	μg	0.7–0.9
Aniline	360	ng	30
2-Toluidine	160	ng	19
2-Naphthylamine	1.7	ng	30
4-Aminobiphenyl	4.6	ng	31
Benz[a]anthracene	20–70	ng	2–4
Benzo[a]pyrene	20–40	ng	2.5–3.5
Cholesterol	22	μg	0.9
γ-Butyrolactone	10–22	μg	3.6–5.0
Quinoline	0.5–2	μg	8–11
Harman	1.7–3.1	μg	0.7–1.7
N'-Nitrosonornicotine	200–3,000	ng	0.5–3
NNK	100–1,000	ng	1–4
N-Nitrosodiethanolamine	20–70	ng	1.2
Cadmium	100	ng	7.2
Nickel	20–80	ng	13–30
Zinc	60	ng	6.7
Polonium-210	0.03–0.5	pCi	1.03–3.7
Benzoic acid	14–28	μg	0.67–0.95
Lactic acid	63–174	μg	0.5–0.7
Glycolic acid	37–126	μg	0.6–0.95
Succinic acid	110–140	μg	0.43–0.62

[a] Literature data (*4,57–61*).

Air Pollution by Tobacco Smoke

The most widely monitored indoor pollutant originating from tobacco is carbon monoxide. In controlled studies of enclosed spaces where machine-smoking occurred in the presence of people, CO levels ranged from 24 to 220 ppm without ventilation and were lowered to 4 to 80 ppm with 6 to 8.5 air exchanges per hour (*5*). Table 3 lists reported values for toxic and carcinogenic tobacco smoke pollutants measured under natural conditions. In most cases, the reported pollution levels for

Table 3. Toxic indoor tobacco smoke pollutants measured under natural conditions.[a]

Pollutant	Location	Concentration
Nitrogen oxide	Workrooms	39–345 μg/m³
Nitrogen dioxide	Workrooms	50 μg/m³
	Restaurants	2–190 μg/m³
Acrolein	Public places	20–100 μg/m³
Benzene	Public places	20–317 μg/m³
N-Nitrosodimethylamine	Restaurants, public places	0.01–0.24 μg/m³
N-Nitrosodiethylamine	Restaurants, public places	<0.01–0.2 μg/m³
Anthanthrene		0.5–3 ng/m³
Benzo[a]fluorene		39 ng/m³
Benzo[ghi]perylene		5.9–17 ng/m³
Benzo[a]pyrene	Restaurants, public places	2.8–760 ng/m³
Benzo[e]pyrene		
Coronene		
Fluoranthene		
Perylene		
Pyrene		
Nicotine	Submarines	15–35 μg/m³
	Public places	1–6 μg/m³
	Restaurants	3–10 μg/m³
	Workrooms	1–138 μg/m³
Particulate matter	Airplanes	< 120 μg/m³
	Taverns	330–980 μg/m³
	Workrooms	3–960 μg/m³

[a] From literature data (*62–71*).

the selected number of SS-derived agents in indoor air exceed many times those reported for polluted urban air. In the case of the volatile carcinogen nitrosodimethylamine, it has been calculated that the exposure of a person in a highly smoke-polluted room is equivalent, per hour, to that of an individual who inhales the smoke of four to eight nonfilter cigarettes (*6*).

It is generally believed, however, that cigarette smoking is probably the single most important source of indoor respirable particulate pollution. Friedman et al. estimated that 63.3% of adults were exposed to passive smoking for a least 1 hr/week (*7*). The exposure decreased with age. A higher percentage were exposed out of the home, usually at work, than in the home (Table 4). Repace and Lowrey estimated that average exposure of the nonsmoking adult population to tars from environmental tobacco smoke was 1.43 mg/day, varying from 0 to 14 mg (*8*). The workplace appeared to be four times as strong a source of exposure as the home because of the greater smoking density there (Table 5). A "typical cigarette smoker" would be exposed to an average of 14 mg of tar per cigarette and 32 cigarettes or 442 mg of tar per day. Thus, the ratio of active to passive smoking would be about 313 to 1.

Uptake of Smoke by Nonsmokers

The development of new biochemical methodologies enables us to obtain more definitive measurements of exposure to tobacco smoke by determining the uptake of tobacco-specific compounds into body fluids and calculating the health risk relative to that of exposure from active smoking. Some of these biochemical measurements of active smoking behavior are applicable to quantitating exposure by passive smoking.

Figure 1 demonstrates the association between cigarette smoking and the plasma levels of nicotine, cotinine, thiocyanate, and carboxyhemoglobin in whole blood. Nicotine and its metabolite, cotinine, are specific measures of tobacco consumption (*9*), while levels of carboxyhemoglobin and thiocyanate can be influenced by a variety of environmental factors (*10*). Cotinine, the major metabolite of nicotine, can be quantitated in plasma, saliva, and urine. Its assessment has proven helpful in differentiating smokers from nonsmokers

Table 4A. Overall percentages of subjects reporting various types and degrees of passive smoking (at least 1 hr/week).[a]

Passive smoking exposure	Total number studied	Positive response	
		Number	Percent
Any	34,861	22,069	63.3
Home	35,169	8,383	23.8
Other small area	35,201	14,223	40.4
Large area	35,135	16,336	46.5
10+ hr/week, any	34,861	12,034	34.5
40+ hr/week, any	34,861	5,551	15.9

[a] Data of Friedman et al. (*7*) by permission.

Table 4B. Distribution of total hours per week of any reported passive smoking: sum of the hours in each of the three areas.[a]

Total hr per week	Number	Percent
0	12,792	36.7
1–9	10,035	28.8
10–39	6,483	18.6
> 40	5,551	15.9
Total	34,861	100.0

[a] Data of Friedman et al. (*7*) by permission.

Table 5. Estimated probabilities of nonsmokers' exposure to tobacco smoke at home and at work.[a,b]

Lifestyle: daily average probability of being exposed (rounded values)		Exposure, mg	
		Modeled daily average	Daily probability-weighted
At work and at home	63 × 62 = 39%	2.27	0.89
Neither at work nor at home	37 × 38 = 14%	0.00	0.00
At home but not at work	62 × 37 = 23%	0.45	0.10
At work but not at home	63 × 38 = 24%	1.82	0.44
Total	100		1.43

[a] The estimated exposure to the particulate phase of ambient tobacco smoke for U.S. adults of working age, at work and at home (these two microenvironments account for an estimated 88% of the average person's—both smokers' and nonsmokers'—time), determined from average concentrations of tobacco smoke calculated for model workplace and home microenvironments, weighted for average occupancy. Nonexclusive probability of being exposed at work, 63%; probability of not being exposed at work, 37%. Nonexclusive probability of being exposed at home, 62%; probability of not being exposed at home, 38%.

[b] Data of Repace and Lowrey (*8*) by permission.

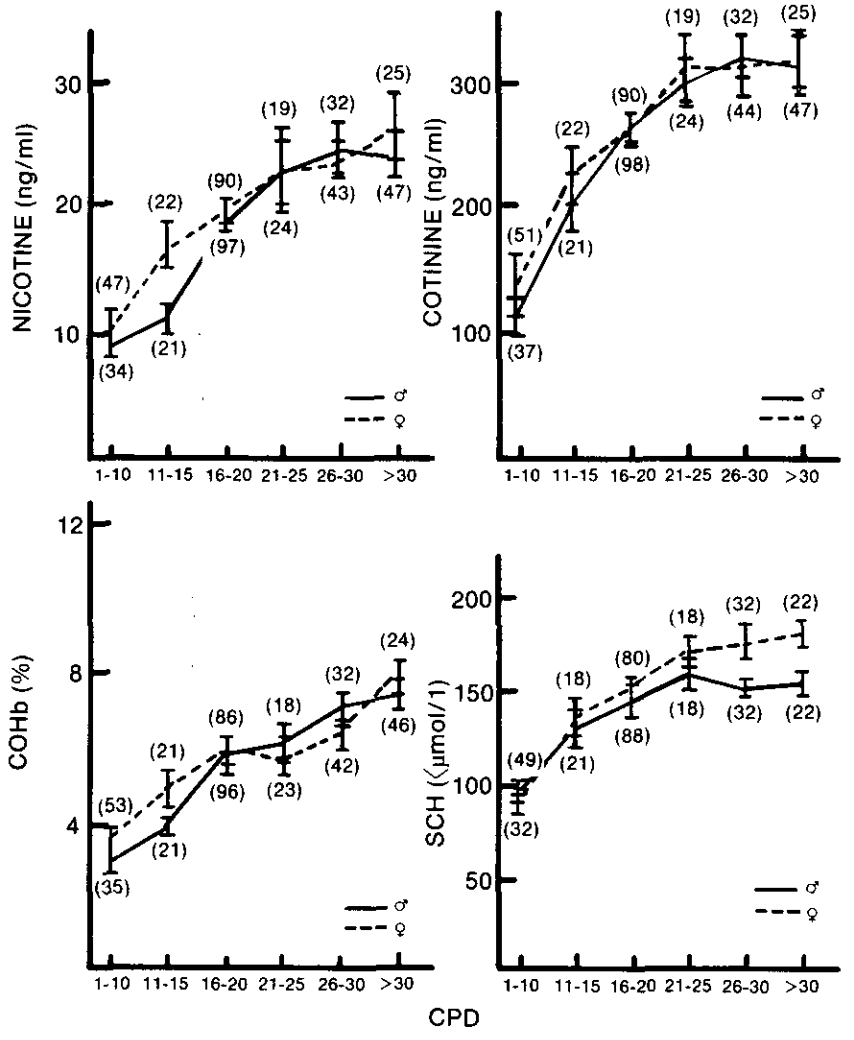

FIGURE 1. Plasma parameters of cigarette smoke absorption as a function of daily numbers of cigarettes consumed (CPD). Data given as the total population smoking all brands of cigarettes (*9*). Reprinted with permission.

even at low levels of daily cigarette use (*11*). Changes in smoking behavior or compensation as smokers switch to low-yield cigarettes can be effectively monitored by measurements of plasma cotinine.

Both nicotine and carboxyhemoglobin have short circulating half-lives such that measurement of these compounds limits their reliability to assess only very recent use of cigarettes (*9*). Cotinine has a relatively long half-life, is specific to tobacco exposure, and can be measured at low levels in biological fluids. Currently, this measurement provides the best index of exposure to environmental tobacco smoke, as well as of active smoking behavior.

The uptake of nicotine and its metabolic conversion to cotinine in nonsmokers has been investigated under controlled conditions in exposure chambers (*1,12*) and in free-living situations among adult (*13,14*) and pediatric (*15*) populations.

To investigate uptake under controlled conditions, a laboratory was constructed to expose nonsmoking subjects to sidestream smoke while exhausting the mainstream smoke from the room (*12*). The characteristics of this laboratory and pollution levels observed in it during the simultaneous smoking of four cigarettes are presented in Table 6. Nonsmoking volunteers remained

Table 6. Test laboratory.[a]

Size	16.3 m^3
Temperature	22 ± 1°C
Air exchange	6 times per hr
Pollutants	Sidestream smoke of four concurrently smoked 1R1 reference cigarettes
Indoor pollution	
Particulate matter	4,600 $\mu g/m^3$
Nicotine	280 $\mu g/m^3$
Hydrogen cyanide	56 $\mu g/m^3$
Carbon monoxide	25 ppm
NO_x	0.91 ppm
Formaldehyde	160 $\mu g/m^3$

[a] Data of Hoffmann et al. (*12*) by permission.

Table 7. Cotinine and nicotine levels in saliva of volunteers exposed to sidestream smoke.[a,b]

Time, min	2 Cigarettes[c] Nicotine, ng/mL	2 Cigarettes[c] Cotinine, ng/mL	3 Cigarettes Nicotine, ng/mL	3 Cigarettes Cotinine, ng/mL	4 Cigarettes Nicotine, ng/mL	4 Cigarettes Cotinine, ng/mL
Base-line	8	1.2	1	1.7	3	1.0
E 20	372	7.0	505	0.3	458	1.3
E 40	347	0.3	712	2.5	825	1.1
E 60	427	0.8	837	5.0	878	2.1
E 80	386	2.3	893	2.5	730	1.4
+30	76	2.3	157	1.5	148	1.7
60	26	1.0	46	3.3	49	1.4
90	13	1.5	26	2.3	31	2.7
120	6	1.5	17	2.8	23	2.5
150	3	2.5	9	2.3	17	3.1
180	13	3.3	14	2.0	24	2.8
210	5	1.5	12	3.5	6	2.0
240	8	5.0	2	1.3	3	1.9
270	6	3.3	4	2.0	6	2.3
300	7	1.0	7	1.0	7	3.5

[a] E = Exposure to sidestream smoke in 16 m^3 chamber.
[b] Data of Hoffmann et al. (*12*) by permission.
[c] Number of cigarettes being smoked throughout the exposure period.

in the room for 80 min, while saliva and blood samples were collected at 20-min intervals during exposure and for 5 hr after leaving the chamber. Tables 7–9 show the analytical profiles of markers of tobacco smoke exposure in saliva, plasma, and urine. Thiocyanate and carboxyhemoglobin levels were not significantly elevated in volunteers following exposure. Nicotine was barely increased in plasma, but its metabolite, cotinine, was significantly elevated 2–3 hr after the start of the exposure. In saliva, nicotine levels rose rapidly to about

Table 8. Cotinine and nicotine levels in plasma of volunteers exposed to sidestream smoke.[a,b]

Time, min	2 Cigarettes[c] Nicotine, ng/mL	2 Cigarettes[c] Cotinine, ng/mL	3 Cigarettes Nicotine, ng/mL	3 Cigarettes Cotinine, ng/mL	4 Cigarettes Nicotine, ng/mL	4 Cigarettes Cotinine, ng/mL
Base-line	1.1	1.7	ND[d]	1.0	0.2	0.9
E 20	0.2	2.2	1	0.8	ND	1.2
E 40	ND	1.5	2.1	0.8	0.3	0.9
E 60	ND	1.3	4.2	0.7	0.3	1.2
E 80	1.1	1.8	1.3	1.1	0.5	1.3
+30	0.2	1.8	2.7	1.6	0.4	1.8
60	0.2	1.9	0.6	2.1	0.8	2.1
90	0.6	2.3	2.9	1.9	0.6	2.6
120	1.5	1.7	0.3	2.1	1.4	2.9
150	0.2	1.4	0.7	2.6	0.7	2.9
180	ND	2.6	0.2	3.0	1.0	3.3
210	ND	1.8	0.7	2.0	0.2	3.3
240	ND	2.1	0.2	1.9	1.1	3.3
270	0.9	2.1	0.2	2.4	0.6	3.4
300	ND		ND	2.5	0.6	3.2

[a] E = Exposure to sidestream smoke in 16 m^3 chamber.
[b] Data of Hoffmann et al. (*12*) by permission.
[c] Number of cigarettes being smoked throughout the exposure period.
[d] ND = not detected.

Table 9. Cotinine and nicotine levels in urine of volunteers exposed to sidestream smoke.[a,b]

Time, min	2 Cigarettes[c] Nicotine, ng/mL	2 Cigarettes[c] Cotinine, ng/mL	3 Cigarettes Nicotine, ng/mL	3 Cigarettes Cotinine, ng/mL	4 Cigarettes Nicotine, ng/mL	4 Cigarettes Cotinine, ng/mL
Base-line	24	14	20	14	17	14
E 80	26	16	34	21	84	28
+150	40	21	94	34	100	46
300	51	21	58	38	48	55

[a] E = Exposure to sidestream smoke in 16 m^3 chamber.
[b] Data of Hoffmann et al.(*12*) by permission.
[c] Number of cigarettes being smoked throughout the exposure period.

800 ng/mL. They quickly subsided after the volunteers left the room. When the volunteers were exposed to the pollutants of two, three, or four cigarettes, a dose-response relationship for nicotine in saliva and cotinine in urine was observed. Further studies of this type confirmed the presence of cotinine in the urine of nonsmokers.

In a study of patients attending an outpatient clinic, Jarvis et al. (*13*) found that the concentration of cotinine in body fluids was related to self-reported exposure to sidestream smoke. Salivary nicotine concentrations corresponded to the dose when exposure and testing occurred on the same day, but measures of thiocyanate and expired carbon monoxide were unrelated to the dose. A summary of the data by Jarvis et al. is presented in Table 10.

A similar study in Japan (*14*) examined exposures at home and in the workplace and revealed a dose-response relationship for cotinine excreted into the urine. The presence of smokers both in the home and at work elevated the cotinine levels with increased exposure time. An arbitrary designation of tobacco smoke density (not smoky, smoky, frequently smoky) as well as the number of smokers at a given site were related to increased cotinine to creatinine excretion ratio levels greater than those noted by researchers in the United States or in England (this discrepancy is believed to be methodo-

Table 10. Measurements of self-reported passive smoking.[a]

	None (r = 46)	A little (n = 27)	Some (r = 20)	A lot (n = 7)	p Value
Expired CO, ppm	5.7	5.6	5.6	5.0	NS
COHb, %	0.94	0.81	0.80	0.80	NS
Nicotine, ng/mL					
Plasma	1.04	0.76	0.72	0.90	NS
Saliva	3.81	4.80	4.44	12.12	< 0.05
Urine	3.87	12.12	11.92	12.12	= 0.06
Cotinine, ng/mL					
Plasma	0.82	1.81	2.52	1.81	< 0.005
Saliva	0.73	2.20	2.80	2.63	< 0.001
Urine	1.55	6.50	8.65	9.36	< 0.001
Thiocyanate					
Plasma, μmole/L	4.81	5.55	5.51	47.4	NS
Saliva mmole/L	1.27	1.50	1.03	1.51	NS
Urine, μmole/L	72.8	80.3	74.2	73.1	NS

[a] Data of Jarvis et al. (*13*) by permission.

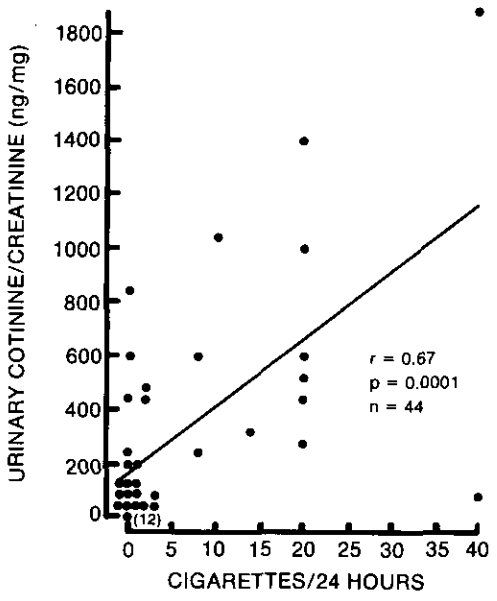

FIGURE 2. Relation between the number of cigarettes smoked by mothers in the previous 24 hr and the urinary concentrations of cotinine in their infants (*17*). Reprinted with permission.

logical in nature). This study did confirm, however, the utility of urinary cotinine to creatinine ratios in evaluating uptake of nicotine by nonsmokers.

Wald et al. reported median urinary cotinine levels of 1645 ng/mL in cigarette smokers as compared to 6 ng/mL in nonsmokers exposed to environmental tobacco smoke and 2 ng/mL in those not exposed (*16*). The cotinine levels in exposed nonsmokers increased substantially with the amount of exposure. The average measures represent a ratio of active to passive smoke exposure of 411, but this does not imply that cancer risk will necessarily be in the same ratio.

Greenberg et al. (*17*) measured the concentrations of nicotine and cotinine in the saliva and urine of infants with and without reported exposure in the household. The concentrations of both compounds were significantly higher in the exposed group than in the group without exposure. The best indicator of chronic exposure was the urinary cotinine to creatinine ratio, with a direct relationship between cotinine excretion by the infants and the self-reported smoking behavior of mothers during the previous 24 hr (Fig. 2).

The results of chamber studies as well as free-living evaluations of nonsmokers exposed to sidestream smoke suggest that measurement of urinary cotinine excretion can provide a reliable, objective indicator of exposure to sidestream smoke.

In summary, there is no question that individuals are exposed to environmental tobacco smoke. Although such exposure may be relatively low compared to active cigarette smoking, uptake of environmental tobacco smoke pollutants begins very early in life and is directly related to the degree of exposure. The degree of exposure is a function of the number of persons contributing to smoke pollution, the amount of tobacco products being smoked, and the dimensions and ventilation characteristics of the rooms and buildings in which exposure occurs, as well as the duration of exposure.

Table 11. Occurrence of five major types of lung cancers in smokers and nonsmokers.[a]

		Male		Female	
Type	Total	Smoker	Never smoker	Smoker	Never smoker
Epidermoid	992	892	7	80	13
Small cell	640	533	4	100	3
Adenocarcinoma	760	492	39	128	101
Large cell	466	389	16	46	15
Bronchioloalveolar cell	68	35	4	13	16
Total	2926	2341	70	367	148

[a] Data of Rosenow and Carr (*18*) by permission.

Risk of Lung Cancer

The relationship of the risk of lung cancer to environmental tobacco smoke has been studied in classic case-control and longitudinal studies. Most of the studies have measured the risk of lung cancer or the odds ratio among nonsmoking lung cancer cases, usually women, in relationship to the smoking habits of the spouse, parents, or co-workers. Only a few studies have included men or smokers as index cases. It is important to note that most lung cancer cases in men occur in current or former cigarette smokers and that a high percentage of lung cancers occurring among nonsmokers, especially women, are predominantly adenocarcinoma rather than epidermoid carcinoma. The estimated incidence of lung cancer among both men and women who were lifetime nonsmokers was only about 10 per 100,000.

In the large series in the Mayo Clinic, only 70 cases (3%) of lung cancer in men occurred among nonsmokers, and apparently 55% of the 70 cases were adenocarcinoma (Table 11). Among women, 148 of 515 cases (29%) occurred among nonsmokers, and 68% were adenocarcinoma (*18*). Similar results are recently reported by Kabat and Wynder (Table 12) (*19*). Community studies in New Orleans (*20*), as well as in Allegheny County, PA (*21*), have reported a very low frequency of lung cancer among nonsmoking men. Therefore, it is probably unlikely that passive smoking accounts for a substantial portion of epidermoid carcinoma of the lung, even though reported relative risks for epidermoid lung cancer associated with passive smoking may be as high or higher than for adenocarcinoma.

At most, there were only about 3000 new lung cancer cases among nonsmoking men in the United States in 1984, and at least half were probably adenocarcinomas. Among women, on the other hand, up to 20% or more of lung cancers may occur among nonsmokers, perhaps 6000 to 8000 a year, but again 4500 of those 6000 are probably adenocarcinomas.

Independent estimates of nonsmokers dying of lung cancer have been made by H. Seidman of the American

Table 12. Histologic type of lung cancer in never smokers and smokers.[a]

	Men		Women	
	No.	%	No.	%
Never smokers				
Kreyberg type I	13	(35.1)	20	(20.6)
Epidermoid/squamous	13	(35.1)	16	(16.5)
Large cell/giant cell	0		4	(4.1)
Kreyberg type II	20	(54.1)	72	(74.2)
Adenocarcinoma	16	(43.2)	60	(61.9)
Alveolar	4	(10.8)	12	(12.4)
Mixed (Kreyberg I and II) and undifferentiated/anaplastic	4	(10.8)	5	(5.2)
Total	37		97	
Smokers				
Kreyberg type I	1187	(63.1)	341	(52.3)
Kreyberg type II	600	(31.9)	279	(42.8)
Mixed (Kreyberg I and II) and undifferentiated/anaplastic	95	(5.0)	32	(4.9)
Total	1882		652	

[a] Data of Kabat and Wynder (*19*) by permission.

Cancer Society. Five-year lung cancer death rates of smokers in 1967 to 1971 from the American Cancer Society's prospective study have been extrapolated to the present, assuming nonsmokers' rates did not increase. These extrapolated rates were then applied to estimated 1985 populations according to the distribution of smokers and nonsmokers by age in the American Cancer Society's prospective study, Cancer Prevention Study II. Deaths were adjusted to comply with the American Cancer Society's estimates of total lung cancer in 1985. The American Cancer Society estimated that 2900 men and 6200 women nonsmokers died of lung cancer in 1985. An unknown proportion of these may be due to passive smoking.

Studies relating environmental tobacco smoke exposure and lung cancer risk are described in Tables 13 and 14. These studies include cohort studies and a number of case-control studies that compare nonsmoking women with lung cancer to nonsmoking women with other diseases. These studies seem to indicate that passive smoke exposure plays a role in causing cancer in nonsmoking women. However, individually, each of these studies—positive or negative—suffers methodologic weaknesses. The problems of greatest concern are the possibility of misclassification of both active and passive smoking status, misclassification of tumor pathology, use of inappropriate controls, and small sample sizes.

Misclassification of Exposure

Misclassification of exposure has been an overwhelming concern of the critics of the published studies. This has been especially true for the studies done in Japan (*22–24*) and Greece (*25*), where surprising numbers of cancers were seen in nonsmokers. The possibility of "closet smoking" by these nonsmoking women married to smokers has been suggested but has never been confirmed. However, if it is true that few Japanese or Greek women smoke, it is not surprising that few of the women with lung cancer are smokers. This does not indicate a problem with these studies unless there are more cancers than could be expected in a nonsmoking population. Misclassification is perhaps of greater concern in some of the other studies where the reported relative risks and sample sizes have been smaller (*20,26–29*) and therefore more likely to change with a small amount of misclassification.

Recall bias in reporting passive smoke exposure is also a major potential problem in the case-control studies. Childhood smoke exposure histories were validated in the North Carolina study, and there did not appear to have been differential recall (*30*). Similar data are not available for smoking by a spouse. In the cohort studies, changes in exposure status over time rather than differential misclassification of passive smoke exposure is of concern. Other studies, such as that in Hong Kong (*26*), have obtained information only on current cigarette smoke exposure, and thus persons with past exposures may be misclassified.

Misclassification of Pathology

Concerns about misclassification of tumor pathology are closely linked with concerns about misclassification of smoking status. Trichopoulos et al. attempted to exclude adenocarcinomas, but 77 of the 102 remaining lung cancers were among nonsmokers (*25*). This is a much larger proportion of nonsmokers among epidermoid cancer patients than would be expected from U.S. data. One possible explanation is that women in the Trichopoulos et al. study were in fact smokers. Alternatively, because pathologic confirmation was not always available and available data were not systematically reviewed, these cases may be misclassified according to lung pathology. In fact, none of the studies included independent review of pathology, and classification may be affected by individual variations in interpretation and changes over time in standards. An exception is the study of Garfinkel et al. in which the histology of both cases and controls was reviewed (*31*).

Sample Size

In many of the studies, there are too few nonsmoking lung cancer cases to produce reliable estimates of the relative risk. For example, some American studies have involved 22 lung cancers, of which only two were in nonsmokers (*30,32*); 35 lung cancers in nonsmokers (*20*); and 29 nonsmoking cases in another study (*27*).

A new American study in four hospitals over an 11-yr period, 1971 to 1981, includes 134 nonsmoking lung cancer cases and 402 controls. All cases and controls were verified histologically. A dose-response relationship of lung cancer was found in relation to the number of cigarettes the husband smoked at home (*31*).

Sample size can also be a problem for cohort studies. Other than the studies by Hirayama (*22–24*), there have

Table 13. Passive smoke exposure in adulthood and cancer risk: case-control studies of lung cancer.

Study	Cases[a]	Control	Exposure	Risk
Greece (*25*)	77 ns females	225 ns female orthopedic patients	Spouse	1.9 light-smoking spouse 2.5 heavy-smoking spouse
Hong Kong (*26*)	84 ns females	139 ns female orthopedic patients	Spouse	0.8 current smoking by spouse
Louisiana (*20*)	10 ns males 25 ns females	180 ns male hospital patients 133 ns female hospital patients ("non-smoking-related" diseases)	Spouse	2.0 males or females with smoking spouse 1.5 both sexes with light exposure 3.1 both sexes with heavy exposure
Multi-Center USA (*19*)	37 ns males 97 ns females	37 ns male hospital patients 97 ns female hospital patients ("non-smoking-related" diseases, 62% other cancers)	Spouse home work	1.3 males exposed at home 3.3 males exposed at work 0.9 females exposed at home 0.7 females exposed at work
North Carolina (*30, 32*)	15 males, s and ns 7 females, s and ns (508 cases all sites)	159 male acquaintances or population controls 330 female acquaintances or population controls (489 acquaintances or population controls)	Spouse (spouse)	1.9 males with spouse exposure ∞ females with spouse exposure (1.6 spouse ever smoked)
New Jersey, Ohio (*31*)	134 ns females	402 ns females with colon cancer matched neighborhood controls	Spouse	1.2 odds ratio
California (*27*)	149 females—adenocarcinoma (50% ns) 71 females—squamous cell carcinoma (almost all smokers)		Spouse work	1.2 adenocarcinoma, spouse 1.3 adenocarcinoma, work 1.0 squamous cell carcinoma, spouse 2.3 squamous cell carcinoma, work
Pennsylvania (*36*)	123 ns female deaths from lung cancer	414 ns female deaths other causes	Spouse	1.4 all women with smoking spouse 1.9 unemployed women with smoking spouse
West Germany (*35*)	39 ns females	"population estimate" prevalence of smoking by married males	Spouse	2.0 to 3.0
Hong Kong (*28*)	200 females	200 population controls	Spouse work	0.51 smokers 1.24 nonsmokers
Hong Kong (*29*)	88 females	137 district controls	Spouse	2-3 times higher risk
Japan (*72*)	19 males 94 females	110 male controls 270 female controls	Spouse	1.8 males 1.5 females

[a]ns = nonsmoker; s = smoker.

been few cohort studies large enough to evaluate lung cancer risk from passive smoking. The study in Scotland by Gillis et al. (*33*) had a very small sample size and a short follow up period. Some relationship between environmental tobacco smoke and lung cancer was seen for men but not women. The study, however, lacked sufficient power to detect a risk for women. The American Cancer Society's cohort study had a large sample but minimal information about environmental tobacco smoke exposure (*34*). A small but inconsistent relationship with husband's smoking was observed.

Choice of Controls

Choice of appropriate comparison groups is always difficult but may be especially difficult for studies of exposure to cigarette smoke. Trichopoulos et al. (*25*) used orthopedic patients as controls, presumably because this might be one diagnosis not related to cigarette smoking. However, controls were from a different hospital than were cases, and it is unclear what problems this might introduce. The studies by Sandler et al. (*30,32*) used acquaintances of cases as controls, but they were not successful in obtaining controls for all subjects. Thus, a second group of random controls was added. While these different groups do not appear to have affected the results, it is possible that some differences have been overlooked. Knoth et al. (*35*) did not use controls at all but inferred a population exposure from data on smoking by males in different age groups. Miller (*36*) neglected to control for age differences between cases and controls. Such adjustment would probably invalidate the reported positive association with passive smoking.

Some studies have used other cancer cases as controls. The recently completed American Cancer Society study used colorectal cancer patients as controls (*31*). One report suggested that colorectal cancer risk may be decreased among smokers (*37*), although this has not been found in many other studies. The multicenter U.S. study used all other cancers for comparison, some of which may be related to both active and passive smoking (*19,38*) and may, therefore, underestimate risk from passive smoke exposure. This may be more true for

Table 14. Passive smoke exposure in adulthood and cancer risk: prospective studies.

Study	Population[a]	Exposure	Outcome	Risk
Japan (*22–23*)	91,540 ns females 1966–1981	Spouse	Total mortality Lung cancer Other cancers	1.45 lung cancer 1.1 all sites (other causes with increased risk: emphysema, nasal sinus cancer, brain cancer)
Japan (*24*)	20,289 ns married males 1966–1981	Spouse	Lung cancer	2.25
Scotland (*33*)	4,067 married males 4,061 married females 1972/6–1982	Spouse	Total mortality Lung cancer Other cancers Noncancer deaths	1.0 all causes, s and ns males 1.5 all causes, ns females 3.3 lung cancer, ns males 1.0 lung cancer, ns females
USA (*34*)	176,739 ns married females 1960–1972	Spouse	Lung cancer mortality	1.3 light-smoking spouse 1.1 heavy-smoking spouse
Amsterdam (*41*)	1,007 married couples 25-year follow-up	Spouse	Total mortality	No consistent risk
California (*39*)	695 ns married females 1974–1983	Spouse	Total mortality IHD mortality	1.2 total mortality 2.3 IHD
MRFIT (*40*)	1,245 ns married males 1972/4–1982	Spouse	Total mortality CHD mortality	2.0 increased risk, total mortality 2.1 increased risk, CHD mortality

[a]ns = nonsmoker; s = smoker.

females than for males, where sites such as the cervix have been increasingly linked with both active and passive smoke exposure.

Other Cancers and Chronic Diseases

Several other studies have examined total mortality, cardiovascular disease, and cancers of nonrespiratory sites. These studies are generally preliminary in nature. Garland et al. reported an excess of ischemic heart disease deaths among nonsmoking women exposed to tobacco smoke, but the study was quite small, and the risks were unstable (*39*). Preliminary results of the follow-up of never-smoking or nonsmoking men in the Multiple Risk Factor Intervention Trial have shown excesses of both total and coronary heart mortality among men whose wives smoked, as compared to those whose wives did not smoke (*40*). Other studies (*24,33*) also offer some support for a possible effect of passive smoking on heart disease risk. Vandenbroucke et al. reported on total mortality in relation to passive smoke exposure, but the study was too small to identify any real effects (*41*). Furthermore, women married to ex-smokers were considered nonexposed, which may have limited the likelihood of observing any effects. In a study to evaluate cancer risk from childhood exposures, which also included data on spouse smoking, a significant association with nonrespiratory sites was observed (*32*). However, the study was not able to control for many known risk factors or potential confounding factors for cancers of specific sites. Hirayama (*23*) has also observed associations between spouse's smoking and nonrespiratory tract cancers but did not obtain data on many potential confounding variables.

Childhood Exposures

Cigarette smoke exposure also occurs in early life, and mothers' or fathers' smoking may be associated with increased cancer risk in childhood or even adulthood. Data from recent biochemical studies indicate that children of mothers and fathers who smoke are meaningfully exposed in utero and in childhood to the potential carcinogens in cigarette smoke (*15,34,37,39–47*). Studies in animals of effects of exposure to particular chemicals, including some that are in cigarette smoke, suggest that these chemicals may be transplacental carcinogens for humans and that effects of transplacental or early life exposures may be greater than effects from similar levels of exposure later in life (*48–51*). Furthermore, animal studies also suggest that resulting tumors may include multiple sites and may be of adult morphology (*49*).

In a large retrospective study of childhood cancers, Stewart et al. (*52*) observed a small but significant relative risk associated with mother's cigarette smoking during pregnancy. In a smaller prospective study, Neutel and Buck (*53*) reported a 30% increase in risk of childhood cancer associated with mothers' smoking that was not quite statistically significant. Case-control studies of individual childhood tumors have also reported positive associations with parents' smoking (*54–56*), although other studies do not report such effects. These studies are summarized in Table 15.

Studies in animals also suggest that some effects from early life exposures may not be apparent until adult life (*47*). If true, this suggests that some studies of parents' smoking and childhood cancers might be negative because an effect might not be apparent until adulthood. Epidemiologic studies in humans have recently sug-

Table 15. Cancer risk and parental smoking: selected studies of children and young adults.

Study	Design[a]	Cancer site	Age	Risk
Preston-Martin (*54*)	C/$\overline{C}$	Brain	to 25	1.5 fathers during pregnancy
Henderson (*73*)	C/$\overline{C}$	Testis	to 40	1.0 mothers
Gold (*56*)	C/$\overline{C}$	Brain	to 20	5.0 smoking mothers who continued in pregnancy
Manning (*74*)	C/$\overline{C}$	Leukemia	to 15	1.0 mothers
Stewart (*52*)	C/$\overline{C}$	All	to 10	1.1 mothers
Neutel (*53*)	cohort	All	to 10	1.3 mothers during pregnancy
Grufferman (*55*)	C/$\overline{C}$	Rhabdomyosarcoma	to 15	3.9 fathers during pregnancy 1.0 mothers in pregnancy

[a] C/$\overline{C}$ = case-control study.

gested the possibility of an association between transplacental or early life exposure to cigarette smoke and adult cancers, including cancers of the respiratory tract and other nonrespiratory sites, although these studies must be considered preliminary (*20,27,32*) (Table 16).

Conclusions

The relationship of environmental tobacco smoke and disease, specifically lung cancer and possibly other respiratory tract cancer, is important. First, there are obvious public health implications, given that perhaps 60% of the population is exposed to environmental tobacco smoke. Second, confounding of environmental tobacco smoke exposure with other environmental and occupational risks is possible. Third, information learned about passive smoking may help increase our understanding of the relationship between long-term exposures to relatively low dose carcinogens and subsequent disease.

A greater number of lung cancers in nonsmokers are found in women, and studies to date, although not conclusive, indicate that environmental tobacco smoke is probably related to lung cancer in women. It is unlikely that a significant effect of environmental tobacco smoke and active cigarette smoking synergistically can be identified from most of these epidemiologic studies.

Exposures very early in life to environmental tobacco smoke may be important in relationship to the subsequent development of cancer and need to be considered. Only a few studies to date have evaluated the relationship between environmental tobacco smoke and subsequent childhood cancers, and almost none have evaluated cancers that occur in adulthood. The short-term effects of environmental tobacco smoke on the cardiovascular system, especially among high-risk individuals, may be of even greater concern than that of cancer.

Further study of the increased risks of lung cancer in relation to environmental tobacco smoke exposure will require larger collaborative studies to identify more lung cancer cases among noncigarette smokers, better delineation of pathology, and more careful selection of controls.

Finally, it may be possible to consider studies of epithelial cells or specific cytology to determine at least evidence of cellular changes in relationship to environmental tobacco smoke exposure. Environmental tobacco smoke exposure is most likely the most important indoor air pollutant.

Table 16. Cancer risk and parental smoking: adults.

Study	Design[a]	Cancer site	Risk
Correa (*20*)	C/$\overline{C}$	Lung	1.7 mothers 1.0 fathers (adjusted for own smoking) 1.4 mothers, 0.8 fathers
Sandler (*32*)	C/$\overline{C}$	All	1.1 mothers 1.5 fathers
Wu (*27*)	C/$\overline{C}$	Lung	1.7 mother, adenocarcinoma 1.3 father, adenocarcinoma 0.2 mother, squamous cell 0.9 father, squamous cell

[a] C/$\overline{C}$ = case-control study.

Research Recommendations

Epidemiologic Studies

Recommendation 1: There should be continued efforts to measure individual exposures to passive smoking. At present, measurement of urinary cotinine appears to be the best method. Other chemicals should be evaluated as well as specific biological markers. Personal direct monitoring should have high priority.

Recommendation 2: Additional case-control studies are needed to evaluate the relationship between passive smoking and lung cancer. Such studies should include primary noncigarette smokers with lung cancer patients as cases and appropriate controls. It is important that these studies include a broad age range; specific pathological type of lung cancer; and careful records of the history of cigarette smoking in parents, spouses, at-work environment, other possible risk factors, occupation, and environmental exposure.

Recommendation 3: Case-control studies should be done to investigate the possible association between passive smoke exposure in childhood and adulthood and risk for cancer of other sites. Such studies should include attention to other known risk factors for cancer at these sites and include data on relevant confounding factors.

Differences between sidestream smoke and mainstream smoke—such as the higher levels of specific carcinogens in fixed volumes of sidestream smoke versus mainstream smoke, smaller particle size, and the possible different deposition in the lung—suggest that passive smoke exposure may not be just a lower dose of active smoke exposure. Passive smoking results in pos-

sible systemic exposures. Preliminary studies have reported associations between passive smoke exposure and nonrespiratory tract sites.

Studies of the health effects of cigarette smoke exposure should attempt to identify a truly nonexposed comparison group. While active smokers are also passive smokers, health effects that are specific to sidestream smoke cannot be identified in studies of smokers versus nonsmokers where nonsmokers also include passive smokers.

Recommendation 4: Childhood cancers and susceptibility to adult cancers should be evaluated in light of early life exposure to passive smoking or to mainstream smoke in utero. Childhood exposure to passive smoking can begin in utero, where the fetus is exposed to the mainstream smoke inhaled by the mother. Exposure can continue through infancy and childhood as sidestream smoke generated by the parents, caretakers, or associated adults is absorbed by the child. The absorption of nicotine by infants has been shown to be dose responsive and can result in high levels of urinary cotinine.

Recommendation 5: If possible, a cohort longitudinal study of passive smoking and lung cancer should be done. The sample size would require about 100,000 middle-aged women with an average cancer risk of 10 per 100,000 per year, followed for up to 10 years. Such large cohorts already exist (NCI breast cancer screening studies, NHLBI cohorts, etc.). In any such study, an attempt should be made in all these studies to build in some measure of passive smoking, such as urinary cotinine, as well as history of exposure. The cotinine could be measured in a nested case-control study.

Recommendation 6: A specific case-control study of well-documented adenocarcinoma of the lung should be done. Variables to be studied should include active smoking, passive smoking, environmental exposures, family history, diet (i.e., vitamin A, carotene), alcohol intake, and other cancers in the case, as well as the family. Validation of the pathological diagnosis is critical in such studies.

Recommendation 7: The distribution of exposure to passive smoking in different population groups should be described by various sampling strategies using existing population study sources and measurement of passive smoking by urinary cotinine and other suitable markers.

Recommendation 8: If possible, the type of study of bronchial epithelial changes in postmortem specimens should be done for noncigarette smokers with attention to passive smoking exposures.

Experimental Studies

Recommendation 9: If possible, the relationship between sidestream smoke exposure or mainstream smoke exposure with lung cancer should be evaluated in animal models. Experimental studies could be particularly useful in elucidating such issues as the relative risks of transplacental versus childhood exposures and their importance to the development of lung cancer.

Recommendation 10: Long-term animal inhalation studies with passive smoke are needed. It is recommended that such studies be done in two animal species, preferably rats and Syrian golden hamsters. Emphasis should be placed on the induction of tumors in the respiratory tract and other organs. Early histopathological changes in the respiratory tract should be investigated in these assays.

Recommendation 11: Animal inhalation studies with passive smoke should also be initiated with respect to transplacental carcinogenesis. Detailed biochemical research is required.

Recommendation 12: In-depth studies are needed to clearly delineate the differences in the physical natures and chemical compositions of sidestream and mainstream smoke. It has been established that the physiochemical nature of passive smoke, the smoke inhaled by nonsmokers, differs significantly from the mainstream smoke inhaled by the active smoker. Data are needed to delineate these differences.

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