4. HAZARD IDENTIFICATION I: LUNG CANCER IN ACTIVE SMOKERS, LONG-TERM ANIMAL BIOASSAYS, AND GENOTOXICITY STUDIES

4.1. INTRODUCTION

Numerous epidemiologic studies have conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen (U.S. DHHS, 1982; IARC, 1986). A clear dose-response relationship exists between lung cancer and amount of exposure, without any evidence of a threshold level. It is, therefore, reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers.

As documented in the previous chapter, the chemical compositions of mainstream smoke (MS) and ETS are qualitatively similar, and both contain numerous known or suspected human carcinogens. In fact, ETS contains essentially all of the same carcinogens identified in MS, and many of these appear in greater amounts in sidestream smoke (SS), the primary component of ETS, than in MS, per unit tobacco burned (Table 3-1). In addition, both MS and SS have been shown to be carcinogenic in animal bioassays (Wynder and Hoffman, 1967; Grimmer et al., 1988), and MS, SS, and ETS have all been found to be genotoxic in in vitro systems (IARC, 1986). Furthermore, as the previous chapter also describes, exposure assessments of indoor air and measurements of nicotine and cotinine levels in nonsmokers confirm that passive smokers are exposed to and absorb appreciable amounts of ETS that might result in elevated lung cancer risk.

This chapter reviews the major evidence for the lung carcinogenicity of tobacco smoke derived from human studies of active smoking and the key supporting evidence from animal bioassays and in vitro experiments. The evidence from the few animal and mutagenicity studies pertaining specifically to ETS is also presented. The majority of this information has already been well documented by the U.S. Department of Health and Human Services (U.S. DHHS) (1982) and the International Agency for Research on Cancer (IARC) (1986). The current discussion mainly extracts and summarizes some of the important issues and principal studies described in those comprehensive reports.

In view of the abundant and consistent human evidence establishing the carcinogenic potential of active smoking to the lung, the bulk of this chapter focuses on the human data. Although EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a) suggest an extensive review of all evidence pertaining to carcinogenicity, we believe that the large quantity of human cancer studies on both MS and ETS provide the most appropriate database from which to evaluate the lung cancer potential of ETS. Thus, the animal evidence and genotoxicity results are given only limited attention here. Similarly, a discussion of the mutagenicity data for individual smoke components would be superfluous in the context of the overwhelming evidence from other, more pertinent sources and is not included. Extensive reviews of these data can be found in the U.S. DHHS (1982) and IARC (1986) publications. Claxton et al. (1989) provide an assessment of the genotoxicity of various ETS constituents.

4.2. LUNG CANCER IN ACTIVE SMOKERS

Studies of active smoking in human populations from many countries provide direct and incontrovertible evidence for a dose-related, causal association between cigarette smoking and lung cancer. This evidence includes time trends in lung cancer mortality rates associated with increasing cigarette consumption, high relative risks for lung cancer mortality in smokers of both sexes observed consistently in numerous independent retrospective and prospective studies, and dose-response relationships demonstrated with respect to smoking intensity and duration and for all four major histological types of lung cancer.

4.2.1. Time Trends

While the overall cancer death rate in the United States has been fairly stable since 1950, the lung cancer death rate has increased drastically for both males and females (Figures 4-1 and 4-2). Age-adjusted lung cancer mortality rates in men have increased from 11 per 100,000 in 1940 to 73 per 100,000 in 1982, leveling slightly to 74 per 100,000 in 1987 (Garfinkel and Silverberg, 1991). In women, lung cancer mortality rates have risen from 6 per 100,000 in the early 1960's to 28 per 100,000 in 1987 (Garfinkel and Silverberg, 1991).

The striking time trends and sex differences seen in lung cancer mortality rates correlate with historical smoking patterns. Increases in lung cancer death rates parallel increases in cigarette consumption with a roughly 20-year lag time, accounting for the latency period for the development of smoking-induced lung cancer. Males started smoking cigarettes in large numbers during the years around World War I, whereas females did not begin smoking in appreciable numbers until World War II. Cigarette consumption per capita (based on the total population age 18 and older) in the United States rose from 1,085 in 1925 to a high of 4,148 in 1973. In the past two decades, cigarette consumption has decreased to 2,888 in 1989 (Garfinkel and Silverberg, 1991). This decline correlates with the leveling off of lung cancer mortality rates in recent years.

Figure 4-1. Age-adjusted cancer death rates* for selected sites, males, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

Figure 4-2. Age-adjusted cancer death rates* for selected sites, females, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

4.2.2. Dose-Response Relationships

More than 50 independent retrospective studies have consistently found a dose-related association between smoking and lung cancer (U.S. DHHS, 1982). Eight major prospective studies from five countries corroborate this association:

- American Cancer Society (ACS) Nine-State Study (white males) (Hammond and Horn, 1958a,b)
- Canadian War Veterans Study (Best et al., 1961; Lossing et al., 1966)
- British Doctors Study (Doll and Hill, 1964a,b; Doll and Peto, 1976; Doll et al., 1980)
- American Cancer Society 25-State Study (Hammond, 1966; Hammond and Seidman, 1980)
- U.S. Veterans Study (Kahn, 1966; Rogot and Murray, 1980)
- California Labor Union Study (Weir and Dunn, 1970)
- Swedish Study (sample of census population) (Cederlöf et al., 1975)
- Japanese Study (total population of 29 health districts) (Hirayama, 1967, 1975a,b, 1977, 1978, 1982, 1985).

Details of the designs of these studies are summarized in Table 4-1. These eight studies together represent more than 17 million person-years and more than 330,000 deaths. Lung cancer mortality ratios from the prospective studies are presented in Table 4-2. Combining the data from the prospective studies results in a lung cancer mortality ratio of about 10 for male cigarette smokers compared with nonsmokers. (Note that these lung cancer mortality ratios underestimate the relative risk of lung cancer to smokers compared with a non-tobacco-smoke-related background risk to nonsmokers [see Chapter 6], given the causal association between ETS exposure and lung cancer in nonsmokers documented in this report.)

This strong association between smoking and lung cancer is further enhanced by very strong and consistent dose-response relationships. A gradient of increasing risk for lung cancer mortality with increasing numbers of cigarettes smoked per day was established in every one of the prospective studies (Table 4-3). Lung cancer mortality ratios for male smokers who smoked more than 20 cigarettes daily were generally 15 to 25 times greater than those for nonsmokers. Marked increases in lung cancer mortality ratios were also seen in all the lowest dose categories. Males who smoked fewer than 10 cigarettes per day had lung cancer mortality ratios 3 to 10 times greater than those for nonsmokers. There is no evidence of a threshold level for the development of smoking-induced lung cancer in any of the studies.

Dose-response relationships with respect to the duration of smoking also have been well established. From the British male physicians study, Peto and Doll (1984) calculated that the

Table 4-1. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
ACS 9-state study	1952	204,547 men [187,783]	Self-administered questionnaire	44 months 11,870 deaths	98.9%
Canadian veterans study	1955-1956	207,397 subjects (aged 30+) [92,000]	Self-administered questionnaire (57% respondents)	6 years 9,491 deaths in men; 1,794 deaths in women	NA
British doctors study	1951	34,440 men (aged 20+)	Self-administered questionnaire (69% respondents)	20 years 10,072 deaths	99.7%
		6,194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1,094 deaths	99%
ACS 25-state study	1959-1960	1,078,894 subjects, first followup: 440,558 men, 562,671 women (aged 35-84); second followup: 358,422 men, 483,519 women	Self-administered questionnaire	4.5 + 5 years 26,448 deaths in men; 16,773 deaths in women	97.4% in women 97.9% in men in first followup
U.S. veterans study	1954	293,958 men (aged 31-84) [248,046]	Self-administered questionnaire (85% respondents)	16 years 107,563 deaths	Almost 100% ascertainment of vital status; 97.6% of death certificates retrieved
California study	1954-1957	68,153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4,706 deaths	NA

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Swedish study	1963	27,342 men, 27,732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5,655 deaths (2,968 autopsies)	NA

Table 4-1. (continued)

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
Japanese study	1965	122,261 men, 142,857 women (aged 40+)	Interview (95% of population in area)	16 years 51,422 deaths	Total

NA = not available.

Source: IARC, 1986.

Table 4-2. Lung cancer mortality ratios--prospective studies

Population	Size	Number of deaths	Nonsmokers	Cigarette smokers
British doctors study	34,000 males	441	1.00	14.0
	6,194 females	27	1.00	5.0
Swedish study	27,000 males	55	1.00	7.0
	28,000 females	8	1.00	4.5
Japanese study	122,000 males	940	1.00	3.76
	143,000 females	304	1.00	2.03
ACS 25-state study	358,000 males	2,018	1.00	8.53
	483,000 females	439	1.00	3.58
U.S. veterans study	290,000 males	3,126	1.00	11.28
Canadian veterans study	78,000 males	331	1.00	14.2
ACS 9-state study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

Source: U.S. DHHS, 1982.

Table 4-3. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day--prospective studies

	Men		Women	
Population	Cigarettes smoked per day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-state study	Nonsmoker	1.00	Nonsmoker	1.00
	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British doctors study	Nonsmoker	1.00	Nonsmoker	1.00
	1-14	7.80	1-14	1.28
	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish study	Nonsmoker	1.00	Nonsmoker	1.00
	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	--
Japanese study (all ages)	Nonsmoker	1.00	Nonsmoker	1.00
	1-19	3.49	<20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. veterans study	Nonsmoker	1.00		
	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	≥40	23.70		
ACS 9-state study	Nonsmoker	1.00		
	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian veterans study	Nonsmoker	1.00		
	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California males in 9 occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1½ pk	9.56		

Source: U.S. DHHS, 1982.

excess annual incidence rates of lung cancer after 45, 30, and 15 years of cigarette smoking were in the approximate ratio of 100:20:1 to each other. The California and Swedish studies also demonstrated an increasing risk of lung cancer in men with longer smoking duration (Table 4-4).

Four of the prospective studies examined lung cancer mortality in males by age at initiation of smoking and found increasing risk with younger age (Table 4-5). Some of the studies also investigated smoking cessation in men and observed a decrease in lung cancer risk with increasing number of years since quitting smoking (Table 4-6). The Cancer Prevention Study II, a study of 1,200,000 people in all 50 states, reveals a similar trend for women who quit smoking (Figure 4-3). The occurrence of higher lung cancer mortality ratios in the groups with only a few years since cessation as compared with current smokers (Table 4-6 and Figure 4-3) is attributable to the inclusion of recent ex-smokers who were forced to stop smoking because they already had smoking-related symptoms or illness (U.S. DHHS, 1990a). The increased lung cancer risks seen in people who started smoking at a younger age and the decreased risks seen with time since smoking cessation suggest both initiation and promotion capabilities of tobacco smoke components.

Additional dose-response relationships have been derived from consideration of the types of tobacco products used. Pipe and cigar smokers, who inhale less deeply than cigarette smokers, have lower risks of lung cancer than cigarette smokers (Table 4-7). Furthermore, the American Cancer Society 25-state study found decreased risks for lung cancer in males and females who smoked cigarettes with lower tar and nicotine content compared with those who smoked cigarettes with higher tar and nicotine content (Table 4-8), although these decreased risks are still substantially higher than the risk to nonsmokers. Similarly, it has been established that smokers of filtered cigarettes have relatively lower lung cancer risks than smokers of nonfiltered cigarettes (Table 4-9). Filters reduce the amount of tars, and hence a portion of the carcinogenic agents, in the MS inhaled by the smoker. Passive smokers, however, do not share in any benefit derived from cigarette filters (see Chapter 3) and may, in fact, be exposed to greater amounts of ETS if smokers of filtered cigarettes smoke a greater number of cigarettes to compensate for any reduction in nicotine uptake resulting from the filters (U.S. DHHS, 1986).

4.2.3. Histological Types of Lung Cancer and Associations With Smoking

A number of epidemiologic studies have also examined the association between various histological types of lung cancer and smoking. The results of some of these investigations are summarized in Table 4-10. Problems in interpreting the results of such studies include differences in the nomenclature, criteria, and verification of tumor classification; inadequacy of some specimens; and the small size of many of the patient groups, resulting in unstable risk

Table 4-4. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)[1]
Weir and Dunn (1970)	1-9	1.13	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	Nonsmokers	1.0	0
Cederlöf et al. (1975)	1-29	1.8 (5)	0.01 (0.008)
	>30	7.4 (23)	0.1 (0.06)
	Nonsmokers	1.0 (7)	0

[1]The mortality ratio among nonsmokers was assumed to be 15.6 per 100,000 per year, as in the American Cancer Society 25-state study. Figures in parentheses were computed by the IARC working group, applying the British doctors' mortality rate among nonsmokers (10.0/100,000 per year).

Source: IARC, 1986.

Table 4-5. Lung cancer mortality ratios for males, by age of smoking initiation--prospective studies

Study	Age of smoking initiation in years	Mortality ratio
ACS 25-state study	Nonsmoker	1.00
	25+	4.08
	20-24	10.08
	15-19	19.69
	Under 15	16.77
Japanese study	Nonsmoker	1.00
	25+	2.87
	20-24	3.85
	Under 20	4.44
U.S. veterans study	Nonsmoker	1.00
	25+	5.20
	20-24	9.50
	15-19	14.40
	Under 15	18.70
Swedish study	Nonsmoker	1.00
	19+	6.50
	17-18	9.80
	Under 16	6.40

Source: U.S. DHHS, 1982.

Table 4-6. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
ACS 25-state study (Hammond, 1966)	1-19 cig./day	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cig./day	
	Current smokers	13.7 (351)
	<1	19.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish study (Cederlöf et al., 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British doctors study (Doll and Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot and Murray (1980)	Current smokers	11.3 (2,609)
	<5	18.8 (47)
	5-9	~7.5 (86)
	10-14	~5.0 (100)
	15-19	~5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA = not available.

Source: IARC, 1986.

Figure 4-3. Relative risk of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II.

Source: Garfinkel and Silverberg, 1991.

Table 4-7. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
ACS 9-state study[1]	Never smoked	1.0	12.8	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	27.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian veterans study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
ACS 25-state study[1]	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish study[1]	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12

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Table 4-7. (continued)

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
British doctors study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
U.S. veterans study[1]	Nonsmokers	1.0		2,609
	Cigarettes	11.3		1,095
	Cigarettes only	12.1		41
	Cigars only	1.7		32
	Pipes only	2.1		517
	Ex-cigarette smokers	4.0		
Norwegian study[1]	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[1]Figures given in original report.

Source: IARC, 1986.

Table 4-8. Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N[1]	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

[1]The mortality rate for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

Source: U.S. DHHS, 1982.

Table 4-9. Relative risk for lung cancer by type of cigarette smoked (filter vs. nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne and Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross and Gibson (1968)	Case-control	0.6
Wynder et al. (1970)	Case-control	0.6
Dean et al. (1977)	Case-control	0.5

Source: IARC, 1986.

Table 4-10. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments	
Doll et al. (1957)		Sex	No. of cases	Relative risk				Nonsmokers, 1.0 (RR)	No. observed
				Amount of tobacco smoked (g)					
				<5	5-14	15-24	25+		
	Kreyberg I	M	829	4.7	10.6	14.3	25.4		3
		F	32	1.0	1.7	8.3			16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1		2
		F	8	1.1	2.3	4.1			5
Hammond and Horn (1958b)		Relative risk no. of packs/day						Nonsmokers, 1.0. Only regular smokers considered	
		<½		½-1		1+			
	Adenocarcinoma	2.0		2.5		7.0			
	Other types	16.3		25.5		88.0			
Doll and Hill (1964a)		Death rate per 1,000 Amount of tobacco smoked (g)						Men only	
		Ex-smokers		1-14	15-24	25+			
	Squamous-cell carcinoma	0.09		0.22	0.33	0.45			
	Small-cell and anaplastic carcinoma	0.05		0.10	0.20	0.38			
	Adenocarcinoma	0.03		0.03	0.12	0.07			

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Table 4-10. (continued)

Reference	Histological type	Results					Comments
Haenszel and Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratio; total group, 1.00
		Never-smokers	Ex-Smokers	Occasional cigarrette smokers	Regular cigarette smokers <1 pack/day	Regular cigarette smokers >1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.58	
Hanbury (1964)		No. of cases (%)					Women only
		"Heavy" and "medium" smokers		Nonsmokers and "remainder"			
	Small-cell carcinoma	18 (47)		21 (34)			
	Undifferentiated carcinoma	9 (24)		14 (23)			
	Squamous-cell carcinoma	9 (24)		12 (19)			
	Adenocarcinoma	2 (5)		15 (24)			

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Table 4-10. (continued)

Reference	Histological type		Results										Comments
Vincent et al. (1965)			Number of cigarettes smoked/day										Women only
		Total no. of cases	None		1-20		21-40		41+		Unknown		
			No.	%	No.	%	No.	%	No.	%	No.	%	
	Squamous-cell carcinoma	19	10	53	3	16	2	10	2	10	2	10	
	Small-cell carcinoma	17	2	12	7	41	6	35	2	12	0	0	
	Adenocarcinoma	64	51	80	6	9	4	6	0	0	3	5	
	Undifferentiated	22	12	54	4	18	6	27	0	0	0	0	
	Others	41	32	78	8	20	1	2	0	0	0	0	
		163	107	66	28	17	19	12	4	2	5	3	

Wynder et al. (1970)	Sex	No. (%)		Heavy = 41+ cigarettes/day
		Cigarette smokers	Heavy smokers	
Kreyberg I	M	191 (91.0)	59 (29.9)	
	F	24 (80.0)	3 (12.0)	
Kreyberg II	M	61 (82.4)	9 (14.1)	
	F	21 (58.3)	1 (4.8)	
Controls	M	199 (47.4)	26 (9.8)	
	F	53 (40.2)	3 (5.4)	

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Table 4-10. (continued)

Reference	Histological type	Results			Comments
Deaner and Trummer (1970)		Pack-years	Number of tumors	Smokers	
	Undifferentiated carcinoma	40	40	40 (100%)	
	Adenocarcinoma	12	19	13 (68%)	
	Squamous-cell carcinoma	52	9	9 (100%)	
Weiss et al. (1972)		Death rate per 1,000 man-years of observation (adjusted for age and race)			
		No. of cigarettes/day			
		1-10	10-19	20+	
	Squamous-cell carcinoma				
	Well differentiated	-	0.8	2.1	
	Poorly differentiated	0.7	0.4	1.0	
	Small-cell carcinoma	-	0.3	0.7	
	Adenocarcinoma	-	0.6	1.0	
Vincent et al. (1977)		No. of cigarettes smoked/day			
		0	1-20	21-40	41+	Other
		14	219	110	120	16
	Squamous-cell carcinoma	28	101	66	53	7
	Adenocarcinoma	4	103	62	56	6
	Small-cell carcinoma	2	40	32	33	0
	Large-cell carcinoma					
	Bronchiolo-alveolar	6	20	9	6	0
	carcinoma	0	9	5	5	0
	Mixed	6	30	19	17	4
	Other					

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Table 4-10. (continued)

Reference	Histological type	Results							Comments
Chan et al. (1979)		Smoking category (kg tobacco smoked during lifetime)							Women only
			<100		100-199		>200		
		Non-smokers	Manufactured	All	Manufactured	All	Manufactured	All	
	Squamous-cell and small-cell carcinomas	1.0	3.6	3.4	3.7	4.2	2.6	4.1	
	Adenocarcinoma	1.0	1.9	1.4	1.4	1.8	1.6	1.7	
Joly et al. (1983)		Relative risk by duration of smoking (years)							Nonsmokers, 1.0
		Men				Women			
		1-29	30-39	40-49	50+	1-29	30-39	40-49	50+
	Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9
	Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0
	Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3
	Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.6	13.1

Source: IARC, 1986.

estimates, particularly in women. There are four major histological types of lung cancer: squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma. Sometimes two broad categories--Kreyberg Group I, containing squamous-cell and small-cell carcinomas, and Kreyberg Group II, containing all other epithelial lung cancers, including adenocarcinomas and large-cell undifferentiated carcinomas--are used for classification. The majority of the studies demonstrate an increase in the risk for lung cancer with increasing amount smoked for all four major histological groups in both males and females. The slope of the gradient for adenocarcinomas, however, is shallower than the slopes for the other types.

4.2.4. Proportion of Risk Attributable to Active Smoking

Table 4-11 presents data on the proportion of lung cancer deaths attributable to smoking in various countries. Differences by sex and between countries largely correlate with differences in the proportion of smokers within these populations and the duration and intensity of cigarette usage. In the early 1960s, 50% of U.S. men and 30% of U.S. women smoked, although these proportions have been declining in recent years (Garfinkel and Silverberg, 1991).

In the United States, deaths from lung cancer currently represent one-quarter of all cancer deaths. The American Cancer Society predicted there would be 143,000 lung cancer deaths in 1991 (Garfinkel and Silverberg, 1991). Over 85% of this lung cancer mortality is estimated to be attributable to tobacco smoking. In other words, the overwhelming majority of lung cancer deaths, which are a significant portion of all cancer deaths, result from smoking. The strong association between smoking and lung cancer and the dose-response relationships, with effects observable at low doses and no evidence of a threshold, make it highly plausible that passive smoking also causes lung cancer in humans.

4.3. LIFETIME ANIMAL STUDIES

The human evidence for the carcinogenicity of tobacco smoke is corroborated in experimental animal bioassays. The main animal evidence is obtained from inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of SS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments.

Negative responses in short-term animal studies (e.g., 60 to 90 days) are not reliable indicators of the carcinogenic potential of a compound because of the long latency period for cancer development. Long-term animal studies at or near the maximum tolerated dose level are used to ensure an adequate power for the detection of carcinogenic activity (U.S. EPA, 1986a).

Table 4-11. Lung cancer deaths attributable to tobacco smoking in certain countries

Country	Year	No. of deaths[1]	Expected deaths in nonsmokers[2]	Crude rate in persons aged 35+		AC[3]	AP[4]
				Observed	In non-smokers		
Canada							
Men	1978	6,435	556	142.8	11.8	5,762	0.9
Women	1978	1,681	487	34.0	9.9	1,194	0.71
England and Wales							
Men	1981	26,297	1,576	228.5	13.3	24,720	0.94
Women	1981	8,430	1,663	63.3	12.4	6,767	0.80
Japan							
Men	1981	16,638	2,868	64.8	10.7	13,184	0.83
Women	1981	6,161	2,593	21.0	8.9	3,568	0.58
Sweden							
Men	1981	1,777	301	85.0	14.0	1,476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72,803	5,778	166.7	12.7	67,024	0.92
Women	1979	25,648	5,736	50.0	11.1	19,912	0.78

[1]From the Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO.
[2]Calculated by IARC, 1986. Slightly overestimates number of expected deaths.
[3]AC, number of cases attributable to smoking.
[4]AP, proportion of cases attributable to smoking.

Source: IARC, 1986.

4.3.1. Inhalation Studies

Although evidence of the carcinogenicity of cigarette smoke originated in humans, attempts were made to develop an inhalation model for smoking in experimental animals in order to study the carcinogenicity of various tobacco products. Such inhalation studies are difficult to conduct, however, because laboratory animals are reluctant to inhale cigarette smoke and will adopt shallow breathing patterns in response to aerosols and irritants. Furthermore, rodents are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals and humans are likely to have different deposition and exposure patterns for the various cigarette smoke components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung.

The Syrian golden hamster has been the most useful animal inhalation model found so far for studying smoking-induced carcinogenesis. It is more tolerant of tobacco smoke than mice and rats and is relatively resistant to respiratory infections. The hamster also has a low background incidence of spontaneous pulmonary tumors and is, in fact, refractory to the induction of lung cancers by known carcinogenic agents. The inhalation of tobacco smoke by the hamster does, however, induce carcinomas of the larynx. In one study (Dontenwill et al., 1973), three groups of 80 male and 80 female Syrian golden hamsters were exposed for 10 minutes to air-diluted cigarette smoke (1:15) once, twice, or three times daily, 5 days per week, for their lifetimes. Preinvasive carcinomas of the upper larynx were detected in 11.3%, 30%, and 30.6% of the animals, respectively, and invasive carcinomas were found in 0.6%, 10.6%, and 6.9%, respectively. No laryngeal tumors were observed in control animals. In another experiment, exposure for 59 to 80 weeks to an 11% or 22% cigarette smoke aerosol twice daily for 12 minutes resulted in laryngeal carcinomas in 3 of 44 and 27 of 57 animals, respectively, providing some evidence of a dose-response relationship for the induction of carcinoma of the larynx by cigarette smoke (Bernfeld et al., 1979). Bernfeld et al. suggest that the greater deposition of tar per unit of surface area in the larynx compared to the lung may explain the high yield of laryngeal cancers and lack of lung tumors in this animal model.

4.3.2. Intrapulmonary Implantations of Cigarette Smoke Condensates

Because of the difficulties with inhalation studies of cigarette smoke, some in vivo studies examine the carcinogenicity of cigarette smoke condensate (CSC) collected from smoking machines. CSC assays may not, however, reveal all of the carcinogenic activity of actual cigarette smoke, because these condensates lack most of the volatile and semivolatile components of whole smoke. In lifetime rat studies, intrapulmonary implants of MS condensate in a lipid vehicle cause a dose-dependent increase in the incidence of lung carcinomas (Stanton et al., 1972; Dagle et al., 1978).

SS condensates have also demonstrated carcinogenicity when implanted into rat lungs (Grimmer et al., 1988). SS emitted by a smoking machine was separated into condensate fractions containing the semivolatiles, the polycyclic aromatic hydrocarbon (PAH)-free particulates and the PAHs with two or three rings, or the PAHs with

four or more rings. These fractions were implanted into female Osborne-Mendel rats, following the procedure of Stanton et al. (1972), at a dose level of one cigarette per animal. At the end of the lifetime study, none of the 35 rats in each of the untreated control, vehicle control, or semivolatile-exposed groups had lung carcinomas. In the group exposed to the fraction containing PAH-free particulates and PAHs with 2 or 3 rings, there was 1 lung carcinoma in 35 animals. In the group exposed to the fraction comprising PAHs with 4 or more rings, there were 5 lung carcinomas in 35 rats. An additional group that was exposed to a dose of 0.03 mg benzo[a]pyrene (BaP) per rat exhibited 3 lung carcinomas in 35 animals. The condensate fraction containing BaP and the other PAHs with four or more rings from the SS generated by a single cigarette contains about 100 ng of BaP. Assuming a linear, nonsynergistic dose-response relationship, this would suggest that less than 1% of the total carcinogenicity of that condensate fraction can be attributed to the BaP present in the smoke.

4.3.3. Mouse Skin Painting of Cigarette Smoke Condensates

In addition, numerous studies have shown that when MS condensate suspended in acetone is chronically applied to mouse skin, significant numbers of the mice develop papillomas or carcinomas at the site of application (e.g., Wynder et al., 1957; Davies and Day, 1969). Mouse skin studies have also demonstrated that MS condensate has both tumor-initiating and tumor-promoting capabilities (Hoffman and Wynder, 1971).

One mouse skin painting study examined the carcinogenicity of SS condensate (Wynder and Hoffman, 1967). Cigarette tar from SS deposited on the funnel of a smoking machine was suspended in acetone and administered to mouse skin. Fourteen of thirty mice developed skin papillomas, and 3 of 30 developed carcinomas. In a parallel assay in the same study, a suspension of MS condensate applied to deliver a comparable amount of condensate to the skin of 100 mice yielded benign skin tumors in 24 and malignant tumors in 6 of the mice. This suggests that the condensate of SS has greater mouse skin tumorigenicity per unit weight than that of MS.

4.4. GENOTOXICITY

Supportive evidence for the carcinogenicity of tobacco smoke is provided by the demonstration of genotoxicity in numerous short-term assays. Extensive reviews of these studies can be found in IARC (1986) and DeMarini (1983); only the highlights are presented here. A few studies deal with whole smoke, but most examine CSC. Tobacco smoke is genotoxic in virtually every in vitro system tested, providing overwhelming supportive evidence for its carcinogenic potential.

In *Salmonella typhimurium*, for example, Basrur et al. (1978) found that both whole MS and MS condensates from various types of tobacco were mutagenic in the presence of a metabolic activating system. SS (Ong et al., 1984) and extracts of ETS collected from indoor air (Löfroth et al., 1983; Alfheim and Ramdahl, 1984; Lewtas et al., 1987; Ling et al., 1987; Löfroth et al., 1988) also exhibit mutagenic activity in this bacterium. Claxton et al. (1989) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette--40%

from the SS particulates and 20% from the semivolatiles. The highly volatile fraction, from either MS or SS, was not mutagenic.

Similarly, cigarette smoke produced mitotic gene conversion, reverse mutation, and reciprocal mitotic recombination in fungi (Gairola, 1982). In addition, CSC's induce mutations, sister chromatid exchanges, and cell transformation in various mammalian cells in culture. Putnam et al. (1985) demonstrated dose-dependent increases in sister chromatid exchange frequencies in bone-marrow cells of mice exposed to cigarette smoke for 2 weeks.

4.5. SUMMARY AND CONCLUSIONS

Lung cancer mortality rates have increased dramatically over the past 60 years in males, and, more recently, in females, with increasing cigarette consumption. High relative risks for lung cancer, associated with the number of cigarettes smoked per day, have been demonstrated in countless studies, with no evidence of a threshold level of exposure. Active smoking induces all four major histological types of human lung cancer--squamous-cell carcinomas, small-cell carcinomas, large-cell carcinomas, and adenocarcinomas--all in a dose-related manner. Dose-response relationships have also been established with respect to duration of smoking. Furthermore, lung cancer risk increases with the younger the age at initiation of smoking and decreases with the longer the time since cessation of smoking. These latter trends, coupled with evidence from mouse skin painting studies, suggest that tobacco smoke has both tumor-initiating and tumor-promoting capabilities.

Inhalation studies in hamsters confirm that MS is carcinogenic to the respiratory tract. In addition, mouse skin painting experiments and intrapulmonary implantations in rats have demonstrated the carcinogenicity of condensates from both MS and SS (the primary component of ETS), with SS condensate having a greater potency than MS condensate in mouse skin painting studies. Numerous genotoxicity tests contribute supporting evidence for the carcinogenic potential of MS and SS smoke and smoke condensates. The mutagenicity of ETS and its extracts has also been established. One study found that SS accounted for 60% of the total mutagenicity per cigarette.

As discussed in Chapter 3, MS and ETS are qualitatively similar in composition, and both contain numerous known or suspected human carcinogens. ETS constituents include essentially all of the same carcinogens found in MS, and many of these appear in greater amounts in SS, and hence, in ETS, than in MS, per unit of tobacco burned. This quantitative comparison is consistent with the observation noted above that SS condensates apparently have even greater carcinogenic potential than MS condensates.

The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest exposure categories, as well as the corroborative evidence of the carcinogenicity of both MS and ETS provided by animal bioassays and in vitro studies and the chemical similarity between MS and ETS (Chapter 3), clearly establish the plausibility that ETS is also a human lung carcinogen. In addition, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern (Chapter 3).

In fact, these observations are sufficient in their own right to establish the carcinogenicity of ETS to humans. According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

Given the strong dose-related associations, with high relative risks consistently observed across numerous independent studies from several countries, and the biological plausibility provided by ancillary evidence of the genotoxicity and animal carcinogenicity of MS and by knowledge of the existence of many specific carcinogenic components within MS, confounding, bias, and chance can all be ruled out as possible explanations for the observed association between active smoking and lung cancer. Therefore, under the EPA carcinogen classification system, MS would be categorized as a Group A (known human) carcinogen. Furthermore, the extensive chemical and toxicological similarities between SS and MS, detailed in Sections 3.2, 4.3, and 4.4, strongly infer that SS is also capable of causing lung cancer in humans, as was documented for MS in Section 4.2. Thus, under EPA's carcinogen classification system, SS also belongs in Group A. Finally, because ETS is composed of SS and exhaled MS, and because ETS is known to be inhaled and absorbed into the body (Section 3.3.2), ETS would similarly be categorized as a Group A carcinogen.

In addition, there exists a vast body of epidemiologic data dealing specifically with lung cancer and exposure to ETS. These data should also be examined in the interest of weighing all the available evidence, as recommended by EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a), both for hazard identification and exposure-response assessment. The rapid dilution of both SS and exhaled MS into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions. Furthermore, while MS and ETS may be qualitatively comparable, active smoking data do not constitute a good basis for quantitative estimation of the health effects of passive smoking because the relative uptake and deposition between active and passive smokers of the agent(s) responsible for these effects are not known (see Chapters 2 and 6). Provided the epidemiologic studies are of sufficient power and adequate study design, this database can offer unique information on the actual lung cancer risk to nonsmokers from exposure to true ambient levels of ETS. The epidemiologic evidence for the human lung carcinogenicity associated specifically with ETS is the subject of Chapter 5. These epidemiologic data are then used as the basis for the calculation of population risk estimates for lung cancer from passive smoking in Chapter 6.