FINAL

Report on Carcinogens
Background Document for

Environmental Tobacco Smoke

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Summary Statement

Environmental tobacco smoke (ETS) is *known to be a human carcinogen* based on studies in humans that indicate a causal relationship between passive exposure to tobacco smoke and human lung cancer (reviewed in IARC V. 38 1986; US EPA 1992, CEPA 1997). Studies also support an association of ETS with cancers of the nasal sinus (CEPA 1997).

Evidence for an increased cancer risk from ETS is from studies examining nonsmoking spouses living with individuals who smoke cigarettes, exposures of nonsmokers to ETS in occupational settings, and exposure to parents' smoking during childhood. Many studies, including recent large population-based case control studies, have demonstrated increased risks of about 20% for developing lung cancer following prolonged exposure to ETS, with some studies suggesting higher risks with higher exposures. Exposure to ETS from spouses smoking or exposure in an occupational setting appears most strongly related to increased risk. There is little or no discernible risk from exposure to ETS only during childhood.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

ETS is a complex mixture of gases and particles comprising smoke from the burning cigarette, cigar or pipe tip (sidestream smoke), mainstream smoke which is not inhaled by the smoker, and exhaled smoke. Sidestream smoke and mainstream smoke contain many of the same chemical constituents including at least 250 chemicals known to be toxic or carcinogenic. There is evidence from animal studies that the condensate of sidestream smoke is more carcinogenic to the skin of mice than equivalent weight amounts of mainstream smoke. Active tobacco smoking has been determined to cause cancer of the lung, urinary bladder and renal pelvis, oral cavity, pharynx, larynx, esophagus, lip, and pancreas in humans. Between 80 to 90% of all human lung cancers are attributed to tobacco smoking.

Exposure of nonsmokers to ETS has been demonstrated by detecting nicotine, respirable smoke particulates, tobacco specific nitrosamines and other smoke constituents in the breathing zone, and by measurements of a nicotine metabolite (cotinine) in the urine. However, there is no good biomarker of cumulative past exposure to tobacco smoke, and all of the information collected in epidemiology studies determining past exposure to ETS relies on estimates which may vary in their accuracy (recall bias). Other suggestions of systematic bias have been made concerning the epidemiological information published on the association of ETS with cancer. These include misclassification of smokers as nonsmokers, factors related to lifestyle, diet, and other exposures that may be common to couples living together and that may influence lung cancer incidence, misdiagnosis of metastatic cancers from other organs in the lung, and the possibility that epidemiology studies examining small populations and showing no effects of ETS would not be published (publication bias).

Three recent population-based (Stockwell *et al.* 1992; Brownson *et al*. 1992; Fontham *et al.* 1994) and one hospital-based (Kabat *et al*. 1995) case control studies have addressed potential systematic biases. The three population-based studies each showed an increased risk from prolonged ETS exposure of a magnitude consistent with prior estimates. The hospital-based study gave similarly increased risk estimates, but the results were not statistically significant.

The potential for publication bias has been examined and dismissed (CEPA 1997), and the reported absence of increased risk for lung cancer for nonsmokers exposed only in occupational settings has been found not to be the case when the analysis is restricted to higher quality studies (Wells 1998). Thus, factors related to chance, bias, and/or confounding have been adequately excluded, and exposure to ETS is established as causally related to human lung cancer.

1 Physical and Chemical Properties

1.1 Chemical Identification

Environmental Tobacco Smoke (ETS) is the sum of sidestream smoke (SS) (interval between puffs), mainstream smoke (MS) emitted at the cigarette mouthpiece during inhalation, compounds diffused through the wrapper, and MS that the smoker exhales (NRC 1986; U.S. EPA 1992; CEPA 1997). Tobacco pyrolysis products are formed both during smoke inhalation and during the interval between inhalations (NRC 1986). Tobacco smoke consists of a complex mixture of gases and particles. Appendix 1 lists the chemicals identified in MS and SS and their concentrations. Carcinogenic nitrosamines have also been quantified. The submicronic and exhaled particles from burning tobacco originate mainly from condensation of the vapors and are high in organic matter content. Upon emission into air, SS may undergo dilution; chemical reactions, including oxidation and reactions between components; deposition; and other chemical and physical changes (U.S. EPA 1992; NRC 1986; CEPA 1997).

One half, or more (by weight), of the smoke generated by a lit cigarette is SS emitted from the smoldering cigarette (U.S. EPA 1992). SS and MS contain many of the same chemical constituents because they originate from similar processes. ETS contains more than 4,000 chemicals. Among these, at least 200 are toxic and 43 were known carcinogens as identified in the 1992 EPA review. Approximately 400 compounds have been quantified in both MS and SS smoke. Although many constituents of MS and SS are the same, their emission rates vary as shown in Table 1-1 (U.S. EPA 1992).

Table 1-1. Typical cigarette SS and MS chemical components and yields

Component	Sidestream	Mainstream	Reference
Tar	24.1 mg	11.4 mg	Rickert *et al.* (1984)
Carbon monoxide	53.0 mg	12.0 mg	Rickert *et al.* (1984)
Carbonyl sulfide	2-3 mg	23-66 mg	CIB (1991) Hoffmann and Hecht (1989)
3-Vinylpyridine	300-450 μg	12.5-13.20 μg	CIB (1991) Hoffmann and Hecht (1989)
Hydrogen Cyanide	14-110 μg	233-275 μg	CIB (1991) Hoffmann and Hecht (1989)
Hydrazine	90 ng	30 ng	CIB (1991) Hoffmann and Hecht (1989)
Nitrogen oxides	500-2000 μg	135-156 μg	CIB (1991) Hoffmann and Hecht (1989)
Nicotine	4.1 mg	0.8 mg	Rickert *et al.* (1984)

Component	Sidestream	Mainstream	Reference
Nitric oxide	2-3 mg	0.2-0.5 mg	Norman *et al.* (1983)
Volatile hydrocarbons			
Ethene	1.2 mg	0.24 mg	Lofroth *et al.* (1987)
Propene	1.3 mg	0.18 mg	Elmenhorst and Schultz (1968)
1,3-Butadiene	0.4 mg	0.03 mg	CIB (1991)
Isoprene	3.1 mg	0.70 mg	Hoffmann and Hecht (1989)
Formaldehyde	1500 μg	30 μg	
Aromatic Compounds			
Benzene	400-500 μg	50 μg	Grimmer *et al.* (1977)
Fluoranthene	1.3 μg	0.27 μg	Patrianakos and Hoffmann (1979)
Benzo[a]pyrene	0.2 μg	0.04 μg	Dong *et al.* (1978)
o-Toluidine	3.0 μg	0.16 μg	CIB (1991)
2-Napthylamine	0.06 μg	0.002 μg	Hoffmann and Hecht (1989)
Quinoline	18 μg	1.7 μg	
N-Nitrosamines			
Nitrosodimethylamine	0.2-1 μg	0.01-0.04 μg	Hoffmann *et al.* (1984)
Nitrosonornicotine	0.15-1.7 μg	0.1-1 μg	CIB (1991)
N-nitrosopyrrolidine	30-390 ng	3.25-5 ng	Hoffmann and Hecht (1989)
N-nitrosodiethanolamine	43 ng	35.8 ng	
Phenol	70-250 μg	54-83 μg	CIB (1991) Hoffmann and Hecht (1989)
Catechol	58-290 μg	22.6-86.5 μg	CIB (1991) Hoffmann and Hecht (1989)
4-Aminobiphenyl	140 ng	4.5 ng	CIB (1991) Hoffmann and Hecht (1989)
Benz[a] anthracene	40-200 ng	20-50 ng	CIB (1991) Hoffmann and Hecht (1989)
NNK	0.2-1.4 μg	0.06-0.2 μg	CIB (1991) Hoffmann and Hecht (1989)
Cadmium	0.72 μg	0.1 μg	CIB (1991) Hoffmann and Hecht (1989)

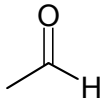
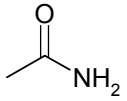
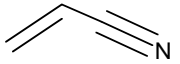
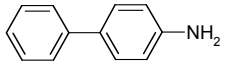
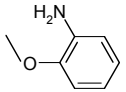
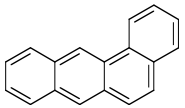
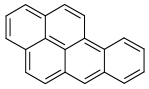
Component	Sidestream	Mainstream	Reference
Nickel	0.2-2.55 µg	0.015-0.085 µg	CIB (1991) Hoffmann and Hecht (1989)
Radioactive isotopes Po-210	0.004 Bq	0.003 Bq	Ferri and Baratta (1992)

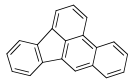
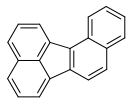
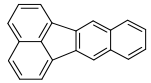
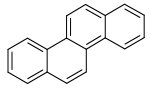
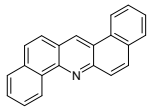
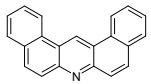
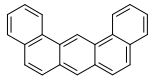
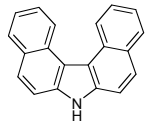
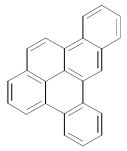
Many polycyclic aromatic hydrocarbons (PAH) have been detected in tobacco smoke (Grimmer *et al.* 1977; IARC 1986). Unsubstituted PAH and alkyl derivatives of PAH have been detected. Several aromatic amines, including the carcinogens o-toluidine, 2-napthylamine, and 4-aminobiphenyl, have been identified in both SS and MS.

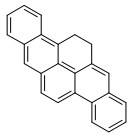
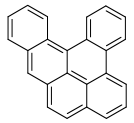
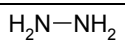
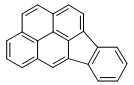
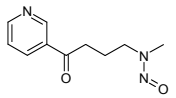
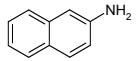
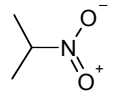
The concentration of chemicals in MS depends on various factors, including the cigarette design (*e.g.*, presence of filter and filter ventilation), smoking patterns, and cigarette brands. In 1992, the U.S. EPA suggested that the SS chemical concentration is relatively constant across a number of products (U.S. EPA 1992). This is consistent with the finding that SS concentrations are primarily related to the weight of tobacco and paper consumed during smoldering, rather than to cigarette design (Guerin *et al.* 1987).

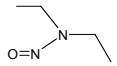
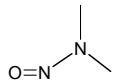
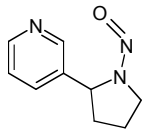
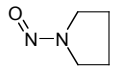
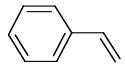
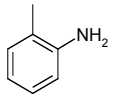
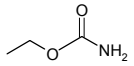
A number of chemicals present in ETS are known or suspected toxicants/irritants with various acute health effects. Prominent among them are the respiratory irritants: ammonia, formaldehyde, and sulfur dioxide. Acrolein, hydrogen cyanide, and formaldehyde affect mucociliary function and, at higher concentrations, can inhibit smoke clearance from the lungs (Battista 1976). Nicotine is addictive and has several pharmacological and toxicological actions, including acute poisoning. Nitrogen oxides and phenol are important toxicants present in ETS. Over 50 compounds in ETS have been identified as known, or reasonably anticipated to be, human carcinogens by various agencies (IARC 1986; CEPA 1997; NRC 1986; U.S.EPA 1992; RoC 1997: http://ehis.niehs.nih.gov/roc/). Most of these compounds are present in the particulate phase (IARC 1986). The following components of ETS, summarized in Table 1-2, have been characterized as toxic and/or carcinogenic.

Table 1-2. Selected chemical carcinogens and toxicants identified in tobacco smoke

Compound	Sidestream conc.	Mainstream conc.	CASRN	Mol. Wt.	Structure	Classification	Reference
Acetaldehyde C_2H_4O	np	np	75-07-0	44.053		2B	CEPA (1997)
Acetamide C_2H_5NO	86-156 μg/cig	70-111μg/cig	60-35-5	59.068		2B	Sakuma *et al.* (1984)
Acrylonitrile C_3H_3N	np	Np	107-13-1	53.063		2A	CEPA (1997)
4-Aminobiphenyl $C_{12}H_{11}N$	np	Np	92-67-1	169.23		1	CEPA (1997)
o-Anisidine C_7H_9NO	np	Np	94-04-0	123.15		2B	CEPA (1997)
Benz[a]anthracene $C_{18}H_{12}$	201 ng/cig (P) 2.5 ng/cig (V)	13.3 ng/cig (P) 0.09 ng/cig (V)	56-55-3	228.29		2A	Grimmer *et al.* (1987)
Benzene C_6H_6	400-500 μg/cig [a]	12-48 μg/cig [b]	71-43-2	78.113		1	a: CIB (1991) b: NRC (1986)
1,3 Butadiene C_4H_6	np	Np	106-99-0	54.091		C	CEPA (1997)
Benzo[a]pyrene $C_{20}H_{12}$	199 ng/cig	44 ng/cig	50-32-8	252.31		2A	Grimmer *et al.* (1977)

Compound	Sidestream conc.	Mainstream conc.	CASRN	Mol. Wt.	Structure	Classification	Reference
Benzo[b]fluoranthene $C_{20}H_{12}$	np	np	205-99-2	252.31		2B	CEPA (1997)
Benzo[j]fluoranthene $C_{20}H_{12}$	np	np	205-82-3	252.31		2B	CEPA (1997)
Benzo[k]fluoranthene $C_{20}H_{12}$	np	np	207-08-9	252.31		2B	CEPA (1997)
Chrysene $C_{18}H_{12}$	np	np	218-01-9	228.29		C	CEPA (1997)
Dibenz[a,h]acridine $C_{21}H_{13}N$	np	np	226-36-8	279.34		2B	CEPA (1997)
Dibenz[a,j]acridine $C_{21}H_{13}N$	np	np	224-42-0	279.34		2B	CEPA (1997)
Dibenz[a, j]anthracene $C_{22}H_{14}$	41 ng/cig	11 ng/cig	224-41-9	278.35		2A	Grimmer *et al.* (1977)
7H-Dibenzo[c,g]carbazole	np	np	194-59-2	267.33		2B	CEPA (1997)
Dibenzo[a,e]pyrene $C_{24}H_{14}$	np	np	192-65-4	302.37		2B	CEPA (1997)

Compound	Sidestream conc.	Mainstream conc.	CASRN	Mol. Wt.	Structure	Classification	Reference
Dibenzo[a,h]pyrene $C_{24}H_{14}$	np	np	189-64-0	302.37		2B	CEPA (1997)
Dibenzo[a,i]pyrene $C_{24}H_{14}$	np	np	191-30-0	302.37		2B	CEPA (1997)
1,1-Dimethylhydrazine $C_2H_8N_2$	np	np	57-14-7	60.099		2B	CEPA (1997)
Formaldehyde CH_2O	80-110 ppm [a]	70-100 μg/cig [b]	50-00-0	30.026		2A	a: Ayer and Yeager (1982) b: NRC (1986)
Hydrazine H_4N_2	94.2 ng/cig	31.5 ng/cig	302-01-2	32.045		2B	Liu *et al.* (1974)
Indeno[1, 2, 3-cd]pyrene $C_{22}H_{12}$	51 ng/cig (P) 0.36 ng/cig (V)	8.1 ng/cig (P) 0.17 ng/cig (V)	193-39-5	276.34		2B	Grimmer *et al.* (1987)
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) $C_{10}H_{13}N_3O_2$	201-540 ng/cig	46-240 ng/cig	64091-91-4	207.23		2B	Brunnemann *et al.* (1983)
2-Naphthylamine $C_{10}H_9N$	np	np	91-59-8	143.19		1	CEPA (1997)
2-Nitropropane $C_3H_7NO_2$	np	np	79-46-9	89.094		2B	CEPA (1997)

Compound	Sidestream conc.	Mainstream conc.	CASRN	Mol. Wt.	Structure	Classification	Reference
Nitrosodiethylamine, N'- $C_4H_{10}N_2O$	8.2-73 ng/cig	1.8-4.8 ng/cig	55-18-5	102.14		2A	Brunnemann and Hoffmann (1978)
Nitrosodimethylamine, N'- $C_2H_6N_2O$	680-1040 ng/cig	1.7-97 ng/cig	65-75-9	74.082		2B	Brunnemann and Hoffmann (1978)
N′-Nitrosonornicotine $C_9H_{11}N_3O$	110-390 ng/cig	81-390 ng/cig	16543-55-8	177.21		2B	Brunnemann *et al.* (1982)
Nitrosopyrrolidine $C_4H_8N_2O$	204-612 ng/cig 28-143 ng/cig 80-500 ng/cig	1.5-29 ng/cig 2.6-52 ng/cig	930-55-2	100.12		2B	Brunnemann and Hoffmann (1978)
Styrene C_8H_8	np	np	100-42-5	104.15		2B	CEPA (1997)
2-Toluidine C_7H_9N	3 μg/cig[a]	160 ng/cig [b]	95-53-4	107.15		2B	a: CIB (1991) b: NRC (1986)
Urethane $C_3H_7NO_2$	np	np	51-79-6	89.094		2B	CEPA (1997)
Vinyl Chloride C_2H_3Cl	np	np	75-01-4	62.499		1	CEPA (1997)
Arsenic As	np	np	7440-38-2	74.9216	As	1	CEPA (1997)
Cadmium Cd	0.72 μg/cig[a]	100 ng/cig[b]	7440-43-9	112.41	Cd	2A	a: CIB (1991) b: NRC (1986)

Compound	Sidestream conc.	Mainstream conc.	CASRN	Mol. Wt.	Structure	Classification	Reference
Chromium VI	np	np	18540-29-9	51.996	Cr^{+6}	1	CEPA (1997)
Lead [Pb]	np	np	7439-92-1	207.2	Pb	2B	CEPA (1997)
Nickel [Ni]	0.2-2.55 μg/cig[a]	20-80 ng/cig[b]	7440-02-0	58.6934	Ni	1	a: CIB (1991) b: NRC (1986)

conc.: concentration, cig: cigarette, np: not provided, P: Particulate phase, V: Volatile phase

Classification: 1, Carcinogenic to humans; 2A, Probably carcinogenic to humans; 2B, possibly carcinogenic to humans (IARC Classification). C, probable human carcinogen (U.S. EPA Classification). D, Chemicals listed under proposition 65 known to cause cancer or reproductive toxicity (CEPA 1997).

2 Human Exposure

The National Institute of Occupational Safety and Health (NIOSH) estimated approximately 29% of the U.S. adult population smoked cigarettes in 1990 (Millar 1991). The prevalence of smoking in the population affects potential exposures to Environmental Tobacco Smoke (ETS). Recent studies in California found that 62% of the total populace (including 46% of nonsmokers), aged 12 years or more, reported exposure to ETS on any given day (Jenkins *et al.* 1992; cited by Branoff *et al*. 1998). NIOSH estimated, based on urinary adduct concentration data, that nonsmokers are exposed to ETS equivalent to smoking 0.1 to 1.0 cigarettes a day (Millar 1991). Based on analyzing respirable suspended particles (RSP) (3.5 μm diameter), Jenkins *et al.* (1996) found that nonsmoking individuals working in smoking environments were more heavily exposed to ETS than those working in nonsmoking environments. They further found that exposure of nonsmokers to their spouses smoking resulted in exposures a factor of two to four times higher than those exposed to ETS in the workplace. Nicotine and RSP concentrations were calculated to determine a 24-hour time weighted average (TWA).

2.1 Biomarkers of Exposure

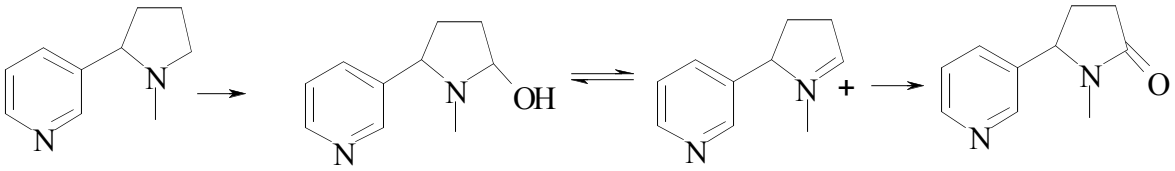
Various biomarkers may be used to gauge ETS exposure in humans. Cotinine, a metabolite of nicotine, is among the most commonly used. Thiocyanate, carbon monoxide, and tobacco-specific *N*-nitrosamines are also used to estimate exposure to ETS. Some of these biomarkers have limited usefulness because they have short half-lives in the body. These measurements can provide inflated exposure estimates when environmental influences such as diet, diesel pollution, chemical plant waste, and natural burning (campfires, wood, *etc.*) contribute to biomarker concentrations.

2.1.1 Nicotine and Cotinine

Nicotine and its main metabolite, cotinine, are specific for tobacco and have been used to determine exposure to ETS. Cigarettes contain 1-7% nicotine by weight, and of this, 15-25% is in mainstream smoke (MS) while 40% is in sidestream smoke (SS). Nicotine is also found in exhaled smoke (approximately 50% of inhaled tobacco smoke is exhaled). The amount of nicotine in exhaled MS, however, is not considered to be significant (Curvall and Enzell 1986). Nicotine is found in common foods, including tomatoes, potatoes, eggplant, and certain teas, but the contribution of nicotine in foods appears small in relation to that from ETS (Pirkle et al. 1996). Assessments of serum samples collected as part of the NHANES III survey revealed that 91.7% of the US population over 4 years of age had detectable serum cotinine levels indicating exposure to tobacco smoke through active or passive smoking (Pirkle et al. 1996). Cotinine levels in body fluids are more typically measured than are those of nicotine because cotinine has a longer half-life (16-20 h vs. 1 h) in the body (Scherer and Richter 1997).

Hair nicotine has now become an effective and reliable marker of ETS exposure. Human hair has a high affinity for airborne nicotine and can be examined to determine exposure during a 1-2 month period. Chamber studies have revealed a linear relationship between the extent of airborne nicotine exposure and its adhesion to hair strands. This relationship has been found to hold up to four to six weeks after exposure. Levels of nicotine in the hair have been used to discriminate between smokers and nonsmokers, and between various levels of self-reported ETS exposure (Jaakkola and Jaakkola 1997).

Nicotine is primarily metabolized in the liver, but processing also takes place in the lungs and kidneys. Nicotine is transformed to cotinine by a two step process:



Nicotine Cotinine

2.1.2 Carbon Monoxide and Carboxyhemoglobin

The presence of ETS can be estimated by measuring carboxyhemoglobin (CO-Hb) in the blood. Although CO-Hb levels can be used to estimate relative degrees of smoke inhalation, they cannot accurately measure ETS exposure. CO has many environmental sources. Humans exhale approximately 0.4 mL/h (0.5 mg/h) of CO. It also comes from the incomplete combustion of organic materials, including motor and heating fuels, and cooking oils. CO-Hb has a brief half-life (3 h) in the blood and sampling must be timed appropriately to be useful (Millar 1991).

2.1.3 Thioethers

Thioethers and mutagenic activity of urine were measured for smokers and nonsmokers. Scherer *et al.* (1996) discovered, in two field studies, that the amount of thioethers in urine (a proposed biomarker for exposure to electrophilic compounds) did not change significantly though a variety of conditions were observed. The study compared various factors including smoking environment, self-reported ETS exposure, cotinine presence in plasma, ETS exposure duration, nicotine on personal sampler, cotinine presence in saliva, and cotinine presence in urine. These results indicated that diet contributes significantly to thioether excretion in nonsmokers.

2.1.4 Thiocyanate

Thiocyanate (SCN) is formed when the hydrogen cyanide (HCN) from tobacco smoke is detoxified by the liver. The U.S. EPA (1992) cited the finding by Butts *et al.* (1974) that SCN could react with ferric ions to yield a product capable of measurement with an autoanalyzer. While SCN^- has a relatively long half-life (10-14 days) and is easily measured in the body, diet can confuse attempts to estimate the levels of tobacco smoke exposure (Scherer and Richter 1997). HCN is found in almonds, beans, and maize, and can be synthesized by bacteria in the colon. Further confounding quantification, SCN is present in cabbage, turnips, mustard, and cow's milk. The SCN levels in a nonsmoker's serum are, ordinarily, low at about 95 μmol/L. However, with the factor of diet, this biomarker cannot always differentiate the SCN levels of a smoker or nonsmoker (Millar 1991).

2.1.5 Tobacco-Specific N*-Nitrosamines*

Tobacco-specific *N*-nitrosamines (TSNA) have been identified in ETS. Four nitrosamines (*N*′-nitrosonornicotine [NNN], *N*-nitrosoanatabine [NAT], *N*-nitrosoanabasine [NAB], and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) have been associated with respiratory tract and pancreatic cancers. SS from domestic cigarettes has been found to contain TSNA

concentrations as follows: NNK (227.7 ng/cig), NAT (140.0 ng/cig), NNN (24.2 ng/cig), and NNK (308.5 ng/cig) (Brunnemann *et al.* 1996). TSNA levels were evaluated (as shown in Table 2-1) to determine ETS exposure (Brunnemann *et al.* 1992).

Table 2-1. TSNA in indoor air

Site	Approx. # of cigarettes smoked	Collection time (h)	Flow rate (L/min)	NNN (ng/L)	NAT (ng/L)	NNK (ng/L)
Bar 1	25-35	3	3.2	22.8	9.2	23.8
Bar 2	10-15	3	3.2	8.3	6.2	9.6
Bar 3	10-15	3	3.2	4.3	3.7	11.3
Restaurant 1[a]	25-30	6	2.15	1.8	1.5	1.4
Restaurant 2[a]	40-50	8	2.1	ND	ND	3.3
Cab[b]	13	3.3	2.15	5.7	9.5	29.3
Train 1	50-60	5.5	3.3	ND	ND	4.9
Train 2	50-60	6	3.3	ND	ND	5.2
Office	25	6.5	3.3	ND	ND	26.1
Smoker's home	30	3.5	3.3	ND	ND	1.9

Brunnemann *et al.* (1992; cited by Brunnemann *et al.* 1996)

ND = not detected

[a] Smoking Section

[b] Windows partially open

Based on these indoor TSNA concentrations, Brunnemann calculated that, in a three hour period (assuming a respiratory rate of 10 L/min), 3.2-41 ng NNN, and 2.5-43 ng NNK would be inhaled (Brunnemann *et al.* 1996). A biomarker study has confirmed that nonsmokers exposed to ETS absorb, retain, and metabolize NNK. TSNA measurements have, therefore, been proposed as a means to monitor exposure to ETS (Hecht *et al.* 1993).

2.2 Environmental Exposure

ETS is ubiquitous. Even nonsmokers, working and living in nonsmoking environments, are exposed to ETS, mainly from inhalation of SS and exhaled MS. Table 2-2 details environmental exposure to ETS. Jenkins *et al.* (1996) collected air samples in work and living spaces and classified results based on questionnaire responses. Demographics of the subject group were comparable to the entire U.S. population, although a larger portion of females participated in this study. Median household income was $41,000 (higher than U.S. median of $37,000). Age of participants ranged mostly from 25-65, based on the study restriction that the participant work a full time eight-hour shift. White collar jobs were highly represented in this study. Racial diversity was matched for the total U.S. population. After analyzing nonsmokers, a 24-hour TWA was found for RSP and nicotine (Table 2-2). Kado *et al.* (1991) used personal sampling pumps to determine indoor ETS exposure at sites where subjects were participants in recreational activities. Siegel (1993) reviewed three journal articles to determine ETS concentrations at homes of nonsmokers. RSP and nicotine levels were also determined for smoking and nonsmoking sections in restaurants (Lambert *et al.* 1993), as summarized in Table 2-2.

Table 2-2. Environmental exposure to ETS

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
Nicotine	Smoking work environment. Smoking away from work environment.	1.47 μg/m^3 median; 2.98 μg/m^3 mean n=157	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. Nicotine levels were measured using gas chromatography with temionic specific (nitrogen selective) detection.	Jenkins *et al.* (1996)
Nicotine	Nonsmoking work environment. Smoking away from work environment.	0.473 μg/m^3 median; 1.21 μg/m^3 mean n=234	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. Nicotine levels were measured using gas chromatography with temionic specific (nitrogen selective) detection.	Jenkins *et al.* (1996)
Nicotine	Smoking work environment. Nonsmoking away from work environment.	0.107 μg/m^3 median; 0.543 μg/m^3 mean n=281	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. Nicotine levels were measured using gas chromatography with temionic specific (nitrogen selective) detection.	Jenkins *et al.* (1996)
Nicotine	Nonsmoking work environment. Nonsmoking away from work environment.	0.031 μg/m^3 median; 0.120 μg/m^3 mean n=808	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. Nicotine levels were measured using gas chromatography with temionic specific (nitrogen selective) detection.	Jenkins *et al.* (1996)
Nicotine	Casino Site	8.02 μg/m^3 median	Personal sampling	Nonsmoking individuals were studied in two separate,	Kado *et al.*

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
	(~100x100x12 feet). Bingo Site (~100x150x16 feet).	(3.3-11-6 μg/m^3 range) n=6 65.5 μg/m^3 median (4.4-85.4 μg/m^3 range) n=6	pumps (1.71 L/min flow rate).	indoor facilities containing smokers. Smoking policies for these two environments were not mentioned. Sampling times range from 40 minutes to 6 hours. The bingo site was classified as a "smoky environment."	(1991)
Nicotine	Smoking section restaurant. Nonsmoking section restaurant.	3.2 μg/m^3 median (1.5-3.8 μg/m^3 range) 1.0 μg/m^3 median (0.2-2.8 μg/m^3 range)	Mass flow controlled pump (4 L/min flow rate).	Seven restaurants in Albuquerque, NM (seating capacity exceeded 100 in all restaurants) were sampled for two consecutive days for 12 hours (11:00 AM-11:00 PM). Pumps were placed within the usual breathing areas except in two restaurants. Nicotine levels in all of the restaurants were lower in nonsmoking sections than in smoking sections (P=0.02, Wilcox paired sample test) with a median difference of 2.2 μg/m^3.	Lambert *et al.* (1993)
Nicotine	Residences.	4.3 μg/m^3 mean (1.6-21 μg/m^3 range) n=91	Compilation of data from three sources (Sterling *et al.* 1987; Guerin *et al.* 1992; Repace 1987).	Review of ambient air surveys on ETS from three sources. Weighted average of the individual study mean concentrations for all measurements taken. Weights used were the number of residences sampled.	Siegel (1993)
Nicotine	Boeing 727-200 NS S	 2.6 μg/m^3 mean (0.03-24.2 μg/m^3 range) n=10 6.8 μg/m^3 mean (0.4-42.2 μg/m^3 range) n=8	Hidden briefcase pump (1 L/min flow rate).	Study shows that segregation of smoking and nonsmoking sections in airplanes was effective in keeping smoke away from nonsmokers. Questions, however, have come because of the author's use of geometric mean, rather than arithmetic mean and results which show that airplane, nonsmoking sections have higher nicotine levels than smoking sections in restaurants (Repace and Lowrey 1988).	Oldaker and Conrad (1987)
Nicotine	Boeing 737-200 NS	 7.7 μg/m^3 mean (0.04-40.2 μg/m^3 range) n=29	Hidden briefcase pump (1 L/min flow rate).	Study shows that segregation of smoking and nonsmoking sections in airplanes was effective in keeping smoke away from nonsmokers. Questions, however, have come because of the author's use of geometric mean, rather than arithmetic mean and results which show that airplane,	Oldaker and Conrad (1987)

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
	S	6.5 μg/m^3 mean (0.08-112.4 μg/m^3 range) n=11		nonsmoking sections have higher nicotine levels than smoking sections in restaurants (Repace and Lowrey 1988).	
Nicotine	Boeing 737-300 NS S	4.2 μg/m^3 mean (0.4-17.2 μg/m^3 range) n=10 21.5 μg/m^3 mean (0.7-76.7 μg/m^3 range) n=7	Hidden briefcase pump (1 L/min flow rate).	Study shows that segregation of smoking and nonsmoking sections in airplanes was effective in keeping smoke away from nonsmokers. Questions, however, have come because of the author's use of geometric mean, rather than arithmetic mean and results which show that airplane, nonsmoking sections have higher nicotine levels than smoking sections in restaurants (Repace and Lowrey 1988).	Oldaker and Conrad (1987)
RSP (3.5 μg diameter)	Smoking work environment. Smoking away from work environment.	33.6 μg/m^3 median; 45.4 μg/m^3 mean n=157	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. RSP concentrations were determined gravimetrically.	Jenkins *et al.* (1996)
RSP (3.5 μg diameter)	Smoking work environment. Smoking away from work environment.	23.3 μg/m^3 median; 31.0μg/m^3 mean n=234	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. RSP concentrations were determined gravimetrically.	Jenkins *et al.* (1996)
RSP (3.5 μg diameter)	Smoking work environment. Smoking away from work environment.	20.5 μg/m^3 median; 27.8 μg/m^3 mean n=281	Personal sampling pump (no flow rate given).	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. RSP concentrations were determined gravimetrically.	Jenkins *et al.* (1996)
RSP	Smoking work environment.	15.2 μg/m^3 median;	Personal sampling pump (no flow rate	Demographics of the total population compared favorably to entire U.S. population. Two pumps, a workplace pump	Jenkins *et al.*

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
(3.5 μg diameter)	Smoking away from work environment.	18.5μg/m^3 mean n=808	given).	and an away-from-work pump, were used to sample atmospheric concentrations of ETS for 24 hours. 87% of participants reported smoking restrictions at work, ranging from a total ban to smoking only in a restricted area. RSP concentrations were determined gravimetrically.	(1996)
Particulate Matter	Casino Site (~100x100x 12 feet). Bingo Site (~100x150x 16 feet).	200 μg/m^3 median (173-245μg/m^3 range) 482 μg/m^3 median (348-526 μg/m^3 range)	Personal sampling pumps with filters from low volume (1.71 L/min flow rate).	Nonsmoking individuals were studied in two separate indoor facilities containing smokers. Smoking policies for these two environments were not mentioned. Sampling times range from 40 minutes to 6 hours. Nicotine studies were done in correlation to determine what portion of particulate matter was based on ETS. Values presented here are total particulate matter and not corrected values.	Kado *et al.* (1991)
Particulate Matter	Smoking section restaurants. Nonsmoking section restaurants.	53.2 μg/m^3 median (21.7-131.0 μg/m^3 range) 27.8 μg/m^3 median (20.7 –69.0 μg/m^3 range)	Mass flow controlled pump (4 L/min flow rate).	Seven restaurants in Albuquerque, NM (seating capacity exceeded 100 in all restaurants) were sampled for two consecutive days for 12 hours (11:00 AM-11:00 PM). Pumps were placed within the usual breathing areas except in two restaurants. In six of seven restaurants, particulate matter levels were lower in nonsmoking sections than in smoking sections (P=0.03, Wilcox paired sample test) with a median difference of 18.6 μg/m^3.	Lambert *et al.* (1993)
Particulates	Residences.	78 μg/m^3 mean (32-700 μg/m^3 range) n=624	Compilation of data from three sources (Sterling *et al.* 1987; Guerin *et al.* 1992; Repace 1987).	Review of ambient air surveys on ETS from three sources. Weighted average of the individual study mean concentrations for all measurements taken. Weights used were the number of residences sampled.	Siegel (1993)

NS: Nonsmoking S: Smoking

2.3 Occupational Exposure

The National Research Council (NRC) estimated that nonsmokers exposed to ETS averaged urinary concentrations of 25 ng/mL cotinine (active smokers had levels of 1,825 ng/mL). Studies have shown varying cotinine levels based on different occupations. It should be noted that concentrations of cotinine are higher for those occupations where workers are exposed to higher levels of tobacco smoke; such as in restaurants, bars, and bowling alleys (Millar 1991). It should also be noted that many people who reported no exposure to ETS do have low levels of systemic cotinine.

ETS exposure levels were also measured by RSP (<2.5 pm). Millar (1991) cited that Repace and Lowrey (1980, 1982) found concentrations in public access buildings that averaged 0.242 $\mu g/m^3$. In later studies, they estimated a 62% probability of nonsmoker exposure in the workplace. Table 2-3 highlights all of the components tested to determine occupational exposure to ETS.

2.3.1 Restaurants

Levels of ETS in restaurants are approximately 1.6-2.0 times higher than other office workplaces and 1.5 times higher than residences of, at least, one smoker. Isolating smokers to a specific section of restaurants was found to afford some protection for nonsmokers, but the best protection resulted from seating arrangements that segregated smokers by a wall or partition. Nonsmokers are still exposed to nicotine and respirable particles. Food-servers, who spend more time in restaurants, are exposed even more to ETS, though they may work in nonsmoking sections (Lambert *et al.*1993).

2.3.2 Bars

Levels of ETS in bars are approximately 3.9-6.1 times higher than in office workplaces and 4.4-4.5 times higher than in residences. Bars are not always compelled to provide smoking and nonsmoking sections and this may account for the higher level of ETS exposure in bars versus restaurants (Siegel 1993).

2.3.3 Airplanes

Mattson *et al.* (1989) studied personal ETS exposure in airplanes. Levels of nicotine found in cabins seem to vary widely owing to unstandardized methods of collection and measurement. Oldaker and Conrad (1987) measured nicotine levels in the passenger cabins of commercial airliners. Using a hidden suitcase pump, they found that the average nicotine concentration in nonsmoking areas was 5.5 $\mu g/m^3$ (0.03-40.2 $\mu g/m^3$ [range, n=49]), while in the smoking sections it was 9.2 $\mu g/m^3$ (0.08-112.4 $\mu g/m^3$ [range, n=26]). Using these data, calculated "cigarette equivalents" for the smoking section ranged from 0.00008-0.15 cigarettes per 55 minute flight. Comparisons of the results, however, have shown some consistencies.

Studies have shown that nonsmoking seats near the smoking section have levels as high as those seats in smoking sections. The type of ventilation system a plane used seemed to be the most important factor in ETS exposure. Planes with 100% fresh air had lower levels of ETS compared to 50% fresh and 50% recirculating air. Recirculating air systems, however, have been used in more new planes because they improve fuel economy. Since attendants are not confined to the nonsmoking section, they had higher ETS exposures than passengers in nonsmoking sections (Mattson *et al.* 1989).

Table 2-3. Occupational exposure to ETS

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
Nicotine	Closed offices: Smoking allowed Smoking restricted Smoking banned	 9.1 μg/m^3 median (<0.1 – 22 μg/m^3 range) 0.6 μg/m^3 (only one site) <0.1 μg/m^3 (only one site)	Passive monitor with an effective sampling rate of 24 mL/m^3.	Closed office means relatively small rooms with one or two occupants. Samples were taken continuously for one week. Worksites were classified as (1) allowed smoking throughout the worksite except for safety restrictions; (2) smoking restricted to designated areas; or (3) smoking banned from the entire premises.	Hammond *et al.* (1995)
Nicotine	Open offices: Smoking allowed Smoking restricted Smoking banned	 8.6 μg/m^3 median (14 μg/m^3 mean) 1.3 μg/m^3 median (3.4 μg/m^3 mean) 0.3 μg/m^3 median (0.7 μg/m^3 mean)	Passive monitor with an effective sampling rate of 24 mL/m^3.	Open office means large rooms, with or without partitions, with many workers. Samples were taken continuously for one week. Worksites were classified as (1) allowed smoking throughout the worksite except for safety restrictions; (2) smoking restricted to designated areas; or (3) smoking banned from the entire premises.	Hammond *et al.* (1995)
Nicotine	Shop: Smoking allowed Smoking restricted Smoking banned	 2.3 μg/m^3 median (4.4 μg/m^3 mean) 0.7 μg/m^3 median (2.2 μg/m^3 mean) 0.2 μg/m^3 median (0.2	Passive monitor with an effective sampling rate of 24 mL/m^3.	Shop offices indicate other types of work areas (besides open and closed offices) dealing with production, shipping, laboratories, and fire stations. Samples were taken continuously for one week. Worksites were classified as (1) allowed smoking throughout the worksite except for safety restrictions; (2) smoking restricted to designated areas; or (3) smoking banned from the entire premises.	Hammond *et al.* (1995)

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
		μg/m^3 mean)			
Nicotine	Offices Restaurants Bars	4.1 μg/m^3 mean (0.8-22.1 μg/m^3 range) n=940 6.5 μg/m^3 mean (1.6-21 μg/m^3 range) n=402 19.7 μg/m^3 mean (7.4-65.5 μg/m^3 range) n=25	Compilation of data from three sources (Sterling *et al.* 1987; Guerin *et al.* 1992; Repace 1987).	Review of ambient air surveys on ETS from three sources. Weighted average of the individual study mean concentrations for all measurements taken. Weights used were the number of restaurants, bars, or offices sampled.	Siegel (1993)
Nicotine	Attendants NS S	4 μg/m^3 mean (median = 3 μg/m^3; range 0.1-71 μg/m^3) 5 μg/m^3 mean (median = 5 μg/m^3; range 0.7-11μg/m^3)	Personal exposure monitor with a pump (3 L/min flow rate).	In-flight nicotine levels were gathered from four attendants and five passengers to determine nicotine levels of the airplane. Nicotine levels were variable, with some nonsmoking sections having comparable levels to smoking sections.	Mattson *et al.* (1989)
Carbon Monoxide	Offices Restaurants Bars	3.0 ppm mean (1.0-3.3 ppm range) n=1161 5.1 ppm mean (0.5-9.9 ppm range) n=229 11.6 ppm mean (3.1-17 ppm range) n=32	Compilation of data from three sources (Sterling *et al.* 1987; Guerin *et al.* 1992; Repace 1987).	Review of ambient air surveys on ETS from three sources. Weighted average of the individual study mean concentrations for all measurements taken. Weights used were the number of restaurants, bars, or offices sampled.	Siegel (1993)

Compound Tested	Area of Exposure	Exposure Levels	Method of Measurement	Comment	Reference
Particulates	Offices	57 μg/m^3 mean (6-256 μg/m^3 range) n=912	Compilation of data from three sources (Sterling *et al.* 1987; Guerin *et al.* 1992; Repace 1987).	Review of ambient air surveys on ETS from three sources. Weighted average of the individual study mean concentrations for all measurements taken. Weights used were the number of restaurants, bars, or offices sampled.	Siegel (1993)
	Restaurants	117 μg/m^3 mean (27-690μg/m^3 range) n=211			
	Bars	248 μg/m^3 mean (75-1320 μg/m^3 range) n=16			

NS = Nonsmoking, S = Smoking

2.4 Regulations

ETS-related regulations defined by Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA) are shown below. Smoking restrictions promulgated by state and local governments are not included in Table 2-4.

Table 2-4 Regulations

EPA Regulations	
PART 63 SUBPART JJJ—National Emission Standards for Hazardous Air Pollutant Emissions: Group IV Polymers and Resins. Promulgated: 61 FR 34200, 06/1/96.	Because coke oven batteries have hazardous environments, smoking and subsequent ETS exposure in the presence of coke oven batteries is not permitted.
PART 175—Carriage by Aircraft—Subpart A—General Information and Regulations. Promulgated: 41 FR 16106, 04/15/76. U.S. Codes: 49 U.S.C. 5101-5127; 49 CFR 1.53.	Aircraft operators may not smoke within 3 meters (10 feet) of a transport incubator unit necessary to protect life, or an organ preservation unit necessary to protect human organs provided.
PART 763 SUBPART E—Asbestos-Containing Materials in Schools. Promulgated: 60 FR 31922, 06/19/95. Personal hygiene.	Workers who identify friable and nonfriable asbestos-containing material (ACM) in public and private elementary and secondary schools by visually inspecting school buildings for such materials may not smoke in the work area.
PART 763 SUBPART G—Asbestos Abatement Projects. Promulgated: 58 FR 34205, 06/23/93.	Workers may not smoke during asbestos abatement projects.
FDA Regulations	
PART 310 SUBPART E—Requirements for Specific New Drugs or Devices. Promulgated: 55 FR 11578, 03/29/90.	Patient package inserts for oral contraceptives—a boxed warning concerning the increased risks associated with combining cigarette smoking and oral contraceptive use.
PART 897—Cigarettes and Smokeless Tobacco. Promulgated: 61 FR 44615, 08/28/96.	This part sets out the restrictions under the Federal Food, Drug, and Cosmetic Act (the Act) on the sale, distribution, and use of cigarettes and smokeless tobacco that contain nicotine.
OSHA Regulations	
PART 1910 SUBPART Z—Toxic and Hazardous Substances. Promulgated: 40 FR 23072, 05/28/75. U.S. Codes: 29 U.S.C. 653, 655, and 657; 29 U.S.C. 655(a); Smoking in work areas.	The employer shall ensure that employees do not smoke in work areas where they are occupationally exposed to asbestos, MDA, α-naphthylamine, and other hazardous substances because of activities in that work area.
PART 1915 SUBPART F—General Working Conditions. Promulgated: 52 FR 31886, 08/24/87.	The employer shall not permit employees to eat or smoke in areas undergoing surface preparation or preservation, or where shipbreaking operations produce atmospheric contaminants.

PART 1915 SUBPART Z—Toxic and Hazardous Substances. Promulgated: 61 FR 43457, 08/23/96.	The employer shall ensure that employees do not smoke in the regulated area.
PART 1926 SUBPART D—Occupational Health and Environmental Controls. Promulgated: 61 FR 31431, 06/20/96.	The employer shall ensure that employees do not smoke in regulated areas where airborne concentrations of MDA exceed, or can reasonably be expected to exceed, the permissible exposure limits.
1926 SUBPART Z—Toxic and Hazardous Substances. Promulgated: 61 FR 43458, 08/23/96.	The employer shall ensure that employees do not smoke in regulated areas with asbestos exposure.

3 Human Studies

Human cancer studies of environmental tobacco smoke have been reviewed by a number of scientific organizations: IARC 1986; U.S. DHHS 1986; NRC 1986; U.S. EPA 1992; and CEPA 1997. Since the IARC report (1986), over 30 epidemiological studies investigating the association of environmental tobacco smoke (ETS) exposure with cancer have been published. This includes both cohort studies and case-control studies of lung, bladder, cervical, nasal sinus, and breast cancer. In addition 12 childhood cancer studies have been reported, where exposure from both ETS and maternal smoking during pregnancy are considered. These studies are summarized in Table 3-1. A number of reviews and meta-analyses have also been published along with studies examining the degree of systematic bias in studies that use spousal smoking as a measure of ETS exposure. These reviews and analyses include Pershagen 1986; Repace and Lowery 1990; Wu-Williams and Samet 1990; Fleiss and Gross 1991; Woodward and McMichael 1991; Wells 1991, 1993; Lee 1992a, 1992b, 1993a, 1993b, 1994a, 1994b, 1995; Tredaniel *et al.* 1993, 1994a, 1994b; LeVois and Layard 1994, 1995; Sterling *et al.* 1996; Kawachi and Colditz 1996; Lee and Forey 1996; Kabat 1990, 1996; Morris 1995; Layard 1993; and Nyberg *et al.* 1997, 1998; and Levois and Switzer 1998.

3.1 IARC report of 1986 (Appendix 3A)

IARC (1986) reported that several studies found an increase in lung cancer in nonsmoking spouses of smokers with increased risk in relation to the extent of the spouse's smoking. Other studies did not show an effect or showed an effect without a dose-reponse. Because of difficulties in determining ETS exposure in these studies, as well as potential confounding by other risk factors, the report concluded that each study was compatible either with an increased risk or with the absence of risk. Since the estimated relative risks were low, additional large scale studies with reliable measures of exposure were recommended. Finally, the report concluded that studies of childhood cancer did not provide clear evidence of an association with parental smoking.

With regard to lung cancer and ETS, IARC (1986) reviewed two major cohort studies: one involving 91,540 nonsmoking women in Japan (Hirayama 1981, 1983, 1984a, 1984b), and the American Cancer Society's cohort of 375,000 nonsmoking women (Garfinkel 1981). The study of Japanese women showed an increasing mortality ratio of lung cancer with the husband's smoking history. The standard mortality rate (SMR) values for lung cancer among nonsmoking women were 1.0, 1.36 (90% CI 0.85-2.18), 1.42 (90% CI 1.01-2.01), 1.58 (90% CI 0.98-2.38) and 1.91 (90% CI 1.34-2.71) when husbands were nonsmokers, ex-smokers, and daily smokers of 1-14, 15-19 and 20+ cigarettes per day. The ACS study, however, did not show a statistically significant increase in lung cancer risk with spousal smoking.

IARC (1986) considered five case-control studies of lung cancer and spousal smoking (Trichopoulos *et al.* 1981, 1983; Correa *et al.* 1983; Kabat and Wynder 1984; Chan and Fung 1982, and Koo *et al.* 1984) and noted that in all of the studies, misclassification of smokers as nonsmokers could have resulted in an inflated risk estimate. This hypothesis is based on the assumption that smoking habits of spouses are correlated. IARC concluded that, "As the estimated relative risks are low, the acquisition of further evidence bearing on the issue may require large-scale observational studies involving reliable measures of exposure both in childhood and in adult life."

3.2 U.S. EPA report of 1992 (Appendix 3B)

The US EPA report (EPA 1992) analyzed data from 27 case-control studies and four cohort studies which examined the relationship of lung cancer to ETS exposure. This included studies published through 1991; Brownson *et al.* 1992 and Stockwell *et al.* 1992 were presented as an addendum. The studies primarily examined lung cancer in nonsmoking women who were classified as exposed or unexposed depending on whether or not the women were married to smokers. This information was obtained by self-report or by proxy. In the studies considered by EPA (1992), there were more than 3,000 lung cancer cases among never-smokers in the case-control studies and 300,000 female never-smokers in the cohort studies. The report calculated a pooled relative risk through meta-analysis methods after adjusting for potential bias due to misclassification of smokers as nonsmokers.

The individual studies were carefully summarized and evaluated. The studies were graded using a specific evaluation form which considered eight general categories (smoking status, ETS exposure, lung cancer indication, interview type, proxy responders, follow-up, design, analysis) and then classified into four tiers based upon their scores (see Appendix A, Table 4 of the report, included in Appendix 3B here). Studies in the lowest tier (Tier 4) were not recommended for further analysis (Chan and Fung 1982; Inoue and Hirayama 1988; Geng *et al.* 1988; Liu *et al.* 1991; Wu-Williams and Samet 1990). The highest rated studies (Tier 1) were Kalandidi *et al.* 1990; Koo *et al.* 1987; Fontham *et al.* 1991; Hole *et al.* 1989; and Pershagen *et al.* 1987. The report estimated a pooled relative risk of lung cancer from ETS exposure of 1.19 (90% CI 1.04-1.35) using all 11 U.S. studies. Restricting consideration to Tier 1 and Tier 2 studies (eight of the 11 U.S. studies), the estimate was 1.22. Nonsmokers with workplace or social exposure but no spousal exposure had a relative risk of 1.34 compared to nonsmokers with no ETS exposure, while nonsmokers with spousal as well as other sources of exposure had a relative risk of 1.59 compared to nonsmokers with no ETS exposure. The report concluded "that ETS is a Group A human carcinogen" since "there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer."

3.3 California EPA report of 1997 (Appendix 3C)

The California EPA report (CEPA 1997) evaluated the studies presented in Table 1, except for Ko *et al.* 1997. The report reviewed each of the studies and summarized the general findings for each cancer type. Regarding lung cancer, five reports published after the U.S. EPA report (EPA 1992) were given special consideration: three large population-based case-control studies (Stockwell *et al.* 1992; Brownson *et al.* 1992; Fontham *et al.* 1994); a smaller hospital-based case-control study (Kabat *et al.* 1995); and a cohort study (Cardenas *et al.* 1997). All were carefully reviewed. Collectively they addressed many of the criticisms of the previous studies such as small sample size, selection bias, misclassification of smokers as nonsmokers, etc. The results of all the studies were consistent with the U.S. EPA finding of a 20% increased risk of lung cancer among nonsmoking women. The report concluded that there is a causal association between ETS and lung cancer.

For nasal sinus cancers, the report concluded that there was strong evidence that exposure to ETS increases the risk of nasal sinus cancer in nonsmoking adults; further studies were recommended to characterize the magnitude of the risk and the dose-response relationship. Both epidemiologic and biochemical evidence suggested that ETS exposure may increase the risk of cervical cancer in nonsmokers. However, although ETS is a plausible bladder carcinogen in nonsmokers, the

limited epidemiologic evidence did not support an association. There was insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and cancers of the breast, stomach, and brain.

For children the evidence was insufficient to determine whether either of the major childhood cancers—acute lymphoblastic leukemia (ALL) or brain cancer—was associated with ETS exposure. Further, the studies do not differentiate between ETS exposure during pregnancy or after delivery. The report considers the evidence to be inadequate for forming firm conclusions on childhood cancers.

3.4 Current Epidemiology Studies

Table 3-1 gives the details of studies published since the IARC report (IARC 1986). For adults, there are ten cohort studies, 15 case-control studies of lung cancer, and ten case-control studies of bladder, breast, cervical, and nasal sinus cancer. For childhood cancers, there are one cohort study and 11 case-control studies of various cancers.

3.4.1 Total Cancers:

For total cancers, the Japanese cohort (Hirayama 1984, 1992) had a significant relative risk, RR=1.23 (90% CI 1.12-1.35) for spouses smoking 20 or more cigarettes per day. For ex-smokers or spousal smoking of 1-19 cigarettes per day the relative risk was smaller but still significant RR=1.12 (90% CI 1.03-1.21). The cancer increases were due primarily to cancers of the lung, nasal sinus, and brain. The other major cohort study (Sandler *et al.* 1989) showed no cancer increase among either male (RR=1.01) or female (RR=1.00) nonsmokers with household smoking exposure in the Washington County, Maryland cohort. When only smoking related cancers were considered, there was an insignificant increase in the females but no increase in the males with RR=1.45 (95% CI, 0.88-2.40) and RR=0.96 (95% CI 0.43-2.16), respectively.

3.4.2 Lung Cancer:

Since the IARC report, there have been 15 case-control studies of lung cancer and ETS exposure from spousal smoking. These studies are often limited in size and do not achieve statistical significance (Akiba *et al.* 1986; Brownson *et al.* 1987; Dalager *et al.* 1986; Koo *et al.* 1987; Kaladidi *et al.* 1990; Kabat *et al.* 1995; Wang *et al.* 1996; Ko *et al.* 1997). Recently, however, three large population-based case-control studies were conducted in the US (Brownson *et al.* 1992; Stockwell *et al.* 1992; Fontham *et al.* 1991; 1994).

Brownson *et al.* (1992) studied 432 lung cancer cases among lifetime nonsmoking white women aged 30-84 years, diagnosed between January 1986 and June 1991. Cases were identified using the Missouri Cancer Registry. Histological verification of primary lung cancer was completed for 76% of the cases. Controls were 1,402 lifetime nonsmoking women identified from driver's license or Medicare files and matched to cases on age. Data on ETS exposure were collected using a structured telephone interview; 65% of case interviews were conducted with surrogates. The interview included detailed questions about each potential source of ETS exposure. Risk of lung cancer was associated with household ETS exposure in adulthood. After adjusting for age and history of lung disease, the OR for >40 pack-years of smoking by the spouse was 1.3 (95% CI, 1.0-1.7). There was a positive trend in risk with increasing pack-years (p=0.06). There was no risk associated with exposure to ETS in childhood.

Stockwell *et al.* (1992) studied 210 lung cancer cases among lifetime nonsmoking women, 93% white, diagnosed between April 1987 and February 1991. Cases in a 28 county area in central Florida were identified from tumor registries of area hospitals and the Florida Cancer Registry. Primary lung cancer was histologically confirmed for all cases. Controls were 301 lifetime nonsmoking women identified by random digit dialing. Smoking status was confirmed by interviews with patients' physicians, at initial contact, and during the interview. Data on ETS exposure were collected using a structured interview administered in person, by telephone, or by mail; 67% of case interviews were conducted with surrogates. Risk of lung cancer was associated with household ETS exposure in both childhood and adulthood. After adjusting for age, race, and education, the OR for 22+ years exposure in childhood was 2.4 (95% CI, 1.1-5.4); the OR for 40+ years exposure in adulthood was 2.4 (1.1-5.3); and the OR for 40+ years lifetime exposure was 2.3 (95% CI, 1.1-4.6). There were positive trends in risk with increasing years of exposure in childhood (p=0.114), adulthood (p=0.025), and lifetime (p=0.004).

Fontham *et al.* (1991; 1994) studied 653 lung cancer cases among lifetime nonsmoking women aged 20 to 79, diagnosed between 1986 and 1990 in 5 major US metropolitan areas. Primary lung cancer was histologically confirmed for 85% of cases. Controls were 1,253 lifetime nonsmoking women identified by random digit dialing or Medicare files and frequency matched to cases on race and age. Lifetime smoking status was confirmed using patients' medical records or interviews with physicians, at initial contact, and during the interview. At the interview, a urine sample was collected; subjects with cotinine levels higher than 100 ng/mg creatinine were excluded. Data on ETS exposure were collected using structured in-person interviews; 36% of the case interviews were conducted with surrogates. Detailed questions were asked about each potential source of ETS exposure. Risk of lung cancer was associated with spousal ETS exposure in adulthood. After adjusting for age, race, study area, education, diet, family history of lung cancer, and employment in high-risk occupations, the OR for 80+ pack-years of spousal exposure was 1.79 (95% CI, 0.99-3.25). There was a positive trend in risk with increasing pack-years (p=0.03). Risk of lung cancer was also associated with occupational exposure (adjusted OR for >30 years exposure = 1.86; 95% CI = 1.24-2.78; trend p = 0.001) and exposure in social settings (adjusted OR for > 30 years exposure = 1.54; 95% CI = 0.93-2.53; trend p = 0.002). There was no risk associated with exposure to ETS in childhood.

A recent prospective cohort study has also examined the relationship of ETS exposure to lung cancer mortality. Cardenas *et al.* (1997) compared 114,286 female and 19,549 male never smokers with smoking spouses to about 77,000 female and 77,000 male never smokers whose spouses did not smoke. All subjects were enrolled in the American Cancer Society's Cancer Prevention Study II; they were friends, neighbors, and relatives of ACS volunteers across the US. At the time of enrollment, subjects completed a questionnaire which collected information on smoking history; data from the spouse's enrollment questionnaire were used as a source of information on ETS exposure. Vital status was determined by personal enquiry by the volunteer who had enrolled the subject and by linkage with the National Death Index. Histological data were available for only 29 of 247 cases; 27 of these were verified as primary lung cancer. Exposure to spousal smoking was associated with lung cancer among women but not men. After adjusting for age, race, education, diet, asbestos exposure, blue collar employment, and history of chronic lung disease, the rate ratio for ever exposure in women was 1.2 (95% CI, 0.8-1.6).

There was a positive trend in risk with increasing number of cigarettes per day smoked by spouse (p=0.03) or pack-years of exposure (p=0.1) but not with increasing years of marriage (p=0.5).

3.4.3 Bladder Cancer:

Two case-control studies have reported findings on ETS and bladder cancer. The study by Kabat *et al.* (1986) had 152 bladder cancer cases, but with passive smoking information on only 40 cases and 72 hospital controls. The results for males and females, and for workplace and home exposures gave inconsistent results that were nonsignificant. A larger study with 826 bladder cancer cases and 792 controls had 142 nonsmoking cases with 217 nonsmoking controls (Burch *et al.* 1989). Passive smoking was not related to bladder cancer in this study although there was a weak association (OR=2.7) with active smoking.

3.4.4 Breast Cancer:

Sandler *et al.*'s (1986) case-control study found a significant association with spousal smoking and pre-menopausal breast cancer OR=7.0 (95% CI 1.4-67.2), but not with post-menopausal breast cancer OR=1.2 (95% CI 0.6-2.6). Only 12 cases of the 59 total were pre-menopausal breast cancers. In a study with 208 cases of breast cancer (94 cases were nonsmokers) a nonsignificant increase was observed for less than 200 cigarette-years RR=1.38 (95% CI 0.92-2.09), but no increase was observed in the high exposure, 200+ cigarette-year group RR=0.84 (95% CI 0.38-1.85) (Smith *et al.* 1994). However, only 13 cases were in the high exposure group. Also for active smoking the risk was not associated with breast cancer OR=1.01 (95% CI 0.81-1.26). Using population controls and 244 breast cancer cases (126 nonsmokers) in Geneva a significant increase was observed for those with spousal smoking OR=2.6 (95% CI 1.6-4.3) (Morabia *et al.* 1996). For those women with high exposures greater than 50 hour/day-years the risk was about the same OR=2.7 (95% CI 1.5-4.7). The risks estimated for ETS exposure were similar to those for active smoking.

3.4.5 Cervical Cancer:

A case-control study of 56 cervical cancer cases among nonsmokers reported an increased risk from spousal smoking OR=2.1 (95% CI 1.2-3.9) (Sandler *et al.* 1985). Adjustments for sexual activity were not made. In a second case-control study of cervical cancer there were 81 cases among nonsmokers and a dose response was reported with respect to the number of hours per day of exposure to ETS (Slattery *et al.* 1989). The incidence in the highest ETS exposure group of 3+ hours per day was significant OR= 3.4 (95% CI 1.2-9.5). In a third case-control study there were only 36 nonsmokers among the cases and no association between ETS and cervical cancer was reported (Coker *et al.* 1992).

3.4.6 Nasal Sinus Cancer:

In a case-control study in Japan, a dose response for nasal sinus cancer in nonsmokers was observed with respect to the number of smokers in the home (Fukuda and Shibata 1990; cited by CEPA 1997). The values were OR=1.4 (0.6-3.5), 2.0 (0.8-4.5) and 5.7 (1.7-19.4) for 1, 1+,and 2+ smokers in the home. There were 50 cases of nasal sinus cancer among nonsmokers in the study. In a second study which included 28 cases of nasal sinus cancers among never smoked men the OR=3.0 (1.0-8.9) among those exposed to spousal smoking (Zheng *et al.* 1993).

3.4.7 Childhood Cancers:

Childhood cancers have been studied in both cohort and case-control studies. Studies have examined the relationship of ETS exposure to total cancers, to brain cancer, and to the leukemias ALL (acute lymphoblastic leukaemia) or AML (acute myeloid leukaemia). There is little consistency in their results. Interpretation of many of these studies is complicated by the difficulty of distinguishing effects of paternal and maternal smoking, and of prenatal and postnatal exposure.

3.4.7.1 All cancers combined:

Buckley et al. (1986) reported that in the U.S. and Canada maternal smoking was not associated with cancer in a group of 1,814 children [OR=1.31 (95% CI 0.9-1.9) for 1-9 cigarettes per day and OR=0.97 (95% CI 0.8-1.2) for 10+ cigarettes per day]. Stjernfeldt et al. (1986a, 1986b, 1992) compared 305 Swedish children age 16 or less with cancer to 340 insulin-dependent childrenand found an exposure-related risk associated with maternal smoking [RR=1.07 (95% CI 0.63-1.80) for 1-9 cigarettes per day and RR=1.56 (95% CI 1.05-2.33) for 10+ cigarettes per day]. McKinney et al. (1987) studied 555 children under the age of 15 with cancer in three regions of the United Kingdom; risk was not associated with maternal smoking [for 1-10 cigarettes per day the risk was OR=1.12 (95% CI 0.85-1.47), and for 11+ cigarettes per day the risk was OR=0.84 (95% CI 0.65-1.09)]. Golding et al. (1990) conducted a nested case-control study of 33 cancers among children age 10 or less in a cohort of 16,193 children born during one week in Great Britain. The risk associated with maternal preenatal smoking was OR=2.69 (95% CI 1.05-6.89). John et al. (1991) studied a group of 223 children younger than 15 in Denver; the risk associated with maternal smoking was OR=1.3 (95% CI 0.7-2.1), and the risk associated with paternal smoking was OR=1.2 (95% CI 0.8-2.1). Klebanoff et al. (1996) reported that maternal smoking during pregnancy was not associated with childhood cancer. Ji et al. (1997) compared 642 children in Shanghai to individually matched controls. Paternal preconception smoking of more than 5 pack-years was associated with all cancers combined [OR=1.7 (95% CI 1.2-2.5)]. Sorahan et al. (1997) compared 2,587 children included in the Oxford Survey of Childhood Cancers to 2,587 controls. There was no association with maternal cigarette smoking during pregnancy, but a positive trend in risk with paternal consumption of cigarettes ($p<0.001$) was found.

3.4.7.2 Childhood brain cancer:

Howe *et al.* (1989) studied 74 cases and 138 controls in Ontario and found a small risk associated with maternal smoking [OR=1.42 (95% CI 0.7-3.0)] but not paternal smoking [OR=1.13 (0.65-2.09)]. Kuijten *et al.* (1990) studied 163 astrocytoma cases younger than 15 and found no association with maternal smoking [OR=1.0 (95% CI 0.6-1.7)]. Pershagen *et al.* (1992) studied a cohort of 497,051 Swedish children aged 5 years of less and found no association of maternal smoking with brain cancer [RR=0.96 (95% CI 0.59-1.56)]. Gold *et al.* (1993) used SEER (Surveillance Epidemiology and End Results) registries to identify 361 cases among children under the age of 18 and found no association with parental smoking. Comparing children with both parents smokers to children with neither parent a smoker, the risk was OR=0.95 (95% CI 0.66-1.36). McCredie *et al.* (1994) compared 82 children under the age of 15 with brain cancer to 164 controls. A significant increase was associated with father's smoking [OR=2.2 (95% CI 1.2-3.8)], but not the mother's smoking [OR=0.9 (95% CI 0.5-1.8)]. Norman

et al. (1996) compared 540 cases ascertained in 10 counties on the US west coast to 801 controls. No association was found with maternal or paternal smoking before pregnancy or maternal smoking during pregnancy. Small increases in risk were associated with paternal smoking during pregnancy in the absence of maternal smoking [OR=1.2 (95% CI 0.90-1.5)] and with maternal exposure to ETS from any source [OR=1.2 (95% CI = 0.95-1.6)]. Ji *et al.* (1997) compared 642 children in Shanghai to individually matched controls. Paternal preconception smoking of more than 5 pack-years was associated with brain tumors [OR=2.7 (95% CI 0.8-9.9)].

3.4.7.2 Childhood lymphomas/leukemias:

Stjernfeldt *et al.* (1986) reported that smoking during pregnancy was associated with ALL; the risk for 1-9 cigarettes per day was OR=1.34 (95% CI 0.7-2.6), and for 10+ cigarettes per day was OR=2.07 (95% CI 1.3-3.3). McKinney and Stiller (1986) and McKinney *et al.* (1987) found no association for maternal smoking [OR=1.0 (95% CI 0.6-1.7) for 1-10 cigarettes per day and OR=0.6 (95% CI 0.4-1.0) for 11+ cigarettes per day]. Buckley *et al.* (1986) studied 742 ALL cases, and found no association with maternal smoking [OR=1.0 (95% CI 0.6-1.5) and OR=0.9 (95% CI 0.7-1.1) for 1-9 and 10+ cigarettes per day, respectively]. Magnani *et al.* (1990) studied 142 Italian children, and found no association of ALL with either maternal or paternal smoking. John *et al.* (1991) studied 73 ALL cases and found an association with smoking [OR=1.9 for maternal and OR=1.4 for paternal smoking]. Pershagen *et al.* (1992) studied a cohort of 497,051 Swedish children aged 5 years of less; the study included 198 solid tumors and 129 lymphatic leukemia cancers. No association with maternal smoking was found for solid tumors (OR =0.96, 95% CI = 0.70-1.32) or lymphatic/leukemia cancers (OR = 1.04, 95% CI = 0.71-1.52). Severson *et al.* (1993) considered AML in 187 children in Minnesota. Parental smoking was not associated with the AML cases [OR=1.2 (95% CI 0.77-1.86)]. Ji *et al.* (1997) compared 642 children in Shanghai to individually matched controls. Paternal preconception smoking of more than 5 pack-years was associated with ALL [OR=3.8 (95% CI 1.3-12.3)] and lymphoma [OR=4.5 (95% CI 1.2-16.8)].

Table 3-1. Human Studies of ETS exposure and cancer, published since IARC (1986) *

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
ADULT CANCERS						
COHORT STUDIES						
Cohort	16 years of mortality follow-up of 91,540 nonsmoking wives in Japan.	Smoking rates of husbands reported by mail surveys. .	2705 cancer deaths. Nonsmoking women whose husbands were ex-smokers or smoked 1-19 cigs/day had a RR=1.12 (90% CI 1.03-1.21) based on 1341 cancer cases. For 20+ cigs/day RR=1.23 (90% CI 1.12-1.35) for 730 cases. RRs for nasal sinus cancers (n=28) were 1.69 (90% CI 0.67-4.20), 2.02 (90% CI 0.64-6.33) and 2.55 (90% CI 1.04-6.27). RRs for brain cancers (n=34) were 3.03 (90% CI 1.07-8.58), 6.25 (90% CI 2.01-19.43), and 4.23 (90%CI 1.53-12.19) both for 1-14, 15-19, and 20+ cigs/day, respectively.	np	The increase in total cancers was due primarily to lung, nasal sinus, and brain. No increases were seen for stomach cancer. Breast cancer was increased at the highest exposure group with RR=1.7 (1.1-2.7).	Hirayama (1984,1992)
Cohort	4,162 nonsmoking men and 14,873 nonsmoking women in Washington County, MD established in 1963 and mortality evaluated in 1975.	A scoring system of household smoking was used. Smoking information was obtained by a private census taken in 1963.	Among nonsmokers 1,248 men and 9,551 women were considered to be passive smokers from their household exposures. Total cancers were not increased, but for smoking related tumors there was a small increase among women RR=1.45 (95% CI 0.88-2.40) and not in men RR=0.96 (95% CI 0.43-2.16).	np	Smoking status was taken in 1963 and mortality was assessed in 1975. Among ETS exposed individuals only 8 cancer deaths among men and 49 among women were observed.	Sandler *et al.* (1989)
Cohort	A cohort of 2413 married women in Alameda, CA of	Husband smoking. Smoking history was independently	Comparing nonsmoking women with smoking husbands with those whose husbands did not smoke had	np	Based on only 147 cancers. Cancer incidence was assessed	Reynolds *et al.* (1987, cited by CEPA 1997)

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	which 1111 were nonsmokers and followed for 17 years.	ascertained for each spouse.	a RR=1.68 for all cancer sites. For smoking related sites the RR=7.0 (1.05-47)(p=0.09).		via automated record linkage to the population-based cancer registry.	
Cohort	1,538 never smoked (243 males, 1295 females), age 45-64 years in West Scotland.	Spousal smoking obtained from a self administered questionaire.	RR=2.41 (95% CI 0.45-12.83) for lung cancer, p=0.3.	Only 9 lung cancer deaths in both groups. The 1538 individuals who were exposed to passive smoking and the group of 917 controls without passive smoking.	np	Hole *et al.* (1989)
Cohort	27,409 nonsmoking females in Sweden.	Spousal smoking, based on questionaire mailed to subjects.	67 lung cancer deaths. RR=3.3 (95% CI 1.1-11.4) for squamous cell and small cell carcinomas of women married to a smoker. Statistically significant ($p<0.05$) increase in small cell carcinomas and squamous cell.	np	Dose response is observed.	Pershagen *et al.* (1987)
Cohort	114,286 female and 19,549 male never smokers compared with about 77,000 female and 77,000 male never smokers. Subjects enrolled in the American Cancer Society's Cancer Prevention Study II.	Spousal smoking obtained from a questionnaire. Vital status obtained by personal inquiry by volunteer or from the National Death Index.	RR=1.2 (95% CI, 0.8-1.6) for ever exposure in women. Positive trend in risk with increasing cigarettes per day smoked by spouse (p=0.03) and pack years of exposure (p=0.1) but not in increasing years of marriage (p=0.5).	Adjusted for age, race, education, diet, asbestos exposure, blue collar employment, and history of chronic lung disease.	There is overall evidence that ETS exposure from smoking spouses may adversely affect lung cancer risk in never-smoking women.	Cardenas et al. (1997)
CASE-CONTROL STUDIES						
Lung Cancer						

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
Case-Control	432 nonsmoking female lung cancer cases and 1402 nonsmoking population-based controls in MO (1986-91).	ETS from parents, spouse, and work based on interviews.	OR=1.0 (95% CI 0.8-1.2) and for 40+ pack-years OR=1.3 (95% CI 1.0-1.7) for lifetime nonsmokers.	np	No increased risk was observed from workplace ETS or from ETS exposures from parents.	Brownson *et al.* (1992)
Case-Control	210 lung cancer cases among nonsmoking females and 301 population-based nonsmoking controls in FL (1987-91).	Smoking spouse based on interviews.	OR=1.6 (95% CI 0.8-3.0) and for those with 40+ years of exposure from husband and others the OR=2.4 (95% CI 1.1-5.3).	np	Risk was strongest for cell types other than adenocarcinomas. No association was observed between ETS exposure in the workplace and lung cancer risk.	Stockwell *et al.* (1992)
Case-Control	653 lung cancer cases among lifetime nonsmoking women age 65 and older with 1253 controls in 5 areas of the U.S. (New Orleans, Atlanta, Houston, Los Angeles, San Francisco) 1985-91.	Spousal smoking information obtained from questionaire completed by subject or next-of-kin.	Adjusted OR=1.29 (95% CI 1.04-1.60) for any tobacco, Adj. OR=1.18 (95% CI 0.96-1.46) for cigarette exposure, and Adj. OR=1.79 (95% CI 0.99-3.25) for 80+ pack-years exposure from spousal smoking (p=0.03).	np	OR=1.39 (1.11-1.74) for ETS workplace exposure with OR=1.86 (1.24-2.78) for 30+ years of workplace exposure ($p<0.01$). ETS exposure during childhood was not associated with lung cancer (OR=0.89 [0.72-1.10]). Women who were exposed as children had higher RRs associated with adult ETS exposure.	Fontham *et al.* (1991, 1994)
Case-Control (Hospital-based)	41 male and 69 female lung cancer cases and 117 male and 187 female controls all never	Spousal smoking obtained by interview.	No significant increases: male OR=1.6 (95% CI 0.67-3.82) female OR=1.08 (95% CI 0.6-1.94).	np	No effects of ETS in the workplace. Relatively small study which the authors interpret as	Kabat *et al.* (1995)

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	smokers. Study was conducted at 6 hospitals in four U.S. cities (New York, Chicago, Detroit and Philadelphia) 1983-90.				unsupportive of an association between ETS and lung cancer.	
Case-control	102 cases of adenocarcinoma of the lung (50 males and 52 females) and 131 controls (cancers of the colon 80 and bone marrow 51).	Passive smoking hours/day (0-3, 4-7, 8+) and pack-years (0, 1-39, 40+) of smoking obtained by interview.	Increased risk among smokers with ORs = 2.62 (95% CI 1.82-3.41) for 1-39 pack years and 5.81 (95% CI 5.01-6.61) for 40+ pack years. For passive smoking OR=1.24 (95% CI 0.53-1.95) for 4-7 hours/day and 1.37 (95% CI 0.54-2.20) for 8+ hours per day. Among nonsmoking females (66 females) OR= 1.68 (95% CI 0.39-2.97) for 4+ hours per day.	Analysis based on logistic regression adjusted for age, income, and occupation.	Increases in risk but limited study size.	Brownson *et al.* (1987)
Case-control	965 lung cancer cases and 959 controls among female nonsmokers in north-east China (Shenyang and Harbin).	Smoking spouse in the home, information obtained by structured pre-coded questionnaire and trained interviewers.	OR=0.7 (95% CI 0.6-0.9) for nonsmokers who lived with a spouse who smoked. A slight increase was seen from workplace exposures OR=1.1.	Heavy exposures to pollutants from coal-burning Kangs in the home.	np	Wu-Williams *et al.* (1990)
Case-control	191 lung cancer cases and 191 controls. Both groups had never smoked.	Exposures in terms of smoker years (number of smokers in the home multiplied by years). Information provided by face to face interviews	The OR for lung cancer among persons who never smoked more that 100 cig and exposure to ≥ 75 smoker-years had an OR=1.11 (95% CI 0.56-2.20). Childhood and adolescence exposure to 25+ smoker years had OR=2.07 (95% CI 1.16-3.68).	Recall bias.	Authors estimate that 17% of lung cancer among nonsmokers is due to childhood and adolescence exposures to ETS.	Janerich *et al.* (1990)
Case-control	144 nonsmoking	Household smoking	OR=1.50 (95% CI 1.01-2.22) for	np	A large proportion of	Sobue (1990)

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	female lung cancer cases and 731 nonsmoking female controls in Osaka, Japan.	information provided by self-administered questionnaire.	other household members smoking in adulthood. For only husband smoking the OR=1.13 (95% CI 0.78-1.63).		controls were cancer patients.	
Case-control	91 cases of life-long nonsmokers and 120 controls.	Spousal smoking information provided in interview.	For contrasting women married to smokers with those married to nonsmokers the RR=1.92 (95% CI 1.02-3.59)	np	Np	Kalandidi *et al.* (1990)
Case-control	Female A-bomb survivors: 94 lung cancer cases and 270 controls.	Spousal smoking information provided by structured questionnaire.	OR=1.5 (90% CI 1.0-2.5)	Surrogate response on smoking.		Akiba *et al.* (1986)
Case-control	135 lung cancer cases among female nonsmokers and 135 controls in Shengyang, China.	Spousal smoking information provided in hospital interviews.	OR=1.11 (95% CI 0.65-1.88)	np	No relationship with spousal smoking rate or smoking duration.	Wang *et al.* (1996)
Case-control	105 nonsmoking female lung cancer cases and 105 controls in Kaohsiung, Taiwan during 1992-3.	Spousal smoking information provided by personal interviews.	OR=1.3 (95% CI 0.7-2.5) for females with smoking spouse.	np	np	Ko *et al.* (1997)
Case-control	200 cases and 200 controls of which 88 never smoked female lung cancer cases and 137 never smoked controls in Hong Kong, China.	Spousal smoking information provided by life-history interviews.	RR=1.64 (95% CI 0.87-3.09) for husbands who have ever smoked.	np	No dose-response by smoking rate or duration.	Koo *et al.* (1987)
Case-control	672 cases and 735 controls of which	Spousal smoking information provided	OR=1.1 (95% CI 0.7-1.8), 1.3 (95% CI 0.8-2.1) and 1.7 (95% CI 1.0-	np	np	Gao *et al.* (1987)

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	246 lung cancer cases of nonsmoking females and 375 controls in Shanghai, China.	by personal interview.	2.9) for 20-29, 30-39 and 40+ years of spousal smoking, respectively.			
Case-control	99 lung cancer cases and 736 controls with no tobacco exposure.	Spousal smoking information provided by pooled data from 3 large incident case control studies.	OR=0.8 (95% CI 0.5-1.3) for spousal smoking and OR=1.24 (95% CI 0.62-2.51) for >40 years exposure.	np	np	Dalager *et al.* (1986)
Bladder Cancer						
Case-control	152 bladder cancer cases (76 males, 76 females) and 492 controls (238 males, 254 females). All reported having never smoked.	Smoking spouse information provided by structured questionnaire.	Inconsistant results that were nonsignificant.	np	Only 40 cases and 72 controls had passive smoking information. The passive smoking history was crude.	Kabat *et al.* (1986)
Case-control	826 bladder cancer cases and 792 controls all from Alberta, Toronto and parts of Ontario.	Home and work exposures to passive smoking among smokers and nonsmokers.	ORs were slightly lower among nonsmokers passively exposed at home or at work. This was true for both males and females.	np	Only 142 cases and 217 controls were nonsmokers. Also the effects on bladder cancer for active smoking were only OR = 2.72. Cases were identified from hospital and medical records, where as the controls were chosed at random from province with listings and matched on basis of age, sex, and area of residence.	Burch *et al.* (1989)

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
Breast Cancer						
Case-control	59 breast cancer cases and 324 controls.	Spousal smoking.	For premenopausal women OR=7.0 (95% CI 1.4-67.2) and post-menopausal women OR=1.2 (95% CI 0.6-2.6).	np	Only 12 cases among pre-menopausal women.	Sandler *et al.* (1986)
Case-control	244 breast cancer cases and 1032 controls in Geneva, Switzerland.	Spousal smoking as well as occupational exposures. Information obtained in face to face interviews	OR for breast cancer related to passive smoking at home OR=2.6 (95% CI 1.6-4.3) for spousal smoking. And for high exposure (>50 hour/day-years) the OR = 2.7 (95% CI 1.5-4.7).	np	No dose-response was observed. ETS effects were similar to the risks of active smoking.	Morabia *et al.* (1996)
Case-control	208 cases of breast cancer and 201 controls in the U.K. (47% were nonsmokers).	Spousal smoking information obtained in interviews by trained personnel.	RR=1.38 (95% CI 0.92-2.09) for 1-200 cigarette-years and RR=0.84 (95% CI 0.38-1.85) for 200+.	np	Unmatched analysis. Only 13 cases in the 200+ group. Occupational exposures were also considered. No dose response effects were seen for any of the exposure variables. For active smoking the OR = 1.01 (95% CI 0.81-1.26) for breast cancer.	Smith *et al.* (1994)
Cervical Cancer						
Case-control	103 Cervical Cancer (CIN II and III) cases and 268 controls.	Passive smoking in home and at work. Information provided by telephone or personal interviews.	Among smokers (66 cases) no trend was observed with passive smoking. Among nonsmokers (37 cases) there was no association with passive smoking.	Age, race, education, number of pap smears, number of sexual partners, and history of genital warts.	Small study. A positive association OR=1.5 (95% CI 0.3-6.2) with husbands smoking after adjusting for the the confounders.	Coker *et al.* (1992)
Case-control	518 cancer cases and 518 controls. Included were 56	Spousal smoking. Information provided by mailed	Cervical cancer OR from passive exposure to cigarett smoke among nonsmokers OR=2.1 (95% CI 1.2-	Effects only observed in those under age 50	Adjustments for sexual activity were not made.	Sandler *et al.* (1985)

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	cervical cancer.	questionnaire.	3.9).	(OR= 2.9 for < 50 yrs and OR= 0.9 for > 50 yrs).		
Case-control	266 cases of cervical cancer and 408 controls. 81 cases and 305 controls were never smokers.	Hours of passive smoking both in and outside the home. Information provided by personal interviews.	ORs were 1.14 (95% CI 0.5-2.9), 1.57 (95% CI 0.5-4.7) and 3.43 (95% CI 1.2-9.5) for 0.1-0.9, 1.0-2.9 and 3.0+ hours per day exposure, respectively.	np	Among active smokers the effect was the greatest among those with the fewest sexual partners.	Slattery *et al.* (1989)
Nasal Sinus Cancer						
Case-control	169 cases of nasal sinus cancers and 338 controls in Hokkaido, Japan.	Number of smokers in the household provided by mailed questionnaire.	ORs were 1.4 (0.6-3.5), 2.0 (0.8-4.5) and 5.7 (1.7-19.4) for 1, 1+ and 2+ smokers in the home, respectively.	np	np	Fukuda and Shibata (1990; cited in CEPA 1997)
Case-control	147 nasal sinus cancers and 449 controls of never smoked U.S. white men.	Spousal smoking. Data collected as part of 1986 National Mortality follow-back Survey conducted by NCHS (National Center for Health Statistics).	OR of ever exposed to spousal passive smoking was 3.0 (95% CI 1.0-8.9).	np	The effect (RR=3.0) was stronger than that of direct heavy smoking OR=2.0 (95% CI 1.0-4.0) in this study.	Zheng *et al.* (1993)
CHILDHOOD CANCERS						
COHORT STUDIES						
Cohort	497,051 children born in Sweden 1982-7. Cancer cases were for those 5 years old and younger.	Maternal smoking. Information obtained from birth data on registry and telephone interviews.	Among 198 solid tumors RR=0.96 (95% CI 0.70-1.32) and 129 lymphatic/hematopoietic tumors RR=1.04 (95% CI 0.71-1.52). For 81 brain tumors RR=0.96 (95% 0.59-1.56).	np	No relationship among cancer sites or amount smoked per day.	Pershagen *et al.* (1992)
CASE-CONTROL STUDIES						
Case-control	163 cases of childhood	Mothers smoking. Information provided	OR=1.0 (95% CI 0.6-1.7) for gestational and child risk ratios	np	np	Kuijten *et al.*

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	astrocytoma and 163 controls.	in telephone interviews	related to mother's smoking.			(1990)
Case-control	82 childhood (0-14) brain cancer cases and 164 controls in New South Wales 1988-90.	Parent smoking. Interviewed at home by trained personnel.	Fathers smoking OR = 2.2 (95% CI 1.2-3.8) and mother who continued smoking during pregnancy OR = 0.9 (95% CI 0.5-1.8).	Control women were of a higher social class.	No observed dose-response. Father's smoking reported by mother and may involve recall bias.	McCredie *et al.* (1994)
Case-control	223 childhood cancer cases and 196 controls aged 0-14 years in Denver, CO.	Parents smoking. Information provided by structured interviews in the home.	For all cancers the OR=1.3 (95% CI 0.7-2.1) for mothers smoking and OR=1.2 (95% CI 0.8-2.1) for fathers smoking.	np	Greater effects were seen for acute lymphocytic leukemia, OR=1.9 and 1.4, respectively.	John *et al.* (1991)
Case-control	74 brain cancer cases among children and 138 controls in Ontario.	Parent smoking. Information obtained in home interviews.	OR=1.42 (95% CI 0.7-3.0) for maternal smoking and OR=1.13 (95% CI 0.61-2.09) for paternal smoking during index pregnancy.	np	np	Howe *et al.* (1989)
Case-control	Among the 16,193 children born one week in April, 1970 in Great Britain. 33 cancers observed during the first 10 years of life and were matched with 99 controls.	Parent smoking information collected by midwives and followed by child health and educaiton study.	Maternal smoking OR=2.69 (95% CI 1.05-6.89) for antenatal smoking.	np	np	Golding *et al.* (1990)
Case-control	305 childhood (0-16 years) cancer cases with 340 insulin-dependent diabetic controls in Sweden.	Maternal smoking. Information provided by structured questionnaire for self-assessment.	For total cancers, RR=1.07 (95% CI 0.63-1.80) and 1.56 (95% CI 1.05-2.33) for 1-9 and 10+ cigarettes per day, respectively. For ALL the RR values are =1.34 (95% CI 0.7-2.6) and 2.07 (95% CI 1.3-3.3).	np	np	Stjernfeldt *et al.* (1986)
Case-control	187 cases of	Parental smoking	OR=1.2 (95% CI 0.77-1.86) for	np	np	Severson *et al.*

Study Type	Population Group	Exposure	Effects	Potential Confounders/ Effects	Comments	References
	childhood AML and 187 matched controls in MN.	information provided by telephone interviews.	maternal smoking during pregnancy.			(1993)
Case-control	555 children age 15 or less with cancer and 1,110 matched controls in 3 regions of the United Kingdom.	Maternal smoking information provided by standard questionnaire.	OR=1.12 (95% CI 0.85-1.47) and OR=0.84 (95% CI 0.65-1.09) for 1-10 and 11+ cigarettes per day, respectively for all childhood cancers. For 171 leukemias the OR=1.0 (95% CI 0.6-1.7) and OR=0.6 (95% CI 0.4-1.0) for the same smoking rates.	np	np	McKinney *et al.* (1987); McKinney and Stiller (1986); both cited by CEPA (1997)
Case-control	1,814 chilhood cancers cases in the US Children's Cancer Study Group and 720 population controls.	Maternal smoking.	OR=1.31 (95% CI 0.9-1.9) and OR=0.97 (95% CI 0.8-1.2) for 1-9 and 10+ cigarettes per day. For the subset of 742 ALL cases the values are OR=1.0 (95% CI 0.6-1.5) and OR=0.9 (95% CI 0.7-1.1), respectively.	np	No association with maternal smoking was seen.	Buckley *et al.* (1986; cited by CEPA 1997)
Case-control	361 cases of brain cancer in 18 and younger children with 1083 controls.	Parental smoking. Information provided by structured interviews at home.	Comparing both parents smoking to neither parent smoking OR=0.95 (95% CI 0.66-1.36) and OR=1.06 (95% CI 0.82-1.37) for mother alone and OR=0.94 (95% CI 0.66-1.33) for father alone.	np	No association was reported with parental smoking.	Gold *et al.* (1993)
Case-control	142 children with ALL, 22 with non-ALL and 19 with NHL in the pediatric hospital of Turin, Italy. 307 hospital controls.	Parental smoking.	For ALL, OR=0.7 (95% CI 0.5-1.1) for maternal smoking and OR=0.9 (95% CI 0.6-1.5) for paternal. For non-ALL the values are 2.0 (95% CI 0.8-4.8) and 0.9 (95% CI 0.3-2.1) respectively.	np	No association was reported with parental smoking.	Magnani *et al.* (1990; cited by CEPA 1997)

np: not provided * For further detail on these studies, see EPA (1992) and CEPA (1997), both in Appendix 3

3.5 Discussion

The carcinogenicity of ETS has been evaluated in a series of comprehensive reviews. IARC (1986) found that the available evidence was insufficient to draw a conclusion, but all subsequent reports have concluded that ETS exposure is causally related to lung cancer in nonsmokers (NRC 1986; US DHHS 1986; EPA 1992; CEPA 1997). EPA (1992) conducted a formal meta-analysis including a total of 3,728 lung cancer cases, 80% of which were reported after the IARC review (1986), and found an overall increase in risk due to spousal ETS exposure of about 20%. This risk was derived by comparing nonsmokers with spousal exposure to nonsmokers without spousal exposure, regardless of other sources of exposure. Since workplace and social sources can make a significant contribution to ETS exposure (Pirkle *et al.* 1996), this calculation most likely underestimates the risk. In fact, when nonsmokers with spousal and other sources of exposure were compared to nonsmokers with *no* ETS exposure, the increase in risk was about 60%. CEPA (1997) reviewed four case-control studies and one cohort study published after the EPA report (Stockwell *et al.* 1992; Brownson *et al.* 1992; Fontham *et al.* 1991; 1994; Kabat *et al.* 1995; Cardenas *et al.* 1997), which collectively addressed many of the problems of earlier studies, and concluded that the results were consistent with the EPA (1992) estimate of a 20% increase in risk due specifically to spousal smoking.

Although it is unlikely that these findings are due to chance, a number of systematic biases have been proposed to account for this small increase in risk. Concerns have been raised regarding the possibilities of selection bias in hospital-based studies; of misclassification of non-lung cancers as lung cancer; of misclassification of former or current smokers as nonsmokers; of misclassification of the extent of ETS exposure in studies using surrogate respondants; and of confounding by dietary factors or occupational exposures. All of these issues are addressed by three recent large population-based studies (Stockwell *et al.* 1992; Brownson *et al.* 1992; Fontham *et al.* 1991; 1994). The possibility of selection bias is essentially eliminated in these studies by the identification of all lung cancer cases in a specified study area together with high response rates (83-90% for cases). The presence of primary lung cancer was confirmed histologically in 75-85% of cases in two of the studies (Brownson *et al.* 1992; Fontham *et al.* 1991; 1994) and all cases in the third (Stockwell *et al.* 1992). Multiple sources of information were used to confirm nonsmoking status; for example, medical records, physicians' reports, screening interviews, structured interviews, and cotinine measurements were used by Fontham *et al.* (1991; 1994). A high proportion (64%) of the interviews in Fontham *et al.* (1991; 1994) were conducted with the cases themselves, rather than surrogates, suggesting that the information on ETS exposure is likely to be accurate. Finally, no confounding by dietary factors or vitamin supplements was observed by Fontham *et al.* (1991; 1994). This study observed an association of lung cancer with ETS after adjusting for age, race, study area, education, diet, family history of lung cancer, and employment in high-risk occupations.

Results from these case-controls studies are supported by the findings of a recent prospective cohort study, in which risk of lung cancer was associated with spousal exposure to ETS (Cardenas *et al.* 1997). The failure of this study's results to achieve statistical significance may be due to the low power of the study (only 96 exposed women with lung cancer were studied) and/or the inadequate measure of exposure, both of which would likely reduce the ability of the study to observe an effect. Nevertheless, the reported risk of 1.2 is consistent with other studies and meta-analyses.

A major concern in studies of ETS exposure and lung cancer has been the possibility that nonsmokers are in fact current or former smokers, particularly since smokers tend to marry smokers. Wald *et al.* (1986) estimated that about 7% of ever smokers would be misclassified as nonsmokers. Two recent studies (Riboli *et al.* 1995; Nyberg *et al.* 1997), using different methodologies, conclude that the misclassification rate is low and unlikely to explain the lung cancer risk from ETS exposure. Riboli *et al.* (1995) conducted a large cross-sectional study to validate self-reported ETS exposure by analysis of urinary cotinine levels. Questionnaire data and urine samples were collected from 1,369 nonsmoking women. Twenty-seven women had cotinine levels between 50 and 150 ng/mg, and 16 of these reported high ETS exposure. Only 20 women (1.5% of 1,369) had cotinine levels above 150 ng/mg, and were probably covert smokers. Nyberg *et al.* (1997) calculated misclassification rates in two large Swedish cohorts who had been questioned regarding smoking habits on two occasions 6 to 10 years apart. Rates were calculated two ways. The first rate was the number of misclassified nonsmokers divided by the total number of ever smokers; the rates in the two cohorts were 4.9-5.0% for men and 4.5-7.3% for women. The second rate was the number of misclassified never smokers divided by the total number of never smokers; the rates in the two cohorts were 11.1-11.5% for men and 1.3-2.2% for women. The authors pointed out that the first rate is similar in many studies, but the second rate is quite variable and depends on the number of nonsmokers in a particular study. As in other studies, most of the misclassified nonsmokers studied by Nyberg *et al.* (1997) had stopped smoking years before and had smoked less than the average smoker. A recent analysis based on urinary cotinine measurements, which combined data from over 8,000 majority women reported in 10 studies, found that the proportion of regular smokers misclassified as nonsmokers was 0.8%; for occasional smokers the proportion was 6.0% (Wells *et al.* 1998). In general, the misclassification rate appears to be quite low in women, who are the subjects of most studies of lung cancer and ETS exposure. Thus it appears unlikely that misclassification of former or current smokers as nonsmokers can explain the association of lung cancer with ETS exposure.

Although much discussion has focused on the possibility that misclassification of smokers as nonsmokers could inflate the risk estimates, there are also sources of exposure misclassification which could reduce the risk estimates. Spousal smoking is considered to be the best single surrogate of ETS exposure, for several reasons. Measurements of cotinine in nonsmokers indicate that that spousal smoking contributes more exposure than workplace smoking (Pirkle *et al.* 1996). Databases on spousal smoking are generally larger and more likely to be accurate, since the data are often collected by interviewing proxies who may have relatively little knowledge of workplace exposures. Exposure in the home is likely to be more uniform than exposure in the workplace, since work environments change frequently. Nevertheless, workplace and social exposures do make a substantial contribution to overall exposure (Pirkle *et al.* 1996), so that categorizing as unexposed women whose husbands do not smoke but who are exposed to ETS in other environments can underestimate the true risk due to ETS exposure. Failure to consider the amount of exposure can also lead to underestimation of the true risk. In most studies, including those with marginal risks associated with ever exposure, risks at the highest level of exposure are more pronounced.

Another concern has been that, while ETS exposure from spousal smoking was associated with lung cancer in many studies, workplace exposure frequently was not. A meta-analysis of 12 studies by LeVois and Layard (1994) found an overall relative risk of 1.01 (95% CI, 0.92-1.11) associated with workplace exposure. A more recent meta-analysis (Wells 1998) established criteria for evaluating the 14 available studies; these criteria were: at least 10 years of exposure

history, no more than 50% surrogate responses for cases, greater than minimal exposure, no active smoking, and availability of raw data. Only 5 studies met these criteria; the combined relative risk was 1.39 (1.15-1.68). The author also reviewed previous meta-analyses, including that by LeVois and Layard (1994), and found that their negative conclusions depended on inclusion of seriously flawed studies and incorrect heavy weights assigned to relative risks less than unity (Wells 1998).

In summary, it appears unlikely that either confounding or other types of bias can account for the risk ascribed to ETS exposure. The consistency of risks observed across individual studies conducted with various populations and methodologies, the presence of an exposure-response relationship in many studies, and the biological plausibility of the relationship all argue strongly that the association of ETS exposure with lung cancer is causal.

Regarding other cancer sites, there is good evidence that ETS exposure is associated with nasal sinus cancer, and suggestive evidence for cervical cancer; available data do not support an association with bladder cancer; and the evidence is inconclusive regarding other sites and childhood cancer.

4 Studies of Cancer in Experimental Animals

4.1 Summary of Earlier Experiments

The International Agency for Research on Cancer (IARC) Working Group reviewed the experimental evidence regarding the induction of pulmonary tumors in experimental animals by tobacco smoke and tobacco smoke condensate (IARC 1986). Pertinent points of this review are summarized below.

4.1.1 Exposure of laboratory animals to tobacco smoke by inhalation

Prior to 1986, attempts to produce lung cancer in experimental animals by exposing them to tobacco smoke were largely unsuccessful. Tobacco smoke-associated tumors in the respiratory tracts of rats (nasal adenocarcinoma and squamous cell carcinoma) and hamsters (laryngeal tumors) have been reviewed (IARC 1986). However, increased incidences of lung tumors *per se* in these species or in mice, rabbits, and dogs had not been reported. A variety of factors may contribute to these findings. For example, rodents are obligatory nose breathers and their complex nasal turbinates may afford protection. Also, experimental animals forced to inhale smoke respond with shallow and hesitant respiratory activity thereby reducing the amount of smoke that gains access to the lower reaches of the lung.

4.1.2 Tobacco smoke condensate

The topical application of cigarette smoke condensate, containing numerous chemicals known to be carcinogenic to laboratory animals and humans, has repeatedly been shown to induce both benign and malignant tumors. Cigarette smoke condensate, applied to the skin, is recognized as a tumor-initiator, tumor-promoter, and co-carcinogen. Instillation of tobacco smoke condensate into the lungs of experimental animals has caused squamous cell carcinoma. Topical application of the condensate to the oral mucosa of mice resulted in the induction of lung tumors in mice (reviewed by IARC 1986). Thus, the carcinogenic potential of tobacco smoke condensate is unequivocal.

4.2 Experiments Conducted Since the Last Review

4.2.1 Exposure of laboratory animals to tobacco smoke by the inhalation route

Witschi *et al*. (1995) conducted a six-month inhalation exposure study of male strain A/J mice to sidestream smoke (SS). Animals were exposed to SS for 6 hours a day, 5 days a week. The characteristics of the SS used in these experiments are summarized in Table 4-1. In addition to assessing effects of tobacco smoke on tumor incidence and tumor multiplicity, these workers determined the effects of exposure to smoke on the replication of epithelial cells in the respiratory tract by measuring the incorporation of BrdU into cells. All experimental and control animals survived for the entire experimental period and there was no treatment-related effect on body weight gain.

Table 4-1. Sidestream smoke characteristics to which A/J mice were exposed 6 hours a day, 5 days a week for 6 months

Measure Parameter	Concentration
Total particulate matter (TPM)	4.1-4.5 ± 0.4-0.6 mg/m^3
Carbon monoxide	17±2 ppm

Witschi *et al.* (1995)

Exposure to SS was associated with occasional, but inconsistent, changes in the incorporation of BrdU into respiratory epithelial cells in the large intrapulmonary airways and maxillar turbinates. Values in smoke-exposed mice were indistinguishable from those in controls between exposure weeks 4 and 16. BrdU incorporation experiments were terminated at 16 weeks. Labeling indices in tracheal epithelium, and in the alveolar zone, were unaffected by exposure to SS for up to 16 weeks.

Lung tumor incidences and tumor multiplicity, in control and smoke-exposed animals, are summarized below. Exposure to tobacco smoke had no effect on pulmonary tumor incidence or tumor multiplicity. The data are summarized in Table 4-2.

Table 4-2. Incidence and multiplicity of lung tumors in A/J mice exposed to sidestream smoke for up to six months

Parameter	Smoke exposed	Air control
Animals with lung tumors	12/36(33%)	12/36(33%)
Animals with 1 lung tumor	9	10
Animals with 2 lung tumors	3	2
Tumors per animal (all animals)	0.42±0.65	0.39±0.60
Tumors per tumor bearing animal	$1.25^{0.45}$	1.07±0.39

Witschi *et al.* (1995)

Finch *et al.* (1996) conducted a six-month bioassay of cigarette smoke in female A/J strain mice. Animals were exposed to cigarette smoke or filtered air for 6 hours a day, 5 days a week for 26 weeks. The cigarette smoke exposure atmosphere used is characterized in Table 4-3.

Table 4-3. Average chamber concentrations to which A/J mice were exposed for 6 hours a day, 5 days a week for up to 6 months

Measure Parameter	Concentration
Total particulate matter (TPM)	248±33 mg/m^3
Carbon monoxide`	231 ppm
Smoke particulate size	0.52±0.05 μm

Finch *et al*. (1996)

Animals exposed to cigarette smoke lost approximately 17% of their beginning body weight during the first week of exposure. After the initial weight loss, smoke-exposed animals gained weight at a similar rate as the controls. The smoke-exposed animals, however, never fully regained their body weight.

At necropsy, the mean lung weight of smoke-exposed mice was significantly higher than that of controls (controls, 188±17 mg vs smoke exposed, 236±22 mg; $p< 0.05$). Tumor incidences in control and smoke-exposed mice were 5/19 and 0/19, respectively. The tumor multiplicity in all animals of control and smoke-exposed mice were 0.32 ± 0.58 and 0 ± 0 ($P < 0.05$), respectively.

Witschi *et al.* (1997a) exposed male A/J strain mice to tobacco smoke 6 hours a day, 5 days a week for 5 months, then afforded some of the animals a 4-month recovery period. Chamber parameters for these experiments are summarized below in Table 4-4.

Table 4-4. Average chamber concentrations to which A/J mice were exposed for 6 hours a day, 5 days a week for up to 5 months

Measure Parameter	Concentration
Total particulate matter (TPM)	87.3±21
Mean mass diameter	0.41±0.02 μ
Geometric Standard Deviation.	1.87±0.12
Nicotine	16.1±6.3 mg/m^3
Carbon monoxide`	244±40 ppm
Smoke particulate size	0.52±0.05 μm

Witschi *et al.* (1997a)

All smoke-exposed animals survived to the termination of the experimental period and there was no effect of exposure on body weight. Smoke-exposed and control animals were indistinguishable with respect to tumor incidence or tumor multiplicity when sacrificed at five months (after cessation of smoke exposure). When animals were given a four-month recovery period, however, both tumor incidence and multiplicity were significantly increased by prior exposure to tobacco smoke. Tumor incidences in mice used in these experiments are summarized in Table 4-5.

Table 4-5. Lung tumor incidences in mice exposed to sidestream smoke for up to five months

Experimental conditions	Parameter	Air controls	Smoke exposed
5 month's exposure	Tumor incidence	2/24 (8%)	6/24 (25%)
	Tumors/animal	0.1±0.1	0.3±0.1
	Tumors/tumor bearing animal	1.0±0.0	1.2±0.2
5 month's exposure and 4 month's recovery	Tumor incidence	9/24 (38%)	20/24 (83%)
	Tumors/animal	0.5±0.2	1.4±0.2
	Tumors/tumor bearing animal	1.3±0.2	1.7±0.2

Witschi *et al*. (1997a)

In a parallel experiment, these researchers attempted to modify the incidence of lung tumors with an agent known to enhance lung tumors in A/J mice, the antioxidant butylated hydroxytoluene (BHT). A/J mice were exposed to tobacco smoke (with Total Suspended Particulate = 53 mg/m^3) for 2.5 months. Concomitantly, they received a diet containing 0.5% of BHT. After the 2.5-month exposure period, animals were given a 6.5-month recovery period before sacrifice.

BHT administration did not influence tumor incidence or multiplicity (see also Section 4.2.2). However, the authors combined the data from this parallel experiment to demonstrate a higher incidence of tumors (and tumor multiplicity) in tobacco smoke-exposed animals (and mice exposed to ETS and BHT) compared with animals exposed to filtered air and exposed to BHT in the diet or given a diet without BHT. The pooled data are summarized in Table 4-6.

Table 4-6. Lung tumor incidences in A/J mice exposed to sidestream tobacco smoke and fed BHT

Experimental conditions	Parameter	Air controls	Smoke exposed

2.5 months in smoke (53 mg TSP/m^3) and 6.5 months recovery	Tumor incidence	23/41 (56%)	28/38 (78%)[a]
	Tumors/animal	0.8±0.1	1.3±0.2[a]
	Tumors/ tumor bearing animal	1.4±0.1	1.8±0.2[a]

Witschi *et al.* (1997a) [a] Significantly greater than control, P<0.05.

The incidence of tumor bearing animals, tumors per animal, and tumors per tumor bearing animal were all elevated significantly in the tobacco smoke-exposed animals.

The effects of tobacco smoke (containing 83.4 mg/m^3 suspended particles) on the incorporation of BrdU into alveolar epithelial cells was also studied. In these experiments, mice were exposed to smoke for one to ten weeks, and given zero to ten weeks of recovery time before the incorporation of BrdU into respiratory epithelium was assessed. While the incorporation indices for BrdU into alveolar cells in smoke-exposed animals tended to be numerically higher than in the control animals, differences were only occasionally statistically significant. The data are summarized in Table 4-7.

Table 4-7. Labeling indices in the Alveolar zone of A/J mice exposed to tobacco smoke then administered BrdU

Exposure groups	Labeling Indices in Alveolar Zone	
Week Number	**Control**	**Sidestream smoke**
1 week exposure	6.9±0.6	10.4±1.0[a]
2 weeks exposure	8.2±0.5	9.8±0.4[a]
4 weeks exposure	6.5±1.0	8.7±1.3
6 weeks exposure	7.4±0.9	8.5±0.8
10 weeks exposure	5.1±0.6	6.0±0.2
10 weeks exposure 1 week recovery	3.7±0.5	6.8±1.4
10 weeks exposure 2 weeks recovery	3.0±0.4	3.2±0.6
10 weeks exposure 4 weeks recovery	3.7±0.7	6.7±0.9[a]
10 weeks exposure 10 weeks recovery	3.2±0.6	5.4±2.1

Witschi *et al.* (1997a) [a] Significantly different from controls (P<0.05)

The carcinogenic properties of the vapor component of SS have also been studied by exposing female A/J mice to filtered and unfiltered tobacco smoke (Witschi *et al.* 1997b). In these experiments, mice were exposed to filtered or unfiltered tobacco smoke for five months (6 h/d, 5 d/wk). Characterization of the inhaled tobacco smokes is shown in Table 4-8.

Table 4-8. Average chamber concentrations to which A/J mice were exposed for 6 hours a day, 5 days a week for up to 5 months

Parameter	Whole smoke	Filtered smoke
Carbon monoxide	23 ±2 ppm	23±2 ppm
Nicotine	13.4±3.3 mg/m^3	3.1±2.0 mg/m^3
Total suspended particulates	78.5±12.4 mg/m^3	0.1±0.2 mg/m^3

Witschi *et al.* (1997b)

Some mice were sacrificed upon cessation of smoke exposure (after five months), while others were given a four-month recovery period.

Animals exposed to unfiltered smoke lost body weight during the first month of the experiment, but they began gaining weight between the first and second months of exposure. The weight gain occurred at a slower rate than that of animals breathing the filtered smoke. The results of this experiment, with respect to tumor incidence and tumor multiplicity, are presented in Table 4-9.

Table 4-9. Lung tumors in strain A/J mice exposed to tobacco smoke for up to five months

Experimental conditions	Parameter	Air controls	Smoke exposed
5 months filtered smoke	Tumor incidence	4/20 (20%)	12/24 (50%)
	Tumors/animal	0.3±0.1 (n=20)	0.7±0.2 (n=24)
	Tumors/tumor bearing animal	1.3±0.3 (n=4)	1.4±0.1 (n=24)
5 months filtered smoke plus 4 months recovery	Tumor incidence	9/24 (38%)	16/24 (67%)
	Tumors/animal	0.5±0.3 (n=24)	1.2±0.3[a] (n=24)
	Tumors/tumor bearing animal	1.2±0.1 (n=9)	1.8±0.4 (n=16)
5 months unfiltered smoke plus 4 months recovery	Tumor incidence	10/24 (42%)	15/26 (58%)
	Tumors/tumor bearing animal	0.5±0.3 (n=24)	1.2±0.3 [a] (n=24)
	Tumors/animal	1.2±0.1 (n=10)	2.3±0.3[a] (n=15)

Witschi *et al.* (1997b) [a]Significantly different from controls, P<0.05

Among animals sacrificed after five months of exposure, lung tumor incidence and tumor multiplicity in animals exposed to filtered smoke were numerically (but not statistically) greater than were those in animals exposed to filtered air.

After the four-month recovery period, lung tumor multiplicity, in the group exposed to filtered smoke, was significantly greater than in animals exposed to air. In addition, tumor multiplicity was significantly greater in unfiltered smoke-exposed animals, given a four-month recovery period, than in air-exposed controls with the same recovery period.

4.2.2 Interactions of cigarette smoke with known carcinogens

Finch *et al.* (1996) pretreated female A/J mice with 100 mg/kg of nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), then exposed them to cigarette smoke, characterized below in Table 4-10.

Table 4-10. Average chamber concentrations to which A/J mice were exposed for 6 hours a day, 5 days a week for 26 weeks

Measure Parameter	Concentration
Total particulate matter (TPM)	248±33 mg/m^3
Carbon monoxide	231 ppm
Smoke particulate size	0.52±0.05 μm

Finch *et al*. (1996)

Exposures were 6 hours a day, 5 days a week for 26 weeks. At necropsy, the lung weights of animals exposed to NNK plus smoke were significantly greater than those from animals exposed to NNK alone (228 ± 13 mg *vs* 190 ± 23 mg, respectively; $p<0.05$). Tumor incidences in the experimental groups are summarized in Table 4-11.

Table 4-11. Lung tumor incidences in A/J mice exposed to tobacco smoke for up to 26 weeks

Parameter	Filtered air	Cigarette smoke	Filtered air + NNK	Cigarette smoke + NNK
Mice with nodules (tumors)	5/19 (26%)	0/19 (0%)	19/20 (95%)	13/16 (81%)
Tumors per animal (all animals)	0.32±0.58	0±0	2.50±1.67	2.50±1.97
Tumors per tumor bearing animal	1.20±0.44	N/A	2.63±1.61	3.09±1.71

Finch *et al*. (1996)

Mice exposed to NNK had a higher incidence of lung tumors than did filtered air controls. Exposure of NNK dosed mice to cigarette smoke affected neither lung tumor incidence, nor the extent of tumor multiplicity.

Witschi *et al.* (1997a) studied the interactions of SS with other chemicals known to influence the incidence of lungs tumors. A/J mice were dosed intraperitoneally with either 500 mg/kg of urethane or 20 mg/kg of 3-methylcholanthrene. The animals were then exposed to tobacco smoke (with Total Suspended Particulates = 53 mg/m^3; 6 h/d, 5 d/wk for 5 mos.) or air.

Half the animals were sacrificed when exposure to tobacco smoke was terminated and the others were given a four-month recovery period. The results are summarized in Table 4-12.

Table 4-12. Lung tumor incidences in A/J mice exposed to tobacco smoke and urethane or 3-methylchlolanthrene

Experimental group	Tumors per lung			
	Treated with urethane		Treated with 3-methylcholanthrene	
	Air exposed	Smoke exposed	Air exposed	Smoke exposed
5 months exposure	11.3±1.2 (n=12)	5.3±0.9[a] (n=12)	6.9±1.6 (n=10)	2.3±0.8[a] (n=9)
5 months exposure, 4 months recovery	16.7±0.9 (n=11)	16.3±1.4 (n=12)	11.9±3.1 (n=11)	8.3±1.2 (n=11)

Witschi *et al.* (1997a)

[a]Significantly less than control ($P<0.05$)

Urethane and 3-methylcholanthrene-induced tumor multiplicity, when measured immediately after cessation of exposure, was significantly reduced by exposure to tobacco smoke. However, after the recovery period, tumor multiplicity was similar in air-exposed and smoke-exposed groups.

The researchers also attempted to modify the incidence of lung tumors, and/or tumor multiplicity, by concomitantly administering an agent known to enhance lung tumor development, the antioxidant butylated hydroxytoluene (BHT). A/J mice were exposed to tobacco smoke (and a diet containing 0.5% of BHT for 2.5 months) and then afforded a 6.5-month recovery period before sacrifice. The results of this experiment are summarized in Table 4-13.

Table 4-13. Lung tumor incidences in A/J mice exposed to tobacco smoke and fed BHT

Parameter	Smoke + BHT	Smoke + control diet	Air + BHT	Air + control diet
Tumor incidence	13/17 (76%)	15/21 (71%)	10/18 (56%)	13/23 (57%)
Tumors/animal	1.5±0.3 (n=17)	1.1±0.2 (n=21)	0.8±0.2 (n=18)	0.7±0.2 (n=23)
Tumors/tumor bearing animal	2.0±0.3 (n=13)	1.5±0.2 (n=15)	1.5±0.2 (n=10)	1.2±0.1 (n=13)

Witschi *et al.* (1997a)

Dietary administration of BHT had no influence on either tumor incidence or tumor multiplicity in A/J mice that had been exposed to tobacco smoke.

5 Genotoxicity

5.1 Prokaryotic Systems

5.1.1 Induction of Mutation in Salmonella typhimurium

Lofroth *et al.* (1983) tested incoming and exhaust air in two large office buildings for mutagenicity to *Salmonella typhimurium* strains TA98 and TA100 under three conditions: days of no activity (Sunday), days of forbidden smoking, and days with smoking permitted. Their results indicated an increase of mutagenicity of both incoming and exhaust air on both days of activity, with the greatest increase on the days when smoking was permitted. The results imply that cigarette sidestream particulate matter can be a substantial source of airborne mutagenicity.

Ong *et al.* (1984) used an *in situ* microbial assay system that permitted entrapment of mutagenic airborne particles from cigarette smoke by infusing unfiltered air into a trapping medium containing bacterial cells. New *S. typhimurium* strains (TA98W, TA100W, and SV50W) were utilized. A three- to five-fold increase in reversion frequency could be seen after 30 minutes of exposure. The rates continued to increase with length of exposure time. The increases were statistically significant compared to controls (Table 5-1). In comparisons with the same test materials in the standard plate incorporation assay, the *in situ* assay system appears to be more effective in detection of cigarette smoke mutagenicity.

Table 5-1. Mutagenicity assay of cigarette smoke by the *in situ* test system[a,d]

Cigarette brand[b]	Treatment time (h)	Control set		Experimental set	
		Survival (%)	Revertant/10^8 survivors[c]	Survival (%)	Revertant/10^8 survivors[c]
A	0.5	100	10.9 (7)	99.0	40.4 (29)
	1	100	10.1 (9)	100.0	46.6 (42)
	2	100	6.7 (7)	100.0	52.7 (52)
	4	100	8.2 (7)	86.1	88.9 (78)
B	0.5	100	5.7 (9)	100.0	18.9 (32)
	1	100	6.0 (9)	100.0	32.4 (50)
	2	100	8.1 (8)	100.0	57.0 (59)
	4	100	10.3 (12)	70.8	86.9 (73)
C	0.5	100	5.4 (8)	76.2	31.6 (31)
	1	100	7.1 (8)	81.0	34.6 (34)
	2	100	4.5 (6)	83.3	58.8 (60)
	4	100	4.9 (5)	80.6	107.0 (97)

Cigarette brand[b]	Treatment time (h)	Control set		Experimental set	
		Survival (%)	Revertant/10^8 survivors[c]	Survival (%)	Revertant/10^8 survivors[c]
D	0.5	100	11.1 (7)	100.0	33.4 (24)
	1	100	12.1 (8)	100.0	44.3 (35)
	2	100	7.3 (4)	88.7	86.9 (59)
	4	100	5.6 (5)	79.9	117.3 (85)

[a]Results are average of three independent experiments. TA98W was tested with S9.

[b]Experiments for different cigarette brands were performed at different times. Four different brands studied were common American cigarettes.

[c]Numbers in parentheses are revertant colonies per plate.

[d]Ong *et al.* (1984)

Samples of sidestream smoke (SS) were collected on a Personal Air Sampler in an apartment during a party representing a highly smoke polluted environment, and in an office with one smoker (Ling *et al.* 1987). *Salmonella* strains TA98 and TA100 were used in both the plate incorporation assay and the microsuspension method. Results indicated that SS is mutagenically active in both assays with the response being enhanced in both strains in the microsuspension assay in the presence of S9. In addition, strain TA100 showed mutagenicity in the absence of S9.

Claxton *et al.* (1989) compiled an overview of the genotoxicity of Environmental Tobacco Smoke (ETS). Their assessment indicated that both particulate-bound organic material and nonparticulate–bound, semi-volatile material contain bacterial mutagens. Appendix 2 presents their summary of genotoxic compounds associated with ETS.

5.2 Mammalian Systems

5.2.1 Sister Chromatid Exchange

Chinese hamster ovary (CHO) cells were treated with tobacco smoke condensate and examined for induction of Sister Chromatid Exchange (SCE) (Chen and Lee 1996). Only a low induction of SCEs was observed.

Collman *et al.* (1986) studied induction of SCEs in lymphocytes of active and passive smokers. While there were significant increases noted for moderate and heavy smokers over nonsmokers, no elevation of SCEs was found in passive smokers compared to nonsmokers.

Sorsa *et al.* (1989) looked for chromosomal damage in heavily exposed nonsmoking restaurant workers and in newborn babies of smoking mothers. Although significant exposure was indicated by biochemical markers (cotinine and thiocyanate values in plasma) significant differences in chromosome aberrations and SCEs could not be detected in the lymphocytes of the subjects. In the results for the restaurant workers, the SCEs for smokers and nonsmokers were given as 8.21 ± 1.19 and 7.47 ± 0.76, respectively. In results for the newborn children, the mean SCEs were 6.1 ± 0.5 in smoking mothers and 5.9 ± 0.5 in nonsmoking mothers.

5.2.2 DNA Adducts

Sprague-Dawley rats were exposed to aged and diluted SS at 0, 0.1, 1.0, and 10 mg total wet particulate matter/m^3 for 6 hours a day for 14 consecutive days (Lee *et al.* 1992). DNA from

lung, heart, larynx, and liver were tested for adduct formation after 7 and 14 days of exposure, and 14 days of recovery. Slight diagonal radioactive zones were observed, but only in lung and heart DNA of animals exposed to the highest concentration. There was no elevation of chromosomal aberrations in alveolar macrophages.

Holz *et al.* (1990) subjected male volunteers to different smoking and passive smoking conditions. Nonsmokers were exposed to the gas phases of ETS in one study, and complete ETS in another. Smoking-related adducts were visible in the peripheral blood monocytes of active smokers only. Effects were not observed in heavily exposed passive smokers.

Daube *et al.* (1997) examined placental DNA for the presence of the 8-hydroxy-2'-deoxyguanosine (8-OHdG) adduct in nonsmokers, nonsmoking women exposed to ETS, and smokers. Levels of 8-OhdG were 0.84 +/-0.11, 0.90 +/- 0.21, and 0.83 +/-0.20/10^5 for the three exposure groups, respectively. The differences between the groups were not significant.

6 Mechanistic and Relevant Studies

6.1 Administration of tobacco-smoke condensate

The International Agency for Research on Cancer (IARC) Working Group reviewed studies in which cigarette smoke condensate extracts were applied to the shaved skin of rodents (IARC 1986). Such treatment was shown to produce a high incidence of papillomas and carcinomas at the sites of application. Numerous technical factors, such as species of test animals, solvents for the condensate, and source of cigarettes affect the quantitative outcome of experiments.

Application of cigarette smoke condensate to mouse skin produces both benign and malignant tumors. The tumors induced are usually epidermal in origin, but may also include an incidence of mastocytomas (Ohmori *et al.* 1981), cited in IARC (1986). Rat skin appears less responsive than mouse skin. McGregor (1976) and McGregor and Myers (1982), cited in IARC (1986), reported only low incidences of benign tumors when cigarette smoke condensate extract was painted on dekeratinized rat skin. The IARC Working Group noted that the results were equivocal. Bernfeld and Homburger (1983), cited in IARC (1986), reported that hamster skin was not responsive to cigarette smoke condensate extract, but their dosed animals were observed for only 46-47 weeks.

It has been reported that sidestream smoke (SS) contains up to ten-fold higher concentrations of known tobacco smoke carcinogens and 50 times more tumorigenic nitrosamines than mainstream smoke (MS) (IARC 1986; Hoffmann *et al.* 1987). Consequently, experiments comparing the relative carcinogenic potencies of SS and MS cigarette smoke condensate are of interest.

SS and MS cigarette smoke condensates were collected and their carcinogenic potencies compared on the skin of female MNRI mice (Mohtashamipur *et al.* 1990). SS condensates were dissolved in acetone, then applied to the shaved backs of mice at concentrations sufficient to deliver weekly doses of 1.7, 3.3, or 5 μg of benzo[a]pyrene/kg body weight (*i.e.*, 5, 10, or 15 mg of condensate, respectively). For these experiments, the quantity of MS smoke condensate applied was the same, regardless of benzo[a]pyrene content (Benzo[a]pyrene content in MS was not reported). Animals were dosed for three months, then observed until natural death.

Application of SS reduced survival of mice as compared to both negative controls (P=0.003) and the MS condensate exposed group (P=0.01). Survival of animals dosed with MS condensate was not different from that of controls. The survival of experimental mice is summarized in Table 6-1.

Table 6-1. Survival of female NMRI mice dosed with extracts of SS or MS cigarette smoke condensate

Experimental Group	n	Mean Life Span (months)	P
Negative control	210	17.9±5.2	-----
Mainstream	210	17.8±4.3	0.43 (relative to control)
Sidestream	210	16.7±4.7	0.003 (relative to control) 0.01 (relative to main-stream)

Mohtashamipur *et al.* (1990)

The incidences of tumors (skin tumors plus mammary tumors beneath the application site) in experimental animals are shown in Table 6-2.

Table 6-2. Number of mice with tumors at or beneath the skin site of application of SS or MS cigarette smoke condensate

Experimental Group	Initial animals	Final animals	Animals with tumors	Animals with precancerous skin lesions
Negative control				
Shaved + acetone	70	42	0	2
Shaved only	70	44	0	1
Untreated	70	43	0	0
Positive control				
5 μg benzo[a]pyrene	70	43	6	13
10 μg benzo[a]pyrene	70	42	23	18
MS smoke				
5 mg	70	58	4	10
10 mg	70	61	0	15
15 mg	70	58	3	10
SS smoke				
5 mg	70	60	5	12
10 mg	70	61	5	21
15 mg	70	61	20	23

Mohtashamipur *et al*. (1990)

The incidences of skin tumors, although generally greater in condensate or benzo[a]pyrene dosed animals, did not necessarily increase in dose-related fashions. Also, the authors noted, tumor

incidence in mice dosed with 15 mg of SS condensate (equivalent to 5 μg/kg of benzo[a]pyrene) was three-fold higher than in animals dosed with 5 μg/kg of benzo[a]pyrene *per se.*

These researchers concluded that their results support the hypothesis that SS poses a greater carcinogenic risk than MS.

6.2 Carcinogenicity of tobacco-specific carcinogens

Approximately 40 carcinogenic substances have been identified in cigarette smoke, and some of these materials are *tobacco-specific* since they are derived only from tobacco alkaloids. Two of these tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), have been reported to cause respiratory tract cancers in animals regardless of the administration route. NNK causes pulmonary tumors in rats, mice, and hamsters. NNN also causes pulmonary tumors in mice. In rats, however, it causes esophogeal and nasal tumors and, in hamsters, tumors of the trachea (Hoffmann and Hecht 1985; Hecht and Hoffman 1988; Rivenson *et al.* 1988; all cited in Hecht *et al.* 1993).

Administration of NNK to A/J mice has been described as a rapid, single-dose model of tumorigenesis (Hecht *et al.* 1991). Single intraperitoneal doses of 0, 5, or 10 μmol of NNK were administered to female A/J mice, then the animals were observed for 3.5 months. The results of this experiment are summarized in Table 6-3.

Table 6-3. Tumorigenicity of NNK in A/J mouse lung

Dose level of NNK (μmol/mouse[1])	Animals with tumor	Lung adenomas/mouse ± standard deviation
0	2/30 (7%)	0.1±0.3
5	27/30 (90%)	2.5±1.7
10	30/30 (100%)	7.3±3.5

Hecht *et al.* (1991)

Groups of 30 mice received single ip injections of NNK

The injection of single doses of NNK produced maximal tumor responses in A/J mice within 3.5 months. In terms of percent of animals with tumors, the response to 5 μmol was similar to that elicited by 10 μmol (90-100%). Under this circumstance, it is not possible to demonstrate dose-response relationships. The dose-response relationship was unequivocal, however, when tumor multiplicity was considered (lung adenomas/mouse).

6.3 Metabolism of tobacco-specific nitrosamines

The metabolism of NNN and NNK in rodents and primates was reviewed (Hecht *et al.* 1994) and two metabolites specific to NNK (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol and its glucuronide) were reported to appear in human urine. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol-glucuronide is considered a detoxification product of NNK, while 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, *per se,* is known to form pyridyloxobutyl adducts with lung and liver DNA (Peterson *et al.* 1991). Metabolically activated NNK and NNN are reported to form hemoglobin and DNA adducts in humans and the DNA adduct concentrations in smokers' lung tissue are higher than in nonsmokers lungs (Hecht *et al.* 1994).

Both NNN and NNK have been demonstrated to undergo oxidative metabolism in human hepatic microsomes and this metabolism results in the formation of highly electrophilic derivatives (Staretz *et al.* 1997a). These researchers also reported that, in rats, NNK metabolism proceeds through intermediates that methylate and pyridyloxobutylate DNA (Staretz *et al.* 1997b). NNK-induced lung tumor incidence in rats was dose-related and there was a correlation between the formation of pyridyloxobutyl DNA adducts and lung tumor incidence.

Inasmuch as the only source of NNK can be tobacco (smoking, chewing, or exposure by ETS), quantitation of the metabolites may be useful in assessing the systemic exposure to tobacco smoke carcinogens associated with inhaling both MS and SS tobacco smoke. In addition, data concerning excretion of NNK metabolites may be useful in quantitating relative carcinogenic risks between active and passive inhalation of tobacco smoke (also discussed in Section 2).

Nonsmokers were exposed to machine-generated SS and then NNK metabolites were measured in their urine (Hecht *et al.* 1993). The controlled environment to which nonsmokers were exposed was considered to be comparable to a heavily smoke-polluted bar. Nicotine concentrations in the experimentally produced environments ranged from 62 to 230 $\mu g/m^3$.

Subjects were exposed for two, 2.5 hour sessions during the experimental day. Urine samples taken every 24 hours were analyzed for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), its glucuronide (NNAL-glucuronide), and cotinine. The experiment was replicated (with the same subjects) six months later.

The results from two experiments conducted at approximately six-month intervals are shown in Table 6-4.

Table 6-4. NNAL, NNAL Glucuronide, and Cotinine excreted in urine (during 24 hours) from men exposed to SS cigarette smoke

Subject No.	NNAL ng/24 h		NNAL Glucuronide ng/24 h		Cotinine µg/24 h	
Study 1	Pre-exposure	Post exposure	Pre-exposure	Post exposure	Pre-exposure	Post exposure
1	<0.6	3.6	-	-	<2	62
2	<0.6	6.0	-	-	<2	66
3	<0.6	15	<1.0	44.2	3.7	123
4	2.7	6.7	25.8	55.3	18	146
5	1.4	4.1	-	-	<2	18
Study 2						
1	<0.6	2.7	<1.0	15.1	<2	92
2	1.3	4.4	5.3	13.1	2.8	57
3	<0.6	4.0	1.4	12.3	4.8	65

Subject No.	NNAL ng/24 h		NNAL Glucuronide ng/24 h		Cotinine µg/24 h	
4	2.1	5.6	11.8	35.0	24	96
5	-	3.7	-	20.3	4.8	48

Hecht *et al*. (1993)

Inhalation of SS smoke clearly increased the urinary excretion of NNAL and its glucuronide by all subjects, regardless of their pre-exposure excretion patterns. The mean excretion of NNAL and its glucuronide after exposure (both experiments combined) was 33.9 ± 20.0 ng/24 h compared to 8.4 ± 11.2 ng/24 h during the pre-exposure period ($P<0.001$). The urinary excretion of cotinine was also significantly increased by exposure to SS (89.6 ± 35.9 *vs* 8.9 ± 9.7 µg/24 h, $P<0.001$). The results of the experiment clearly show that the nonsmokers absorbed NNK from the experimental environment and metabolized it to NNAL and the glucuronide(Hecht *et al.* 1993).

The molar ratio of NNAL plus NNAL-glucuronide to cotinine in the urine of the experimentally exposed nonsmokers was 1:4600 ± 1800. The molar ratio of NNAL and NNAL-glucuronide to cotinine in the urine of 11 cigarette smokers was reported to be 1:3900 (Carmella *et al.* 1993). The close agreement between the molar ratios derived from the different experiments raised the possibility that urinary excretion of NNAL and its metabolite might have utility in understanding if a quantitative relationship exists between active and passive relative to systemic absorption of toxic materials.

Mean urinary excretion of NNAL and its glucuronide by nonsmokers exposed to SS was 33.9±20 ng/24h. The 11 smokers from the Camella *et al.* (1993) study excreted 4.0±1.7 µg/24 h. These comparisons (between two very small groups) may indicate that the NNK uptake was approximately 120 times greater in cigarette smokers than in nonsmokers exposed to SS (Hecht *et al.* 1993).

NNAL-glucuronide is considered to be a detoxification product of NNK metabolism (Carmella *et al.* 1995). The urinary ratio of NNAL:NNAL-glucuronide is highly variable between individuals, varying by 16-fold within a group of 61 cigarette smokers. On an intra-individual basis, however, the ratio remains relatively constant. Carmella *et al.* (1995) hypothesized polymorphism, with respect to ability of individuals to glucuronidate NNAL.

The urine of nine ETS-exposed, nonsmoking hospital workers were analyzed for NNAL-glucuronide and cotinine. NNAL-glucuronide was present in the urine of exposed workers (0.059±0.028 pg/mL) and the levels of the glucuronide were correlated with the urinary concentration of cotinine (Parsons *et al.* 1998). This observation supports the possibility that urinary concentrations of NNAL-glucuronide or the combined concentrations of NNAL and the glucuronide may act as quantitative biomarkers for exposure to ETS.

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Appendix 1

CONCENTRATIONS OF COMPOUNDS ASSOCIATED WITH MAINSTREAM AND SIDESTREAM TOBACCO SMOKE AND INDOOR AIR POLLUTED WITH TOBACCO SMOKE

Compound	Sample type	Concentration range Low	High	Units
Acetamide	MS	70.00	111.00	µg/cig
Acetamide	SS	86.00	156.00	µg/cig
Acetic acid	MS	333.00	809.00	µg/cig
Acetic acid	MS	272.00	475.00	µg/cig
Acetic acid	SS	1241.00	2187.00	µg/cig
Acetic acid	SS	695.00	1148.00	µg/cig
Acrolein	IA	0.90	1.30	ppm
Acrolein	IA	0.02	0.12	mg/m^3
Acrolein	IA	6.00	10.00	ppm
Acrolein	IA	0.01	0.19	mg/m^3
Acrolein	SS	50.00	70.00	ppm
Acrolein (gas only + people)	IA	130.00	190.00	$µg/m^3$
Acrolein (people absent)	IA	119.00	133.00	$µg/m^3$
Acrolein (people present)	IA	10.00	48.00	$µg/m^3$
Acrolein control air	IA	0.00	5.00	ppm
Aldehydes (gas only + people)	IA	1290.00	1350.00	$µg/m^3$
Aldehydes (generic)	IA	0.39	1.37	mg/m^3
Aldehydes (people absent)	IA	1100.00	1370.00	$µg/m^3$
Aldehydes (people present)	IA	391.00	622.00	$µg/m^3$
Alkoxyl radicals	MS	8.00 x 10 spins/c		
Alkoxyl radicals	SS	6.00 x 10 spins/c		
Ammonia	MS	79.40	131.00	µg/cig
Ammonia	MS	95.30	163.00	µg/g smoked
Ammonia (cigars)	MS	30.50	322.00	µg/g smoked
Ammonia (cigars)	MS	148.00	288.00	µg/product
Ammonia	SS	5.14	5.77	mg/cig
Ammonia	SS	6.11	7.18	mg/g smoked
Ammonia (cigars)	SS	6.98	106.00	mg/cig
Ammonia (cigars)	SS	9.34	20.50	mg/g smoked
Anatabine	MS	2.40	20.10	µg/cig
Anatabine	SS	0.00	2.40	µg/cig

Compound	Sample type	Concentration range		Units
		Low	High	
Anthanthrene	IA			Qual (ng/m^3)
Anthanthrene	IA	3.00		ng/m^3
Anthanthrene	MS	22.00		ng/cig
Anthanthrene	SS	39.00		ng/cig
Anthracene	IA			Qual (ng/m^3)
Anthracene	MS, P	23.60		ng/cig
Anthracene	MS, V	0.10		ng/cig
Anthracene	SS, P	670.00		ng/cig
Anthracene	SS, V	40.00		ng/cig
Benz[*a*]anthracene	IA			Qual(ng/m^3)
Benz[*a*]anthracene	MS, P	13.30		ng/cig
Benz[*a*]anthracene	MS, V	0.09		ng/cig
Benz[*a*]anthracene	SS, P	201.00		ng/cig
Benz[*a*]anthracene	SS, V	2.50		ng/cig
Benz[*e*]acenaphthylene	IA			Qual (ng/m^3)
Benzene	IA	0.05	0.15	mg/m^3
Benzene (breath, nonsmokers)	IA	2.50		µg/m^3
Benzene (breath, smokers)	IA	16.00		µg/m^3
Benzene (homes, nonsmokers)	IA	4.40	9.20	µg/cm^3
Benzene (homes, smokers)	IA	4.80	16.00	µg/m^3
Benzo[*a*]fluorene	IA			Qual (ng/m^3)
Benzo[*a*]fluorene	IA	39.00		ng/m^3
Benzo[*a*]fluorene	MS	184.00		ng/cig
Benzo[*a*]fluorene	SS	751.00		ng/cig
Benzo[*a*]pyrene	IA			Qual (ng/m^3)
Benzo[*a*]pyrene	IA	7.10	21.70	ng/m^3
Benzo[*a*]pyrene	IA	6.20	144.00	ng/m^3
Benzo[*a*]pyrene	IA	22.00		ng/m^3
Benzo[*a*]pyrene	MS	44.00		ng/cig
Benzo[*a*]pyrene	MS, P	10.90		ng/cig
Benzo[*a*]pyrene	MS, V	0.08		ng/cig
Benzo[*a*]pyrene	SS	199.00		ng/cig
Benzo[*a*]pyrene	SS, P	103.00		ng/cig
Benzo[*a*]pyrene	SS, V	0.48		ng/cig
Benzo[*a*]pyrene control	IA	0.00	0.69	ng/m^3

Compound	Sample type	Concentration range Low	High	Units
Benzo[*a*]naphtho[2,1-d]thiophene	MS, P	2.80		ng/cig
Benzo[*a*]naphtho[2,1-d]thiophene	MS, V	0.21		ng/cig
Benzo[*a*]naphtho[2,1-d]thiophene	SS, P	50.00		ng/cig
Benzo[*a*]naphtho[2,1-d]thiophene	SS, V	1.10		ng/cig
Benzo[*b/c*]fluorene	MS	69.00		ng/cig
Benzo[*b/c*]fluorene	SS	251.00		ng/cig
Benzo[*b/j/k*]fluoranthene	IA	35.00		ng/m^3
Benzo[*b/j/k*]fluoranthene	MS	49.00		ng/cig
Benzo[*b/j/k*]fluoranthene	SS	260.00		ng/cig
Benzo[*e*]fluorene	IA			Qual (ng/m^3)
Benzo[*e*]pyrene	IA			Qual (ng/m^3)
Benzo[*e*]pyrene	IA	18.00		ng/m^3
Benzo[*e*]pyrene	IA	3.30	23.40	ng/m^3
Benzo[*e*]pyrene	MS	25.00		ng/cig
Benzo[*e*]pyrene	MS, P	6.70		ng/cig
Benzo[*e*]pyrene	MS, V	0.13		ng/cig
Benzo[*e*]pyrene	SS	135.00		ng/cig
Benzo[*e*]pyrene	SS, P	75.00		ng/cig
Benzo[*e*]pyrene	SS, V	0.74		ng/cig
Benzo[*e*]pyrene control	IA	3.00	5.10	ng/m^3
Benzo[*ghi*]fluoranthene	IA			Qual (ngL/m^3)
Benzo[*ghi*]perylene	IA			Qual (ng/rn^3)
Benzo[*ghi*]perylene	IA	17.00		ng/m^3
Benzo[*ghi*]perylene	MS	39.00		ng/cig
Benzo[*ghi*]perylene	MS, P	7.10		ng/cig
Benzo[*ghi*]perylene	MS, V	0.09		ng/cig
Benzo[*ghi*]perylene	SS	98.00		ng/cig
Benzo[*ghi*]perylene	SS, P	41.00		ng/cig
Benzo[*ghi*]perylene	SS, V	0.62		nit/cig
Benzofluoranthenes (b+j+k)	MS, P	20.50		ng/cig
Benzofluoranthenes (b+j+k)	MS, V	0.22		ng/cig
Benzofluoranthenes (b+j+k)	SS, P	196.00		ng/cig
Benzofluoranthenes (b+j+k)	SS, V	1.38		ng/cig

Compound	Sample type	Concentration range		
		Low	High	Units
Benzoic acid	MS	14.00	28.00	µg/cig
Benzoic acid	SS	12.00	23.00	µg/cig
Benzoic acid, *m*-hydroxy-	MS	8.00	64.00	µg/cig
Benzoic acid, *m*-hydroxy-	SS	3.00	15.00	µg/cig
Benzonitrile	MS	5.00	6.00	µg/cig
Benzonitrile	SS	33.00	57.00	µg/cig
Bipyridyl, 2,3'-	MS	9.90	27.40	µg/cig
Bipyridyl, 2,3'-	SS	20.00	73.00	µg/cig
Bipyridyl, 5-methyl-2,3'-	MS	6.60	14.70	µg/cig
Bipyridyl, 5-methyl-2,3'-	SS	6.00	14.00	µg/cig
Butylrolactone, gamma-	SS	40.00	103.00	µg/cig
Butylrolactone, gamma-	MS	11.00	22.00	µg/cig
Carbon monoxide	IA	2.00	23.00	ppm
Carbon monoxide	IA	0.00	1.20	ppm
Carbon monoxide (gas only + people)	IA	23.00	26.00	ppm
Carbon monoxide (people absent)	IA	21.00	25.00	ppm
Carbon monoxide (people present)	IA	18.00	22.00	ppm
Carbon monoxide (people present)	IA	3.70	4.20	ppm
Carbon monoxide control	IA	0.00	15.00	ppm
Carbon monoxide control	IA	0.00	0.50	ppm
Carbon monoxide (artificial cond.)	IA	8.00	16.00	ppm
Carbon monoxide (natural cond.)	IA	9.00		ppm
Carbon, total	IA	207.00		$\mu g/m^3$
Carbon, elemental	IA	11.90		$\mu g/m^3$
Carbon, organic	IA	195.00		$\mu g/m^3$
Carboxyhemoglobin (blood, passive)	IA	0.55		%
Carboxyhemoglobin (blood, smoker)	IA	3.38		%
Carboxyhemoglobin (blood, no smoking)	IA	0.57		%

Compound	Sample type	Concentration range		
		Low	High	Units
Catechol	MS	148.00	362.00	µg/cig
Catechol	SS	138.00	292.00	µg/cig
Catechol, 2-methyl-	MS	6.00	13.00	µg/cig
Catechol, 2-methyl-	SS	8.00	21.00	µg/cig
Catechol, 3-methyl-	MS	31.00	62.00	µg/cig
Catechol, 3-methyl-	SS	24.00	47.00	µg/cig
Catechol, 4-ethyl-	NIS	27.00	102.00	µg/cig
Catechol, 4-ethyl-	SS	19.00	68.00	µg/cig
Catechol, 4-methyl-	SS	25.00	55.00	µg/cig
Catechol, 4-methyl-	MS	29.00	80.00	µg/cig
Catechol, 4-vinyl-	MS	23.00	113.00	µg/cig
Catechol, 4-vinyl-	SS	7.00	40.00	µg/cig
Catechols (all catechols)	MS	25.00	328.00	µg/cig
Catechols (all catechols)	SS	88.00	212.00	µg/cig
Coronene	IA	0.50	1.20	ng/m^3
Coronene control	IA	1.00	2.80	ng/m^3
Cotinine (plasma, nonsmoker)	IA	1.40		ng/mL
Cotinine (plasma, passive smoker)	IA	2.10		ng/mL
Cotinine (plasma, smoker)	IA	52.40		ng/mL
Cresol, *m*-	MS	11.00	18.00	µg/cig
Cresol, *m*-	MS	17.00	26.00	µg/cig
Cresol, *m*-	SS	13.00	24.00	µg/cig
Cresol, *m*-	SS	18.00	34.00	µg/cig
Cresol, *o*-	MS	13.00	19.00	µg/cig
Cresol, *o*-	SS	14.00	24.00	µg/cig
Cresol, *p*-	MS	30.00	37.00	µg/cig
Cresol, *p*-	MS	32.00	47.00	µg/cig
Cresol, *p*-	SS	30.00	46.00	µg/cig
Cresol, *p*-	SS	45.00	62.00	µg/cig
Cyclopentenone, 2,3-dimethyl-2-	MS	9.00	23.00	µg/cig
Cyclopentenone, 2,3-dimethyl-2-	SS	21.00	39.00	µg/cig
Cyclopentenone, 2-	MS	21.00	27.00	µg/cig
Cyclopentenone, 2-	SS	70.00	103.00	µg/cig
Cyclopentenone, 2-*OH*-3-methyl-2-	MS	3.00	5.00	µg/cig
Cyclopentenone, 2-*OH*-3-methyl-2-	SS	24.00	30.00	µg/cig
Cyclopentenone, 2-methyl-2-	MS	17.00	22.00	µg/cig
Cyclopentenone, 2-methyl-2-	SS	49.00	95.00	µg/cig

Compound	Sample type	Concentration range		
		Low	High	Units
Dibenz[*a, j*]anthracene	IA	6.00		ng/m^3
Dibenz[*a, j*]anthracene	MS	11.00		ng/cig
Dibenz[*a, j*]anthracene	SS	41.00		ng/cig
Ethylbenzene (breath, nonsmokers)	IA	0.80		µg/m^3
Ethylbenzene (breath. smokers)	IA	2.60		µg/m^3
Ethylbenzene (homes, nonsmokers)	IA	3.50	5.10	µg/m^3
Ethylbenzene (homes, smokers)	IA	3.50	8.30	µg/m^3
Ethylmethylenephenanthrene	IA			Qual (ng/m^3)
Fluoranthene	IA			Qual (ng/m^3)
Fluoranthene	IA	99.00		ng/m^3
Fluoranthene	MS	272.00		ng/cig
Fluoranthene	MS, P	61.30		ng/cig
Fluoranthene	SS	1255.00		ng/cig
Fluoranthene	SS, P	669.00		ng/cig
Fluoranthene	SS, V	16.90		ng/cig
Formaldehyde	IA	1.50	2.10	ppm
Formaldehyde	IA	0.10	0.16	ppm
Formaldehyde	SS	80.00	110.00	ppm
Formic acid	MS	210.00	478.00	µg/cig
Formic acid	SS	341.00	665.00	µg/cig
Furaldehyde, 2-	MS	15.00	43.00	µg/cig
Furaldehyde, 2-	SS	113.00	290.00	µg/cig
Furaldehyde, 5-methyl-	MS	6.00	29.00	µg/cig
Furaldehyde, 5-methyl-	SS	20.00	127.00	µg/cig
Furfuryl alcohol	MS	18.00	65.00	µg/cig
Furfuryl alcohol	SS	73.00	283.00	µg/cig
Furoic acid, 2-	MS	44.00	107.00	µg/cig
Furoic acid, 2-	SS	25.00	60.00	µg/cig
Glutaric acid	MS	10.00	58.00	µg/cig
Glutaric acid	SS	6.00	18.00	µg/cig

Compound	Sample type	Concentration range		
		Low	High	Units
Glycolic acid	MS	37.00	126.00	µg/cig
Glycolic acid	SS	35.00	77.00	µg/cig
Guaiacol, 4-vinyl-	SS	24.00	32.00	µg/cig
Guaiacol, 4-vinvl-	MS	23.00	36.00	µg/cig
Guaiacol, 4-vinyl-	MS	16.00	30.00	µg/cig
Guaiacol, 4-vinyl-	SS	15.00	37.00	µg/cig
HCN	IA	0.01	0.08	mg/m^3
HCN (gas only + people)	IA	82.00	86.00	$µg/m^3$
HCN (people absent)	IA	50.00		$µg/m^3$
HCN (people present)	IA	10.00	14.00	$µg/m^3$
Hydrazine	MS	31.50		ng/cig
Hydrazine	SS	94.20		ng/cig
Hydroquinone	MS	114.00	300.00	µg/cig
Hydroquinione	SS	91.00	285.00	µg/cig
Hydroquinone, methyl-	MS	23.00	39.00	µg/cig
Hydroquinone, methyl-	SS	21.00	41.00	µg/cig
Hydroxypropionic acid, 3-	M S	2.00	31.00	µg/cig
Hydroxypropionic acid, 3-	SS	1.00	29.00	µg/cig
Indeno[1,2,3-*cd*]pyrene	IA			Qual (ng/m^3)
Indeno[1,2,3-*cd*]pyrene	MS, V	0.17		ng/cig
Indeno[1,2,3-*cd*]pyrene	SS, P	51.00		ng/cig
Indeno[1,2,3-*cd*]pyrene	SS, V	0.36		ng/cig
Indeno[1,2,3-*cd*]pyrene	MS, P	8.10		ng/cig
Isoquinoline	MS	1.60	2.00	µg/cig
Isoquinoline	SS	5.00	9.00	µg/cig
Lactic acid	MS	63.00	174.00	µg/cig
Lactic acid	SS	45.00	123.00	µg/cig
Levulinic acid	MS	29.00	56.00	µg/cig
Levulinic acid	SS	25.00	49.00	µg/cig
Limonene	MS	15.00	49.00	µg/cig
Limonene	SS	63.00	397.00	µg/cig

Compound	Sample type	Concentration range		Units
		Low	High	
Lutidine, 2, 4-	SS	35.00	315.00	µg/cig
Lutidine, 2, 6-	MS	1.40	33.00	µg/cig
Lutidine, 2, 6-	SS	1.40	33.00	µg/cig
Lutidine, 3, 5-	MS	0.00	17.00	µg/cig
Lutidine, 3, 5-	SS	22.00	251.00	µg/cig
Methylenephenanthrene, 4, 5-	IA			Qual (ng/m^3) 1
Methylnaphthalene, 1-	SS	30.00		µg/cig
Methylnaphthalene, 1-	MS	1.02		µg/cig
Methylnaphthalene, 2-	MS	1.21		µg/cig
Methylnaphthalene, 2-	SS	31.60		µg/cig
Methylnitrosoamino-pyridyl-butanone	MS	46.00	240.00	ng/cig
Methylnitrosoamino-pyridyl-butanone	SS	201.00	540.00	ng/cig
Methylphenanthrene, 1-	IA			Qual (ng/m^3)
Methylphenanthrene, 2-	IA			Qual (ng/m^3)
Methylphenanthrene, 3-	IA			Qual (ng/m^3)
Methylphenanthrene, 4/9-	IA			Qual (ng/m^3)
Myosmine	MS	13.10	33.00	µg/cig
Myosmine	SS	73.00	224.00	µg/cig
Naphthalene	MS	2.76		µg/cig
Naphthalene	SS	45.50		µg/cig
Neophytadiene	MS	66.00	232.00	µg/cig
Neophytadiene	SS	70.00	421.00	µg/cig
Nicotine	IA	25.00	1010.00	$µg/m^3$
Nicotine	IA	0.70	3.10	$µg/m^3$
Nicotine	IA	1.00	10.30	$µg/m^3$
Nicotine	IA	1.70	180.00	pg/m^2 min
Nicotine	MS	1720.00	3330.00	µg/cig
Nicotine	MS	1483.00	3149.00	µg/cig
Nicotine	SS	3210.00	5830.00	µg/cig
Nicotine	SS	2987.00	6588.00	µg/cig

Compound	Sample type	Concentration range		Units
		Low	High	
Nicotine (gas only + people)	IA			Traces only
Nicotine (people absent)	IA	130.00		μg/m^3
Nicotine (people present)	IA	102.00		μg/m^3
Nicotine, office buildings	IA	1.70	180.00	pg/m^2 min
Nicotyrine	MS	4.20	20.20	μg/cig
Nicotyrine	MS	17.00	41.00	μg/cig
Nicotyrine	SS	49.00	211.00	μg/cig
Nicotyrine	SS	93.00	263.00	μg/cig
Nitrogen dioxide	IA	0.00	0.03	ppm
Nitrogen dioxide	IA	58.00		ppb
Nitrogen dioxide (gas only + people)	IA	0.01	0.03	ppm
Nitrogen dioxide (people absent)	IA	0.00		ppm
Nitrogen dioxide (people present)	IA	0.00		ppm
Nitrogen dioxide control	IA	27.00		ppb
Nitrogen oxide	IA	0.30	0.60	ppm
Nitrogen oxide	IA	0.00	9.00	ppb
Nitrogen oxide (gas only + people)	IA	0.31	0.40	ppm
Nitrogen oxide (people absent)	IA	0.48	0.59	ppm
Nitrogen oxide (people present)	IA	0.30	0.60	ppm
Nitrogen oxide control	IA	5.00		ppb
Nitrogen oxides (combined)	IA	59.00	218.00	ppb
Nitrosoamine, methylethyl-	MS	0.10	9.10	ng/cig
Nitrosoamine, methylethyl-	MS	0.00	1.80	ng/cig
Nitrosoamine, methylethyl-	SS	9.00	75.00	ng/cig
Nitrosoamine, methylethyl-	SS	0.00	27.00	ng/cig
Nitrosoanabasine. *N*'-	SS	15.00	40.00	ng/cig
Nitrosoanatidine, *N*'-	MS	82.00	167.00	ng/cig
Nitrosoanatidine, *N*'-	SS	61.00	220.00	ng/cig
Nitrosodiethylamine	MS	0.00	4.80	ng/cig
Nitrosodiethylamine	SS	8.00	73.00	ng/cig
Nitrosodiethylamine, *N*-	MS	1.80	4.80	ng/cig
Nitrosodiethylamine, *N*-	SS	8.20	73.00	ng/cig
Nitrosodiethylamine (artificial)	IA	0.00	0.01	ng/L
Nitrosodiethylamine (natural conditions)	IA	0.00	0.20	ng/L

Compound	Sample type	Concentration range		
		Low	High	Units
Nitrosodimethylamine	MS	1.70	97.00	ng/cig
Nitrosodimethylamine	MS	0.00	27.00	ng/cig
Nitrosodimethylamine	SS	680.00	1770.00	ng/cig
Nitrosodimethylamine	SS	143.00	415.00	ng/cig
Nitrosodimethylamine	SS	460.00	1880.00	ng/cig
Nitrosodimethylamine, *N*-	MS	1.70	97.00	ng/cig
Nitrosodimethylamine, *N*-	SS	680.00	1040.00	ng/cig
Nitrosodimethylamine (artificial)	IA	0.02	0.15	ng/L
Nitrosodimethylamine (natural conditions)	IA	0.00	0.70	ng/L
Nitrosoethylmethylamine, *N*-	MS	81.00	390.00	ng/cig
Nitrosoethylmethylamine, *N*-	SS	9.40	30.00	ng/cig
Nitrosonornicotine	MS	81.00	390.00	ng/cig
Nitrosonornicotine	SS	110.00	390-00	ng/cig
Nitrosopyrrolidine	MS	2.60	52.00	ng/cig
Nitrosopyrrolidine	MS	1.50	29.00	ng/cig
Nitrosopyrrolidine	SS	204.00	612.00	ng/cig
Nitrosopyrrolidine	SS	28.00	143.00	ng/cig
Nitrosopyrrolidine	SS	80.00	500.00	ng/cig
Nitrosopyrrolidine, *N*-	MS	2.60	51.70	ng/cig
Nitrosopyrrolidine, *N*-	SS	204.00	387.00	ng/cig
Octane (breath smokers)	IA	1.10		$\mu g/m^3$
Octane (breath, nonsmokers)	IA	0.10		$\mu g/m^3$
Octane (homes, nonsmokers)	IA	1.70	3.10	$\mu g/m^3$
Octane (homes, smokers)	IA	1.50	4.70	$\mu g/m^3$
Parvoline	MS	0.00	4.30	µg/cig
Parvoline	SS	10.00	145.00	µg/cig
Pentadien-4-olide, 2,4-	MS	8.00	41.00	µg/cig
Pentadien-4-olide, 2,4-	SS	71.00	256.00	µg/cig
Perylene	IA			Qual (ng/m^3)
Perylene	IA	11.00		ng/m^3
Perylene	IA	0.70	1.30	ng/m^3
Perylene	MS	9.00		ng/cig
Perylene	SS	39.00		ng/cig
Perylene control	IA	2.80	1.70	ng/m^3

Compound	Sample type	Concentration range		Units
		Low	High	
Phenanthrene	IA			Qual (ng/m^3)
Phenanthrene	MS, P	74.80		ng/cig
Phenanthrene	MS, V	2.10		ng/cig
Phenanthrene	SS, P	2149.00		ng/cig
Phenanthrene	SS, V	248.00		ng/cig
Phenol	MS	79.00	136.00	µg/cig
Phenol	MS	77.00	139.00	µg/cig
Phenol	SS	69.00	241.00	µg/cig
Phenol	SS	157.00	289.00	µg/cig
Phenol, 4-vinyl-	MS	18.00	45.00	µg/cig
Phenol, 4-vinyl-	SS	25.00	57.00	µg/cig
Phenols	IA	7.40	11.50	µg/m^3
Phenylacetic acid	MS	18.00	38.00	µg/cig
Phenylacetic acid	Ss	11.(0	30.00	µg/cig
Picoline, 3-	MS	12.00	22.00	µg/cig
Picoline, 3-	SS	90.00	166.00	µg/cig
Picoline, alpha-	MS	12.30	189.00	µg/cig
Picoline, alpha-	SS	128.00	1090.00	µg/cig
Pyran-4-one, 5,6-diOH-3, 5-diOH-2-ME	MS	13.00	153.00	µg/cig
Pyran-4-one, 5,6-diOH-3, 5-diOH-2-ME	SS	0.00	143.00	µg/cig
Pyrazine, 2,3-dimethyl-	SS	0.00	50.00	µg/cig
Pyrazine, 2-methyl-	MS	0.00	8.60	µg/cig
Pyrazine, 2-methyl-	SS	0.00	8.60	µg/cig
Pyrene	IA			Qual (ng/m^3)
Pyrene	IA	66.00		ng/m^3
Pyrene	IA	4.10	9.40	ng/m^3
Pyrene	MS	270.00		ng/cig
Pyrene	MS, P	43.00		ng/cig
Pyrene	MS, V	1.90		ng/cig
Pyrene	SS	1011.00		ng/cig
Pyrene	SS, P	466.00		ng/cig
Pyrene	SS, V	10.30		ng/cig
Pyrene control	IA	2.80	7.00	ng/m^3

Compound	Sample type	Concentration range		Units
		Low	High	
Pyrene, 1-methyl-	IA			Qual (ng/m^3)
Pyrene, 2-methyl-	IA			Qual (ng/m^3)
Pyrene, 4-methyl-	IA			Qual (ng/rn^3)
Pyridine	MS	32.40	648.00	µg/cig
Pyridine	MS	16.00	20.00	µg/cig
Pyridine	SS	336.00	3420.00	µg/cig
Pyridine	SS	187.00	262.00	µg/cig
Pyridine, 2-(3-pentyl)-	MS	0.00	1.50	µg/cig
Pyridine, 2-(3-pentyl)-	SS	0.00	143.00	µg/cig
Pyridine, 2-ethyl-	MS	2.60	35.00	µg/cig
Pyridine, 2-ethyl-	SS	2.60	35.00	µg/cig
Pyridine, 3-acetyl-	MS	3.80	6.40	µg/cig
Pyridine, 3-acetyl-	SS	9.00	11.00	µg/cig
Pyridine, 3-cyano-	SS	24.00	64.00	µg/cig
Pyridine, 3-cyano-	MS	2.40	4.20	µg/cig
Pyridine, 3-ethyl-	MS	4.00	6.00	µg/cig
Pyridine, 3-ethyl-	SS	71.00	960.00	µg/cig
Pyridine, 3-ethyl-	SS	21.00	36.00	µg/cig
Pyridine, 3-ethyl-4-methyl-	SS	6.40	34.00	µg/cig
Pyridine, 3-ethyl-4-methyl-	MS	0.00	1.50	µg/cig
Pyridine, 3-hydroxy-	MS	125.10	211.40	µg/cig
Pyridine, 3-hydroxy-	MS	90.00	119.00	µg/cig
Pyridine, 3-hydroxy-	SS	152.00	167.00	µg/cig
Pyridine, 3-hvdroxv-	SS	157.00	191.00	µg/cig
Pyridine, 4-ethyl	SS	27.00	379.00	µg/cig
Pyridine, 4-i-butvi	MS	0.00	4.50	µg/cig
Pyridine, 4-i-butvi	SS	17.00	287.00	µg/cig
Pyridine, methylvinyl-	MS	2.20	4.10	µg/cig
Pyridine, methylvinyl-	SS	12.00	19.00	µg/cig
Pyrrole	MS	16.00	23.00	µg/cig
Pyrrole	SS	140.00	272.00	µg/cig
Styrene (breath, nonsmokers)	IA	0.30		µg/m^3
Styrene (breath, smokers)	IA	1.10		µg/m^3
Styrene (homes, nonsmokers)	IA	0.80	1.10	µg/m^3
Styrene (homes, smokers)	IA	1.10	2.20	µg/m^3

Compound	Sample type	Concentration range		Units
		Low	High	
Succinic acid	MS	112.00	163.00	µg/cig
Succinic acid	SS	65.00	70.00	µg/cig
Succinic acid, methyl-	MS	4.00	31.00	µg/cig
Succinic acid, methyl-	SS	1.00	13.00	µg/cig
Tar radical sol in *t*-butylbenzene	MS			Qualitative
Tar radical sol in *t*-butylbenzene	SS			Qualitative
Thiocyanate (plasma, nonsmoker)	IA	70.80		µmol/L
Thiocyanate (plasma, passive smoker)	IA	71.80		µmol/L
Thiocyanate (plasma, smoker)	IA	70.70		µmol/L
Thioethers (urine, nonsmoker)	IA	6.00		mmol/mL
Thioethers (urine, passive smoker)	IA	6.40		mmol/mL
Thioethers (urine, smoker)	IA	6.30		mmol/mL
Toluene	IA	0.04	1.04	mg/m^3
Valeric acid, 3-methyl-	MS	20.00	261.00	µg/cig
Valeric acid, 3-methyl-	SS	20.00	384.00	µg/cig
Vinylphenol, *p*-	MS	21.00	51.00	µg/cig
Vinylphenol, *p*-	SS	21.00	45.00	µg/cig
Xylene, *m*- + p- (breath, nonsmokers)	IA	2.10		$µg/m^3$
Xylene, *m*- + *p*- (breath, smokers)	IA	5.50		$µg/m^3$
Xylene, *o*- (breath, nonsmokers)	IA	0.80		$µg/m^3$
Xylene, *m*- + *p*- (homes, nonsmokers)	IA	10.00	13.00	$µg/m^3$
Xylene, *m*- + *p*- (homes, smokers)	IA	10.00	20.00	$µg/m^3$
Xylene, *o*- (breath, smokers)	IA	1.60		$µg/m^3$
Xylene, *o*- (homes, nonsmokers)	IA	4.00	5.20	$µg/m^3$
Xylene, *o*- (homes, smokers)	IA	3.20	7.10	$µg/m^3$
Xylenol, 2,6-	MS	8.00	16.00	µg/cig
Xylenol, 2,6-	SS	8.00	20.00	µg/cig

a Listings are given in alphabetical order by compound and special conditions are noted in parentheses within the column labeled 'Compound'. The sample type is categorized in the second column as IA, indoor air; SS, sidestream smoke; MS, mainstream smoke; P, associated with particulate matter; and V, associated with volatile compounds.

(Claxton *et al*. 1989)

Appendix 2

THE GENOTOXICITY OF COMPOUNDS ASSOCIATED WITH ENVIRONMENTAL TOBACCO SMOKE

Compound	CAS Number	Bioassay Results [a]	
Acetamide	60-35-5	CCC	+
		CT	+
		ST	-
Acetic acid	64-19-7	ST	-
Acrolein	107-02-8	ST	+
Anthracene	120-12-7	CCC	I
		CT	-
		CYC	-
		MNT	-
		ST	-
Benz[*a*]anthracene	56-55-3	CCC	+
		CT	+
		REC	-
		ST	+
		V79	+
Benzene	71-43-2	CCC	+
		CYI	+
		MNT	+
		SCE	-
		TRM	+
Benzo[*a*]pyrene	50-32-8	CCC	+
		CT	+
		CYC	-
		MDR	+
		MNT	+
		MST	+
		SCE	+
		SRL	+
		ST	+
		V79	+
Benzo[*b*]fluoranthene	205-99-2	CCC	+
Benzo[*e*]pyrene	192-97-2	CCC	I
		CT	-
		REC	-
Benzo[*ghi*]perylene	191-24-2	ST	+

Compound	CAS Number	Bioassay Results [a]	
Benzoic acid	65-85-0	ST	-
Butyrolactone, gamma	96-48-0	ST	-
Cresol, *m-, o-,* and *p-*	9548-7	ST	-
Dibenz[*a, j*]anthracene	224-41-9	ST	+
Formaldehyde	50-00-0	ASPD	+
		CCC	+
		MDR	+
		NEU	+
		REC	+
		SRL	+
		ST	+
Hydrazine	302-01-2	CCC	+
		ST	+
Hydroquinone	123-31-9	ALC	+
		ST	-
Indeno[1, 2, 3-*cd*]pyrene	193-39-5	CCC	+
Isoquinoline	119-65-3	ST	-
Limonene	5989-27-5	ST	-
Naphthalene	91-20-3	ST	-
Nicotine	54-11-5	NEU	-
		ST	-
Nitrosodiethylamme, *N*′-	55-18-5	CCC	+
		CT	+
		CYC	+
		L5	+
		MDR	+
		MST	-
		REC	+
		SCE	+
		ST	+
		V79	+
Nitrosodimethylamine, *N*′-	62-75-9	ARA	+
		CCC	+
		CT	+
		CYG	+
		CYG	-
		L5	+
		MNT	+/-

Compound	CAS Number	Bioassay Results [a]	
		MST	-
		NEU	+
		SCE	+
		SRL	+
		ST	+
		V79	+
		YEA	+
Nitrosonornicotine	16543-55-8	CCC	+
Nitrosopyrrolidine	930-55-2	CCC	+
Perylene	198-55-0	SCE	-
Phenanthrene	85-01-8	ALC	+
		CCC	I
		CT	-
		CYC	-
		ST	-
Phenol	108-95-2	NEU	-
Pyrene	129-00-0	CCC	I
		CT	-
		CYC	-
		ST	-
		V79	-
Pyridine	110-86-1	SCE	+
		ST	-
Toluene	108-88-3	SCE	-
		ST	-

[a] Bioassay information is extracted from Graedel *et al*. (1986) as cited by Claxton *et al*. (1989).

Abbreviations used for bioassay results are as follows: ALC, Allium cytogenetics assays; ARA, Arabidopsis mutagen assay; ASPH, Aspergillus mutagen assay; CCC, whole animal carcinogen assays; CT, cell transformation bioassays; CY, mammalian cytogenetic bioassays; L5, L5178Y mouse lymphoma assay; MDR, manunalian cell DNA repair assays; NINT, micronucleus assays; MST, mouse spot test; NEU, Neurospora assays; REC, DNA repair-deficient bacterial assays; SCE, sister-chromatid exchange assays; SRL, sex-linked recessive lethal assays in Drosophila; ST, Salmonella assays; TRM, Tradescantia mutagen assays; V79, V79 Chinese hamster mutation assays; and YEA, Yeast mutation tests. Results are recorded as +, positive; -, negative; and I, Indefinite.

FINAL

Report on Carcinogens
Background Document for

Environmental Tobacco Smoke

Appendix 3A – IARC (1986)
Vol. 38. Evaluation of the carcinogenic risk of chemicals to humans – Tobacco Smoking Epidemiology Studies of Cancer in Humans pp. 199-375

Appendix 3B – U.S.EPA (1992)
Respiratory health effects of passive smoking: lung cancer and other disorders. EPA/600/6-90/006F Chapter 5: Hazard Identification II: Interpretation of Epidemiologic Studies on Environmental Tobacco Smoke and Lung Cancer

Appendix A Table 4-10
Study scores for tier assignments

Appendix 3C – California EPA (1997)
Health Effects of Exposure of Environmental Tobacco Smoke.
Chapter 7: Carcinogenic Effects

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Appendix 3A – IARC (1986)
Vol. 38. Evaluation of the carcinogenic risk of chemicals to humans – Tobacco Smoking Epidemiology Studies of Cancer in Humans pp. 199-375

Appendix 3B – U.S.EPA (1992)
Respiratory health effects of passive smoking: lung cancer and other disorders. EPA/600/6-90/006F Chapter 5: Hazard Identification II: Interpretation of Epidemiologic Studies on Environmental Tobacco Smoke and Lung Cancer Report Appendix A Table 4-10. Study scores for tier assignments

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