5. HAZARD IDENTIFICATION II: INTERPRETATION OF EPIDEMIOLOGIC STUDIES ON ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

5.1. INTRODUCTION

The Centers for Disease Control attributed 434,000 U.S. deaths in 1988 to smoking (CDC, 1991a). Major disease groups related to smoking mortality include lung cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke, with smoking accountable for an estimated 87%, 82%, 21%, and 18% of total deaths, respectively. Lung cancer alone accounted for about 25% to 30% of the total smoking mortality, with some 100,000 deaths. The age-standardized annual lung cancer mortality rates for 1985 are estimated at 12 per 100,000 for females and 15 per 100,000 for males who never smoked but 130 per 100,000 for female cigarette smokers and 268 per 100,000 for male cigarette smokers, a relative risk of 10.8 and 17.4, respectively (Garfinkel and Silverberg, 1991).

Chapter 4 discusses the biological plausibility that passive smoking also may be a risk factor for lung cancer because of the qualitative similarity of the chemical constituency of sidestream smoke, the principal source of environmental tobacco smoke (ETS), and mainstream smoke taken in during the act of "puffing" on a cigarette, and because of the apparent nonthreshold nature of the dose-response relationship observed between active smoking and lung cancer. Although the relative risk of lung cancer from passive smoking would undoubtedly be much smaller than that for active smoking, the ubiquity of ETS exposure (Chapter 3) makes potential health risks worth investigating.

This chapter analyzes the data from the large number of epidemiologic studies on ETS and lung cancer that contain data on the effects of ETS on never-smoking women. Although some of the studies involve male nonsmokers and former smokers of both sexes, the female never-smokers comprise the large majority of the database--more than 3,000 cases and 6,000 controls in the 27 case-control studies and almost 300,000 female never-smokers followed in the 4 cohort studies. Whenever study data are separated by sex and smoking status, women never-smoker results are used. The use of a more homogeneous group allows more confidence in the results of combined study analyses. All of the studies used provide data on adult home exposure to ETS. Some also provide information on childhood and/or workplace exposure, but there is far less information on these exposures; therefore, in order to develop one large database for analysis, only the female exposures from spousal smoking are considered. The exposure surrogate used is a report of the husband's smoking status. Wherever a measure of the amount of exposure to husband's smoking is available, additional analyses are performed to examine effects in the highest exposure groups (Section 5.3.3.2) and dose-response relationships (Section 5.3.3.3). Virtually all of the 31 studies available classify never-smoking women as "exposed" or "unexposed" to ETS based on self- or proxy-reported smoking in the subject's environment, usually according to whether or not a woman is married to a smoker. In addition, 17 studies provide sufficient information for highest exposure group and exposure-response analyses. Other analyses of the data include adjusting for the potential upward bias of smoker misclassification (Section 5.2.2); examining confounders, effect modifiers, and

sources of potential bias (Section 5.4); and pooling qualitatively higher ranked studies (Section 5.5). It is hoped that by analyzing the data in several different ways, a clear picture will emerge (Section 5.6).

Throughout this chapter, one-tailed tests of significance ($p = 0.05$) are used, which increases the statistical ability (power) to detect an effect. The 90% confidence intervals used for the analyses performed are consistent with the use of the one-tailed test. The justification for this usage is based on the *a priori* hypothesis (from the plausibility of a lung cancer effect documented in Chapters 3 and 4) that a positive association exists between exposure to ETS and lung cancer.

Epidemiologic evidence of an association between passive smoking and lung cancer first appeared 10 years ago in a prospective cohort study in Japan (Hirayama, 1981a) and a case-control study in Greece (Trichopoulos et al., 1983). Both studies concluded that the lung cancer incidence and mortality in nonsmoking women was higher for women married to smokers than for those married to nonsmokers. Although there are other sources of exposure to ETS, particularly outside the home, the assumption is that women married to smokers are exposed to more tobacco smoke, on average, than women married to nonsmokers. These two studies, particularly the cohort study from Japan, evoked considerable critical response. They also aroused the interest of public health epidemiologists, who initiated additional studies.

At the request of two Federal agencies--the U.S. Environmental Protection Agency (Office of Air and Radiation) and the U.S. Department of Health and Human Services (Office of Smoking and Health)--the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses of the evidence from 10 case-control and 3 cohort (prospective) studies. It concludes, "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

The NRC committee was particularly concerned about the potential bias in the study results caused by the fact that current and former smokers may have incorrectly reported themselves as lifelong nonsmokers (never-smokers). Using reasonable assumptions for misreported smoking habits, the committee determined that a plausible range for the true relative risk is 1.15 to 1.35, with 1.25 the most likely value. When these relative risks also are corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a plausible range of 1.24 to 1.61.

Two other major reports on passive smoking have appeared: the Surgeon General's report on the health consequences of passive smoking (U.S. DHHS, 1986) and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987a). The Surgeon General's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in

> some populations with exposures to ETS lead to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. Included in the 1987 IARC report is a citation from the summary statement on passive smoking of a previous IARC report that the epidemiologic evidence available at that time (1985) was compatible with either the presence or absence of lung cancer risk. Based on other considerations related to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report (IARC, 1986) states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of cancer.

In the years since those reports, the number of studies available for analysis has more than doubled. There are now 31 epidemiologic studies available from eight different countries, listed in Table 5-1

Table 5-1. Epidemiologic studies on ETS and lung cancer in this report and tier ranking

Study	Tier[1]	Country	Within country	References
AKIB	2	Japan	Hiroshima	Akiba et al. (1986)
BROW	3	United States	Colorado	Brownson et al. (1987)
BUFF	3	United States	Texas	Buffler et al. (1984)
CHAN	4	Hong Kong		Chan and Fung (1982)
CORR	2	United States	Louisiana	Correa et al. (1983)
FONT	1	United States	Five metro areas	Fontham et al. (1991)
GAO	3	China	Shanghai	Gao et al. (1987)
GARF	2	United States	New Jersey, Ohio	Garfinkel et al. (1985)
GENG	4	China	Tianjin	Geng et al. (1988)
HUMB	2	United States	New Mexico	Humble et al. (1987)
INOU	4	Japan	Kanajawa	Inoue and Hirayama (1988)
JANE	2	United States	New York	Janerich et al. (1990)
KABA	2	United States	New York	Kabat and Wynder (1984)
KALA	1	Greece	Athens	Kalandidi et al. (1990)
KATA[2]		Japan		Katada et al. (1988)
KOO	1	Hong Kong		Koo et al. (1987)
LAMT	2	Hong Kong		Lam et al. (1987)
LAMW	3	Hong Kong		Lam (1985)
LEE	2	England		Lee et al. (1986)
LIU	4	China	Xuanwei	Liu et al. (1991)
PERS	1	Sweden		Pershagen et al. (1987)
SHIM	2	Japan	Nagoya	Shimizu et al. (1988)
SOBU	2	Japan	Osaka	Sobue (1990)
SVEN	2	Sweden	Stockholm	Svenson et al. (1989)

Table 5-1. (continued)

Study	Tier	Country	Within country	References
TRIC	3	Greece	Athens	Trichopoulos et al. (1981, 1983)
WU	2	United States	California	Wu et al. (1985)
WUWI	4	China		Wu-Williams and Samet (1990)
BUTL(Coh)	2	United States	California	Butler (1988)
GARF(Coh)	3	United States		Garfinkel (1981)
HIRA(Coh)	2	Japan		Hirayama (1984)
HOLE(Coh)	1	Scotland	Paisley Renfrew	Hole et al. (1989)

[1]Tier rankings refer to this report's ratings of studies for utility of studying the association of ETS and lung cancer, where "1" is highest (see Section 5.5 and Section A.3).
[2]KATA has no tier number because the odds ratio cannot be calculated.

. Twenty-seven studies employ case-control designs, denoted by the first four letters of the first author's name for convenient reference, and four are prospective cohort studies, distinguished by the designation "(Coh)." Six case-control studies, FONT (USA), JANE (USA), KALA (Greece), LIU (China), SOBU (Japan), and WUWI (China), have been published as recently as 1990. The small cohort study from Scotland (Gillis et al., 1984) has been updated and is now included under the name HOLE(Coh); another small cohort study on Seventh-Day Adventists in the United States, an unpublished dissertation, is included as BUTL(Coh). The abstracts for a second case-control study by Kabat and Wynder and a new one by Stockwell and colleagues are included in Section A.4, but insufficient information is available to include their results.

Because of coincidental timing, the 1986 reports of the Surgeon General and the NRC review approximately the same epidemiologic studies. More specifically, the NRC report includes nine of the studies shown in Table 5-1: AKIB, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC; WU was available but not included because the crude data were not reported. (Crude data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excluded an earlier version of the KOO study and the studies by Knoth et al. (1983) (no reference population was given), Miller (1984) (did not report on lung cancers separately), and Sandler et al. (1985) (included very few lung cancers). Aside from WU, these studies also are omitted from this report for the same reasons.

Tables 5-2

Table 5-2. Studies by location, time, size, and ETS exposure

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
Greece	KALA	1987-89	90	116	71	60
Greece	TRIC	1978-80	40	149	73	52
Hong Kong	CHAN	1976-77	84	139	60	53
Hong Kong	KOO	1981-83	86	136	59	49
Hong Kong	LAMT	1983-86	199	335	58	45
Hong Kong	LAMW	1981-84	60[4]	144[4]	62[4]	44[4]
Japan	AKIB	1971-80	94	270	78	70
Japan	HIRA(Coh)	1965-81	S)Q91,540	S)Q	S)))Q76	))))Q
Japan	INOU	1973-83	22	47	82	64
Japan	SHIM	1982-85	90	163	58	56
Japan	SOBU	1986-88	144	731	56	54
USA	BROW	1979-82	19	47	21	15
USA	BUFF	1976-80	41	196	80	84
USA	BUTL(Coh)	1976-82	S)Q9,207[5]	S)Q	S)))Q34[5]	S)))Q
USA	CORR	1979-82	22	133	64	46
USA	FONT	1985-88	420	780[6]	70	63[6]
USA	GARF	1971-81	134	402	67	61
USA	GARF(Coh)	1959-72	S)Q176,739	SQ	S)))Q72	S)))Q
USA	HUMB	1980-84	20	162	75	56
USA	JANE	1982-84	191	191	*[7]	60[7]
USA	KABA	1961-80	24	25	54	60
USA	WU	1981-82	29[8]	62[8]	*	*
W. Europe						
Scotland	HOLE(Coh)	1972-85	S)Q1,784	S)Q	S)))Q73	S)))Q
England	LEE	1979-82	32	66	69	68

Table 5-2. (continued)

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
W. Europe (continued)						
Sweden	PERS	1961-80	67	*	49	*
Sweden	SVEN	1983-85	34	174	71	66
China	GAO	1984-86	246	375	77	74
China	GENG	1983	54	93	63	44
China	LIU	1985-86	54	202	83	87
China	WUWI	1985-87	417	602	49	55

[1]Time during which cases occurred.
[2]Number of subjects included in ETS analyses; where numbers differ for spousal smoking and other exposures, those for spousal smoking are given.
[3]Spousal smoking unless otherwise noted.
[4]Adenocarcinoma only. Data for all cell types were available only for general passive smoke exposure, which showed 77% of 75 cases and 56% of 144 controls exposed.
[5]Figure pertains to "spouse pairs" cohort, which is of principal interest regarding ETS; a subgroup of this cohort comprised the "ASHMOG" cohort.
[6]Figure is for population controls; study also included 351 colon cancer controls (66% exposed).
[7]ORs but no exposure prevalences are presented for spousal smoking in the source. The value shown for controls is taken from KABA, as closest to JANE in time and location; no exposure percentage is assumed for cases.
[8]Adenocarcinoma only. Analyses for other cell types included smokers while adjusting for smoking status.

*Data not available.

Table 5-3. (continued) Selected characteristics of the individual ETS studies included in this report. The

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
ARBA	0	0	60.8	63.9	Hospitalized	Age (± 5), sex,	No[5]
ARIB	90	88	70.2	*	Atomic bomb survivor population	residence, marital status, med. subject[3]	
			35-95				
BAL	0	0	≤76	≤76	Orthopedic patients	Age (± 5), sex,	No[5]
BROW	69	39	66.3	68.2	Cancer cases[4]	Age, sex	No[5]
BUFF	82	76	36-79	35-79	Cancer cases[6]	Age (± 5), sex	No[5]
CHAN	*	*	39-70	39-70	Orthopedic patients	Matched but	No[5]
KOO	0	0	*	*	"Healthy"[12]	Age (± 5), residence, unspecified housing	No[5]
CORR	*	*	*	*	Hospital patients[7]	Age (± 5), sex,	No[5]
LAMT	0	0	*	*	"Healthy"[13]	Age (± 5),	No[5]
FONT	34	10[8]	20-79	20-79	Cancer cases[9]	Age, (for cancer	Yes
NAMW	*	*	67.5	66	Hospitalized	Age, smoking	No[5]
GAO	0	*	35-69	35-69	General population	Age (± 5), residence[14]	No[5]
LEE	38[15]	38	35-74	35-74	Patients[16]	Age, sex,	No[5,17]
LARE	38	*	≥40	≥40	Cancer cases[9]	Age (± 5), hospital, hospital location, time of	Yes
GENG	0	0	≤65	≤65	*	Age (± 2), sex,	No[5]
LIU	0	0	52	52	General population?	Age (± 2), sex, village	Yes
HUMB	*	*	≤85	≤85	General population	Age (± 10), sex, ethnicity	No[5]
PERS	*[18]	*	*[19]	*	*[20]	Age (± 1), sex	Yes
SHIM	0	0	59	58	Patients[21]	Age (± 1),	No[5]
			35-81	35-81			Yes
JANE	33[10]	33[10]	67.1[10]	68.1[10]	New York State	Age, sex,	Yes
SOBR	0	0	60	56	Patients	None	No
SVEN	0	0	66.3		Dept. of Motor Vehicles	Age, smoking history	No[5]
					population		

[1]"Ca" and "Co" stand for "cases" and "controls," respectively.
[2]Single values are the average or median. Paired values are the range.
[3]Participation in RERF biennial medical examination program.
[4]Persons with cancers of bone marrow or 20-79 in Colorado Central Cancer Registry.
[5]Not matched on personal smoking status (e.g., smoker/nonsmoker).
[6]Population-based and decedent comparison subjects selected from hospital and Federal records.
[7]Assorted ailments.
[8]0% for general population and 10% for colon cancer controls.
[9]Colorectal cancer.
[10]Includes males and females and long-term ex-smokers.
[11]Diseases not related to smoking.
[12]Selected from a healthy population.
[13]Living in neighborhood of matched case.
[14]"Similar" but not actually matched.
[15]Applies only to the 143 patients in the followup study.
[16]Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[17]Ongoing study modified for passive smoking.
[18]Not overall percentages given.
[19]Two control groups: 15 to 65 and 35 to 85 for both cases and controls, respectively.
[20]Two control groups were randomly chosen from the cohort under study.
[21]Patients in the same or adjacent wards with other diseases.
[22]Entire study population, including smokers.
[23]Frequency matched by 5-year age group to age distribution of cases reported in study area 2 years prior to initiation of study.

*Data not available.

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studies are grouped by country in Table 5-2, which indicates the time period of data collection in each study, sample size, and prevalence of ETS exposure for each study. The geographical distribution of the current epidemiologic evidence is diverse. By country, the number of studies and its percentage of the total number of studies over all countries is as follows: China (4, 13%), England (1, 3%), Greece (2, 6%), Hong Kong (4, 13%), Japan (6, 19%), Scotland (1, 3%), Sweden (2, 6%), and United States (11, 35%). (One of the

studies from Japan, KATA, does not appear in most of the tables because the odds ratio cannot be calculated.) The studies differ by size, however, which has to be taken into account in analysis. There are two large cohort studies, GARF(Coh) and HIRA(Coh), conducted in the United States and Japan, respectively, and two very small ones, BUTL(Coh) and HOLE(Coh), from the United States and Scotland, respectively. There are two exceptionally large case-control studies--FONT and WUWI of the United States and China; the first was designed specifically to assess the association between ETS and lung cancer, whereas the second has broader exploratory objectives.

The accrual periods of the case-control studies are typically 2 to 4 years in length (exceptions with longer periods are AKIB [9 years], INOU [10 years], GARF [10 years], KABA [19 years], and PERS [9 years]) and occur between the early 1970s and late 1980s (exceptions are KABA [1961-1980] and PERS [1961-1980]). The two large cohort studies were conducted relatively early (GARF(Coh), 1959-72; HIRA(Coh), 1965-81). Differences in study duration or accrual period should not be consequential for hazard identification, which is the topic addressed in this chapter, but both factors affect the estimation of population risk (Chapter 6). Earlier study results are more uncertain for projection of current risk, and parameter values used for modeling are more uncertain when based on extended study periods. Table 5-2 also demonstrates variability across studies in the percentages of cases and controls classified as exposed to ETS. For example, at the extremes for U.S. studies alone, BUFF and BROW classify 84% and 15% of controls as exposed to ETS, respectively. Statistical variability and differences across subpopulations sampled are partially explanatory, but a major factor is differences between researchers' criteria for classification of subjects as exposed to ETS. This issue affects study comparability and observed values of relative risks, which affect both hazard identification and characterization of population risk.

Another example of a study feature of broad consequences in both case-control and cohort studies is the method of diagnosis or confirmation of lung cancer and exclusion of secondary lung cancers in subjects classified as having lung cancer, as shown in Table 5-4

Table 5-4. Diagnosis, confirmation, and exclusion of lung cancer cases

	Diagnosis/Confirmation (%)[1]					
Study	Histology		Cytology	Radio./ clinical	Other/ unspec.	Excluded secondary LC[2]
AKIB[3]	53		4	43	0	Y
BROW	S)))) Q	100	S)))) Q			Y
BUFF[3,4]	S)))) Q	100	S)))) Q			Y
CHAN[3,4]	82				18	N
CORR[3]	97				3	Y
FONT	100					Y
GAO[3,5]	43		38	19	10	Y
GARF[5]	100					Y
GENG[3]	85			4	11	N
HUMB[6,7]	S)))) Q	83	S)))) Q		17	Y
INOU	*		*	*	*	N
JANE[3]	99			1		Y
KABA	100					Y
KALA	48		38		14	Y
KATA	100					N
KOO	94				6	Y
LAMT	S)))) Q	100	S)))) Q			Y
LAMW	S)))) Q	100	S)))) Q			Y
LEE	*		*	*	*	N
LIU[8]	S)))) Q	17	S)))) Q	83	0	N
PERS	83		16		1	Y
SHIM	100					Y
SOBU	100					Y
SVEN[3]	70		29		1	Y
TRIC[3]	28		37	35		N
WU	100					Y
WUWI[3]	42		32	26		Y
BUTL(Coh)[9]		100				Y
GARF(Coh)	*		*	*		N

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Table 5-4. (continued)

Study	Diagnosis/Confirmation (%)[1]				
	Histology	Cytology	Radio./ clinical	Other/ unspec.	Excluded secondary LC[2]
HIRA(Coh)	*	*	*		N
HOLE(Coh)[10]	*	*	*		N

[1]Figures apply to confirmation of original diagnosis when conducted.
[2]Y (for "yes") if specifically indicated; otherwise, N (for "no").
[3]Not restricted to never-smokers (contains former smokers or ever-smokers).
[4]Inconsistency in article. May be 100% histology.
[5]Diagnostic information was reviewed for study.
[6]Includes males.
[7]Available histologic specimens (17 cases) reviewed by pathologists. Poor agreement between review diagnoses and original cancer registry diagnoses (8 of 17 cases). Only reviewed cases, however, are presented in article.
[8]Includes male ever- and never-smokers and one female ever-smoker (control).
[9]Includes one former smoker.
[10]Death certificate diagnosis checked against Scottish cancer registry records.

*Data not available.

. Accurate classification of subjects vis-a-vis the presence or absence of primary lung cancer is essential to the validity of results; inaccurate classification can reduce the chance of detecting a positive association between ETS exposure and lung cancer, if it exists, by biasing the observed relative risk toward unity. (*Note*: "Relative risk" is used to mean the estimate of the true [but unknown]
relative risk. For case-control studies, the estimate used is the odds ratio. For editorial convenience, "relative risk" is used for both case-control and cohort studies.)

The large majority of the studies (27 of 31 total) are of the case-control type, which are subject to more potential sources of bias than the cohort studies (see discussion in Section 5.4.1).

To continue the overview depicting some basic similarities and differences between studies that may affect analysis of their results, some additional characteristics of the case-control studies alone are summarized in Table 5-3. The percentage of proxy response is high for some studies, but there is little basis for assessing the direction or magnitude of potential bias from this source. The age range of subjects differs across studies, but there is insufficient information on age distributions within studies to evaluate the effect of age or to adjust for differences between studies. The source of control subjects is a potential source of bias in some studies.

The table heading "ETS sample matched" refers to whether design matching applies to the ETS subjects (the never-smokers used for ETS/lung cancer analysis). As indicated under "matched variables," controls are virtually always matched (or at least similar) to cases on age and usually on several other variables as well that the researcher suspects may affect comparability of cases and controls. The matching often refers to a larger data set than the ETS subjects only, however, because many studies included smokers and investigated a number of issues in addition to whether passive smoking is associated with lung cancer. When the data on ETS subjects are extracted from the larger data set, matching is not retained unless smoking status was one of the matching variables.

Although matching is commonly used as a method to reduce potential confounding, effective techniques also may be implemented during analysis of the data (e.g., the use of poststratification or logistic regression adjustment for unmatched, stratified, or frequency-matched samples). Use of a method of analysis that adjusts for known or suspected confounders and factors that may interact with ETS exposure to affect risk of lung cancer is particularly important for studies that are not designated as "ETS sample matched" in Table 5-3. Even with matched data, a method of analysis that controls for confounding, such as the use of matched pairs or regression techniques, is preferable. In fact, Breslow and Day (1980, p. 32) describe the main purpose of matching in a case-control study as permitting use of efficient analytical methods to control confounding by the factors used for matching.

The analysis for hazard identification in this report follows two approaches. The first approach (Section 5.3) treats all studies equally, i.e., statistical methods are applied to all studies without regard to differences in study utility for the task of hazard identification. Differences in study size, of course, are taken into account by the statistical methods. Statistical inference includes estimation, with confidence intervals, and hypothesis testing for an effect (an increased relative risk in ETS-exposed subjects) and for an upward trend (an increase in relative risk as some measure of ETS exposure increases). The second approach (Section 5.5) is motivated by the heterogeneity of the study evidence, as described above. Study size aside, some studies have higher utility than others for assessing questions related to ETS and lung cancer and thus should be given more weight. To implement this extended data interpretation, all studies are first reviewed individually for sources of bias and confounding that might affect interpretation of results for assessing ETS and lung cancer and then assigned a tier number from 1 to 4 accordingly. Tier 1 contains those studies of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. (*Note:* Study utility does not mean study quality. Utility is evaluated with respect to the research objectives *of this report*, while the objectives of individual studies often differ.) Pooled estimates of relative risk by country are then recalculated by tiers, beginning

with the studies of highest utility (Tier 1) and adding studies from Tiers 2, 3, and 4 successively to see what effect a judgment of utility has on the overall outcome in each country. The criteria used in evaluating studies and the procedure for assigning them to tiers are described in Appendix A, which also contains the individual study reviews.

The selection of the most appropriate relative risk estimate to be used from each study is addressed in Section 5.2.1. In Section 5.2.2, each chosen relative risk estimate is adjusted downward to account for bias expected from some smokers misrepresenting themselves as nonsmokers. This topic has been a contentious issue in the literature for several years, with claims that this one source of systematic upward bias may account entirely for the excess risk observed in epidemiologic studies. Recent detailed investigation of this topic by Wells and Stewart (unpublished) make that claim unlikely (Appendix B). They found that a reasonable correction for bias, calculated on a study-by-study basis, is positive but small. Following this methodology, this report makes reductions in the relative risk estimates at the outset for each study individually before statistical inference or pooling estimates from studies of the same country. This is in contrast to the NRC report (1986), which makes the same downward adjustment to all studies (applied to an overall estimate of relative risk obtained after pooling all study estimates).

The estimates adjusted for smoker misclassification bias are the basis for statistical inference in Sections 5.3 (without regard to tier classification) and 5.5 (analysis by tier classification). Section 5.4 reviews the study results on potential modifying factors. Conclusions are then drawn for hazard identification (i.e., whether ETS is causally associated with increased lung cancer mortality) based on the total weight of evidence. Chapter 6 of this report addresses the upward adjustment on the U.S. relative risk estimate for background ETS exposures and the U.S. population risk of lung cancer from ETS.

5.2. RELATIVE RISKS USED IN STATISTICAL INFERENCE

5.2.1. Selection of Relative Risks

Two considerations largely affect the choice of relative risk (RR): (1) whether other relevant cofactors are taken into account (namely, potential confounders and risk modifiers that may be correlated with ETS exposure), and (2) the source and place of ETS exposure used. The alternatives (not yet adjusted for smoker misclassification) are shown by study in Tables 5-5

Table 5-5. Estimated relative risk of lung cancer from spousal ETS by epidemiologic study (crude and adjusted for cofactors)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
AKIB	1.52 (0.96, 2.41)	**1.5** **(1.0, 2.5)**
BROW	**1.52[4]** **(0.49, 4.79)** 1.82[4,5] (0.45, 7.36)[6]	* 1.68[4,5] (0.39, 6.90)[6]
BUFF	**0.81[7]** **(0.39, 1.66)**	*
CHAN	**0.75[5]** (0.48, 1.19)	*
CORR	**2.07[8]** **(0.94, 4.52)**	*
FONT[9]	1.37 (1.10, 1.69) 1.21 (0.94, 1.56) 1.32 (1.08, 1.61)	**1.29** **(1.03, 1.62)** 1.28 (0.98, 1.66) *
GAO	**1.19** **(0.87, 1.63)**	1.34[10,11]
GARF	**1.31** **(0.93, 1.85)**	1.70[12] (0.98, 2.94)[6]
GENG	**2.16** **(1.21, 3.84)**	*
HIRA[13]	**1.53[10]** **(1.10, 2.13)**	1.64[10] *
HUMB	2.34 (0.96, 5.69)	**2.2** **(0.9, 5.5)**
INOU	**2.55[14]** **(0.90, 7.20)**	2.54[10,15] *
JANE	**0.86** **(0.57, 1.29)**	0.93/0.44[16]

(continued on the following page)

Table 5-5. (continued)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
KABA[17]	**0.79** **(0.30, 2.04)**	*
KALA	1.62[18] (0.99, 2.65) 1.41 (0.78, 2.55)	**1.92** **(1.02, 3.59)[6]** *****
KATA	*[19]	*
KOO	**1.55** **(0.98, 2.44)**	1.64
LAMT	**1.65** **(1.22, 2.22)**	*
LAMW	**2.51[20]** **(1.49, 4.23)**	*
LEE	**1.03** **(0.48, 2.20)**	0.75/1.60[21]
LIU	0.74 (0.37, 1.48)	**0.77** **(0.35, 1.68)**
PERS	1.28 (0.82, 1.98)	**1.2** **(0.7, 2.1)[6]**
SHIM	**1.08[22]** **(0.70, 1.68)**	*
SOBU	1.06[18] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[18] (0.78, 1.63)[6] **1.57** **(1.07, 2.31)[6]**
SVEN	**1.26[5]** **(0.65, 2.48)**	1.4[5]
TRIC	**2.08[23]** **(1.31, 3.29)**	*
WU	**1.41[24]** **(0.63, 3.15)**	1.2 (0.6, 2.5)[6]
WUWI	**0.79** **(0.64, 0.98)**	0.7

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Table 5-5. (continued)

Case-control	Never-smokers Crude RR[1,2]	Never-smokers Adj. RR[1,2,3]
BUTL(Coh)	2.45[25]	**2.02 (0.48, 8.56)[6]**
GARF(Coh)	*	**1.17[10] (0.85, 1.61)[6]**
HIRA(Coh)	**1.38 (1.03, 1.87)**	1.61 *
HOLE(Coh)[26]	2.27 (0.40, 12.7)	**1.99 (0.24, 16.7)[6]**

[1]Parentheses contain 90% confidence limits, unless noted otherwise. When not represented in the original studies, the crude ORs and their confidence limits were calculated (or verified) by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. Odds ratios are shown for case-control studies; relative risks are shown for cohort studies.
[2]ORs for never-smokers apply to exposure from spousal smoking, unless indicated otherwise.
[3]Calculated by a statistical method that adjusts for other factors (see Table 5-3), but not corrected for smoker misclassification.
[4]Adenocarcinoma only. Data for crude OR values communicated from author (Brownson).
[5]Exposure at home and/or at work.
[6]95% confidence interval.
[7]Exposure to regularly smoking household member(s). Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.
[8]Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.
[9]The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15-0.18.
[10]Composite measure formed from categorical data at different exposure levels.
[11]For GAO, data are given as (number of years lived with a smoker, adjusted odds ratio [OR]): (<20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).
[12]Estimate for husband smoking 20 cig./day.
[13]Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study. This case-control study is not counted in any summary results where HIRA(Coh) is included.
[14]OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.
[15]For INOU, data are given as (number of cig./day smoked by husband, adj. OR): (<19, 1.58), (20+, 3.09).
[16]From subject responses/from proxy responses.

(continued on the following page)

Table 5-5. (continued)

[17]For second KABA study (see addendum in study description of KABA in Appendix A), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.
[18]For the first value, "ETS-exposed" means the spouse smokes; for the second value, "ETS-exposed" means a member of the household other than the spouse smokes.
[19]OR is not defined because number of unexposed subjects is zero for cases or controls.
[20]Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).
[21]From subject responses/from spouse responses.
[22]From crude data, estimated to be: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.
[23]Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).
[24]Raw data for WU are from Table 11 of Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.
[25]RR is based on person-years of exposure to spousal smoking. "Prevalence" in those units is 20%.
[26]RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adjusted RR is 1.39 (95% C.I. = 0.29, 6.61).

*Data not available.

and 5-6

Table 5-6. Effect of statistical adjustments for cofactors on risk estimates for passive smoking[1]

Case-control study	Exposure Source[2]	Exposure Place[3]	Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
AKIB	Sp	A	1.52	**1.5**	A,L,O,V	LR
BROW	Sp	A	**1.52**	*	*	*
	A	P	1.82	1.68	A,I,O	LR
BUFF	Co	H	**0.81**	*	*	*
CHAN	A	A	**0.75**	*	*	*
CORR	Sp	A	**2.07**[7]	*	*	*
	M(C)	A	1.66[7]	1.36[7]	Sm	R
FONT	Sp	A	1.37[8]	**1.29**[8]	A,E,I,L,R	LR
	Sp	A	1.21[9]	1.28[9]	A,E,I,L,R	LR
GAO	Sp	A	**1.19**	1.34[10]	A,E	R
	A	A	*	0.9	A	LR
GARF	Sp	H	**1.31**	1.70	A,SES,H,Yd	R
GENG	Sp	A	**2.16**	*	*	*
HIRA	Sp	A	**1.53**[10]	1.64[10]	A,F,Oh,	S
	Sp	A	1.53	1.50	F	S
HUMB	Sp	A	2.34	**2.2**	A,R	R
INOU	Sp	A	**2.55**	2.54[10]	A	S
JANE	Sp	A	**0.86**	0.93/0.44[11]	A,L,R	M,S
	A(C)	H	*	1.09/2.07[12]	A,R	
KABA	Sp	A	**0.79**	*	*	*
KALA	Sp	A	1.62	**1.92**	A,E,Ir	LR
	OC	H	1.41	*	*	*
KOO	Sp	A	**1.55**	1.64	A,E,B,Yc	LR
	Co	H	1.34	1.68	A,E,B,Yc	LR
LAMT	Sp	A	**1.65**	*	*	*

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Table 5-6. (continued)

Case-control study	Exposure Source[2]	Exposure Place[3]	Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
LAMW	Sp	*	2.01[13]	*	*	*
	A	*	**2.51**[14]	*	*	*
LEE	Sp	A	1.3[15]	1.60[15]	A	S
			0.75	0.75		
			[**1.03**	1.00]		
	Co	H	0.80	0.87[10]	A	S
LIU	Co	A	0.74	**0.77**	C	LR
PERS	Sp	A	1.28	**1.2**	A,V	M
	Sp	A	1.28	1.47[10]	A	S
SHIM	Sp	H	**1.08**	*	*	*
SOBU	Sp	A	1.06	1.13	A,E	S
	OC	A	1.77	**1.57**	A,E	S
SVEN	A	H,W	1.1/1.8[16]	1.2/2.1[16]	A	S
			(1.26)	(1.4)		
TRIC	Sp	A	**2.08**	*	*	*
WU	Sp	A	**1.41**[17]	1.2	A,L	M
					As	LR
WUWI	Sp	P	**0.79**	0.7	A,E,L	LR
	Co	P	0.78	0.7	A,E,L	LR
BUTL (Coh)	Sp	A	2.45	**2.02**	A	S
GARF (Coh)	Sp	A	*	1.27/1.10[18]	A	S
				1.17	A,E,L,R,Oh	S
				1.37/1.04[18]		
HIRA (Coh)	Sp	A	**1.38**	1.61	Ah	S
HOLE (Coh)	Co	A	2.27	**1.99**	A,SES	S

[1]Values used for inference in this report are shown in boldface.
[2]Source: A = anyone; (C) = childhood; Co = cohabitant(s); M = mother; OC = cohabitant(s) other than spouse; Sp = spouse.
[3]Place: A = anywhere; H = home/household; P = proximity of subjects; W = workplace.
[4]OR for case-control studies; RR for cohort studies.

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Table 5-6. (continued)

[5]Adjustment factors: A = age of subject; Ah = age of husband; As = age started smoking; B = number of live births; C = cooking habits; E = education; F = fish consumption; H = hospital; I = income; Ir = interviewer; L = location; O = occupation of subject; Oh = occupation of husband; R = racial or ethnic group; SES = socioeconomic status; Sm = active smoking; V = vital status; Yc = years since exposure ceased; Yd = year of diagnosis.
[6]LR = logistic regression; R = regression; M = matched analysis; S = stratified.
[7]Bronchioalveolar carcinoma excluded. Spousal smoking OR = 1.77 with bronchioalveolar carcinoma excluded; no corresponding value reported for maternal smoking.
[8]Population controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.52 and 1.47, respectively).
[9]Colon cancer controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.35 and 1.44, respectively).
[10]Composite measure formed from categorical data at different exposure levels.
[11]Cases and controls matched on A, L, and N; first value is from subject; second value is from proxy sources.
[12]1-24 smoker-years/$\geq$ 25 smoker-years.
[13]Adenocarcinoma only.
[14]All cell types.
[15]First value is for smoking information provided by patient's spouse; second value is for information provided by patient herself; third value (in brackets) utilizes available data from either source with subject classified as exposed if either source so indicates.
[16]Exposed at home but not at work or vice versa/exposed both at home and at work followed by weighted average of exposed strata.
[17]Crude OR from Table 11 of Surgeon General's report (U.S. DHHS 1986); note that adjusted OR from WU is not restricted to never-smokers and analysis includes only adenocarcinoma.
[18]Spouse smokes 1-20 cig. per day/spouse smokes $\geq$ 20 cig. per day. The composite RR is 1.17.

*Data not available.

, with the ones selected for analysis in this report in boldface type. Table 5-5 lists the RRs and their

confidence intervals, along with explanatory footnotes, and Table 5-6 provides information on source and place of exposure and on the adjusted analysis. Because most studies include spousal smoking, and interstudy comparisons may be useful, spousal smoking was the preferred ETS surrogate in all except for LAMW and SOBU. In LAMW, spousal smoking data are limited to cases with adenocarcinoma; in SOBU, the data for cohabitants are separate from data for spousal smoking, and much of the ETS exposure appears to result from the cohabitants. Only data for broader exposure to ETS than spousal smoking alone were collected in BUFF, CHAN, SVEN, and HOLE(Coh).

After exposure source and place are taken into account in the choice of RR values in Table 5-6, an adjusted RR is considered preferable to a crude RR unless the study review in Section A.4 indicates a problem with the adjustment procedure. Of the 31 studies, 20 provide both an adjusted and crude RR, where the "adjusted estimate" is based on the author's use of a statistical procedure that takes potential confounding factors into account, usually by stratification or logistic regression. Based on the decision rule just described, our choice of RR is the smaller of the crude and adjusted values in 14 of the 20 studies providing both estimates. In several studies, RR values in addition to those shown in Table 5-6 might be considered (see Table 5-7

Table 5-7. Alternative estimates of lung cancer relative risks associated with active and passive smoking

Study	Active/ passive	ETS exposure	Controls exp. (%)	Alternative estimate	Comparison estimate[1]
BUFF[2]	Passive	Household members regularly smoking for 33+ years	71	Crude OR 0.95 (0.38, 2.40)	0.81
FONT[3]	Passive	Spousal smoking, all types	63	Crude OR 1.52[4] (1.19, 1.96)	1.37
				Adj. OR 1.47	1.29
			66	Crude OR 1.35[5] (1.02, 1.80)	1.21
				Adj. OR 1.44	1.28
			64	Crude OR 1.47[6] (1.15, 1.87)	1.32
				No adj. OR	*
HUMB[7]	Passive	Spousal cigarette smoking[7]	57	Crude OR 1.8 (0.6, 5.4)	2.3
				adj. OR 1.7	2.2
KOO[8]	Passive	Home and/or workplace exposure over lifetime[8]	64	Crude OR 1.36 (0.83, 2.21)	1.34
				Adj. OR 1.86	1.64
PERS[9]	Active	N.A.[10]	37[11]	Crude OR 4.2	*
SHIM[12]	Passive	Total household ETS exposure[12]	77	Crude OR 1.36	1.08
BUTL (Coh)	Active	N.A.[10]	14[11]	Adj. RR 4.0[13]	*
HIRA[14] (Coh)	Active	N.A.[10]	44[11]	Adj. RR 3.79	2.67
HOLE[15] (Coh)	Active	N.A.[10]	56[11]	Adj. RR 4.2	*

[1]Nearest equivalent from Tables 5-5 or 5-6.
[2]Values in Tables 5-5 and 5-6 include household smoking for any duration. Lung cancer may have a long latency period, however, so the extended exposure may be of interest.
[3]As in Table 5-5 except for adenocarcinoma alone.
[4]Population controls only.
[5]Colon cancer controls only.
[6]Control groups combined.
[7]Values in Tables 5-5 and 5-6 include spousal smoking of cigars and pipes.
[8]Value in Table 5-6 is for household cohabitant smoke exposure during adulthood.

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Table 5-7. (continued)

[9]Estimate is based on papers by Cederlöf et al. (1975) and Floderus et al. (1988) describing larger populations on which Pershagen study was based.
[10]Not applicable because alternative estimate is for active smoking.
[11]Percentage ever-smokers.
[12]Composite estimate from crude ORs for exposure from husband, parents, and father-in-law. Values in Tables 5-5 and 5-6 consider only spousal smoke exposure.
[13]Rough estimate based on data in Fraser et al. (1991). The prevalence of female ever-smoking is estimated from KALA and TRIC studies, which were conducted in similar conservative societies.
[14]Compares active smokers with never-smokers unexposed to ETS, thus providing a reference group more truly unexposed to tobacco smoke. The value in Table 5-5 is the more conventional comparison of ever-smokers with never-smokers, regardless of passive smoking status.
[15]Estimate is from adjusted RR for both sexes combined with assumption that female RR is 75% of male RR.

*Data not available.

). They were not found to be the best choices, however, for comparison between studies.

5.2.2. Downward Adjustment to Relative Risk for Smoker Misclassification Bias

There is ample evidence that some percentage of smokers, which differs for current and former smokers, misrepresent themselves as never-smokers (sometimes the wording of a

questionnaire may not be explicit enough to distinguish former smokers from never-smokers) (see Appendix B). It has been argued that the resultant misclassification of some smokers as nonsmokers produces an upward bias in the observed relative risk for lung cancer from ETS exposure (i.e., the observed RR is too large). The essence of the supporting argument is based on smoking concordance between husband and wife--a smoker is more likely than a nonsmoker to have been married to a smoker. Consequently, the smoker misclassified as a nonsmoker is more likely to be in the ETS-exposed classification as well. Because smoking causes lung cancer, a misclassified smoker has a greater chance of being a lung cancer case than a nonsmoker. The net effect is that an observed association between ETS exposure and lung cancer among people who claim to be never-smokers may be partially explainable by current or former active smoking by some subjects.

The potential for bias due to misreported smoking habits appears to have been noted first by Lee (see discussion in Lehnert, 1984), and he emphasizes it in several articles (e.g., Lee, 1986, 1987a,b). In Lee, 1987b, it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported never-smokers in epidemiologic studies. Lee's estimates of bias due to smoker misclassification appear to be overstated, however, for reasons discussed in Appendix B.

The NRC report on ETS (1986) devotes considerable attention to the type of adjustment for smoker misclassification bias. It follows the construct of Wald and coworkers, as described in Wald et al., 1986; Wald was the author of this section in the 1986 NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from spousal smoking is shown in Figure 2 of Wald et al. (1986). A similar example is in Table 12-5 of the NRC report.

Both Lee's and Wald's work adjust an overall relative risk estimate, pooled over several studies, downward, rather than address each individual study, with its own peculiarities, separately. Furthermore, statistical analysis over the studies as a whole is conducted first, and then an adjustment is made to the overall relative risk estimate. The recent work of Wells and Stewart (Appendix B) on this subject makes an adjustment to each individual study separately. Consequently, the pertinent adjustment factors that vary by study and type of society can be tailored to each study and then applied to the observed data before any statistical analysis. The latter procedure is applied in this report.

The methodology to adjust for bias due to smoker misclassification and the details of its application to the ETS studies are provided in Appendix B. The results of the adjustment and estimate of bias are given in Table 5-8

Table 5-8. Estimated correction for smoker misclassification

Case control	Never-smokers RR[1] Uncorrected[2] (1)	Corrected[3] (2)	Bias[4] (1)/(2)		Ever-smokers OR used[5]
AKIB	_____	1.5 (1.0, 2.5)	_____	1.00	2.38
BROW	1.52 (0.49, 4.79)		1.50 (0.48, 4.72)	1.01	4.30
BUFF	0.81 (0.39, 1.66)		0.68 (0.32, 1.41)	1.20	7.06
CHAN	0.75 (0.48, 1.19)		0.74 (0.47, 1.17)	1.01	3.48
CORR	2.07 (0.94, 4.52)		1.89 (0.85, 4.14)	1.10	12.40
FONT	1.29 (1.03, 1.62)		1.28 (1.03, 1.60)	1.01	8.0
GAO	_____	1.19 (0.87, 1.63)	_____	1.00	2.54
GARF	1.31 (0.93, 1.85)		1.27 (0.91, 1.79)	1.03	6.0
GENG	_____	2.16 (1.21, 3.84)	_____	1.00 (0.995)	2.77
HIRA	1.53 (1.10, 2.13)		1.52 (1.10, 2.12)	1.01	3.20
HUMB	2.2 (0.9, 5.5)		2.00 (0.83, 4.97)	1.10	16.3
INOU	_____	2.55 (0.90, 7.20)	_____	1.00 (0.996)	1.66
JANE	0.86 (0.57, 1.29)		0.79 (0.52, 1.17)	1.09	8.0
KABA	0.79 (0.30, 2.04)		0.73 (0.27, 1.89)	1.08	5.90
KALA	_____	1.92 (1.13, 3.23)	_____	1.00	3.32
KATA	*		*	*	*
KOO	1.55 (0.98, 2.44)		1.54 (0.98, 2.43)	1.01	2.77
LAMT	1.65 (1.21, 2.21)		1.64 (1.21, 2.21)	1.01	3.77

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Table 5-8. (continued)

Case control	Never-smokers RR[1] Uncorrected[2] (1)	Corrected[3] (2)	Bias[4] (1)/(2)		Ever-smokers OR used[5]
LAMW	_____	2.51 (1.49, 4.23)	_____	1.00 (0.996)	4.12
LEE	1.03 (0.48, 2.20)		1.01 (0.47, 2.15)	1.02	4.61
LIU	_____	0.77 (0.35, 1.68)	_____	1.00	*
PERS	1.2 (0.7, 2.1)[6]		1.17 (0.75, 1.87)	1.03	4.2
SHIM	1.08 (0.70, 1.68)		1.07 (0.7, 1.67)	1.01	2.8
SOBU	_____	1.57 (1.13, 2.15)	_____	1.00	2.81
SVEN	1.26 (0.65, 2.48)		1.20 (0.63, 2.36)	1.05	6.00
TRIC	_____	2.08 (1.31, 3.29)	_____	1.00	2.81
WU	1.41 (0.63, 3.15)		1.32 (0.59, 2.93)	1.07	4.38
WUWI	0.79 (0.64, 0.98)		0.78 (0.63, 0.96)	1.01	2.24
BUTL (Coh)	2.02[7] (0.48, 8.56)[6]		2.01 (0.61, 6.73)	1.00	4.0
GARF (Coh)	1.17[7] (0.85, 1.61)[6]		1.16 (0.89, 1.52)	1.01	3.58
HIRA (Coh)	1.38 (1.03, 1.87)		1.37 (1.02, 1.86)	1.01	3.20
HOLE (Coh)	1.99[7] (0.24, 16.7)[6]		1.97 (0.34, 11.67)	1.01	4.2

[1]OR for case-control studies; RR for cohort studies.
[2]Adjusted OR in Table 5-5 is used unless the confidence interval is unknown or the study review (Appendix A) is critical of the method(s) used.
[3]Corrected (2) (estimate and confidence interval) equals uncorrected (1) times ratio [(2)/(1)]. All corrected 95% confidence intervals have been converted to 90% confidence intervals.
[4]Values shown are the lower of (calculated ratio, 1). Calculated ratios less than 1 are shown in parentheses.
[5]The crude OR for ever-smokers in Table 5-5 is used in the calculations for the corrected value (Appendix B), when available. Ever-smoker ORs for GARF, JANE, PERS, and SHIM are approximated from the data of other studies for suitable location and time period. The ever-smoker ORs for BUTL(Coh) and (LEE) are based on data in Fraser et al. (1991) and Alderson et al. (1985), respectively.
[6]95% confidence interval.
[7]Adjusted RR value in Table 5-5.

. In general, the biases are low in East Asia, or in any traditional society such as Greece, where female smoking prevalence is low and the female smoker risk is low. Some of the calculated biases are slightly less than unity when carried to three decimal places. This may result from the assumption in the calculations that there is no passive smoking effect on current smokers.

5.3. STATISTICAL INFERENCE

5.3.1. Introduction

Table 5-9

Table 5-9. Statistical measures by individual study and pooled by country, corrected for smoker misclassification[1]

Location	Study	Relative weight[2] (%)	Power[3]	P-value Effect[4]	P-value Trend[5]	RR[6]	Confidence interval 90%
Greece	KALA	43	0.39	0.02	0.04	1.92	(1.13, 3.23)
Greece	TRIC	57	0.45	<0.01	<0.01	2.08	(1.31, 3.29)
Greece	**ALL**	**5**		**<0.01**		**2.01**	**(1.42, 2.84)**
HK	CHAN	20	0.43	>0.5	*	0.74	(0.47, 1.17)
HK	KOO	20	0.43	0.06	0.16	1.54	(0.98, 2.43)
HK	LAMT	45	0.73	<0.01	<0.01	1.64	(1.21, 2.21)
HK	LAMW	15	0.39	<0.01	*	2.51	(1.49, 4.23)
HK	**ALL**	**14**		**<0.01**		**1.48**	**(1.21, 1.81)**
Japan	AKIB	15	0.42	0.05	0.03	1.50	(1.00, 2.50)
Japan	HIRA (Coh)	35	0.75	0.04	<0.01	1.37	(1.02, 1.86)
Japan	INOU	3	0.17	0.07	<0.03	2.55	(0.90, 7.20)
Japan	SHIM	16	0.37[7]	0.38	*	1.07	(0.70, 1.67)
Japan	SOBU	30	0.66	0.01	*	1.57	(1.13, 2.15)
Japan	**ALL**	**19**		**<0.01**		**1.41**	**(1.18, 1.69)**
USA	BROW	1	0.15	0.28	*	1.50	(0.48, 4.72)
USA	BUFF	3	0.17	>0.5	*	0.68	(0.32, 1.41)
USA	BUTL (Coh)	1	0.18	0.17	*	2.01	(0.61, 6.73)
USA	CORR	3	0.22	0.10	0.01	1.89	(0.85, 4.14)
USA	FONT[8]	35	0.93	0.03	0.04	1.28	(1.03, 1.60)
USA	GARF	15	0.60[7]	0.12	<0.02	1.27	(0.91, 1.79)

(continued on the following page)

Table 5-9. (continued)

Location	Study	Relative weight[2] (%)	Power[3]	P-value Effect[4]	P-value Trend[5]	RR[6]	Confidence interval 90%
USA	GARF (Coh)	25	0.92	0.18	*	1.16	(0.89, 1.52)
USA	HUMB	2	0.20	0.10	*	2.00	(0.83, 4.97)
USA	JANE	10	0.44[7]	>0.5	*	0.79	(0.52, 1.17)
USA	KABA	2	0.17[7]	>0.5	*	0.73	(0.27, 1.89)
USA	WU	3	0.21	0.29	*	1.32	(0.59, 2.93)
USA	**ALL**	**34**		**0.02**		**1.19**	**(1.04, 1.35)**
Scotland	HOLE (Coh)	100	0.09	0.26	*	1.97	(0.34, 11.67)
Eng./Wales	LEE	100	0.20	0.50	*	1.01	(0.47, 2.15)
Sweden	PERS	68	0.45[7]	0.27	0.12	1.17	(0.75, 1.87)
Sweden	SVEN	32	0.24	0.31	*	1.20	(0.63, 2.36)
W. Europe	**ALL**	**5**		**0.22**		**1.17**	**(0.84, 1.62)**
China	GAO	28	0.66	0.18	0.29	1.19	(0.87, 1.62)
China	GENG	8	0.32	0.01	<0.05	2.16	(1.21, 3.84)
China	LIU	4	0.18	>0.5	*	0.77	(0.35, 1.68)
China	WUWI	60	0.89[7]	>0.5	*	0.78	(0.63, 0.96)
China	**ALL**	**22**		**>0.5**		**0.95**	**(0.81, 1.12)**

[1]Misclassification is discussed in Section 5.2.2 and Appendix B.
[2]A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3]*A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4]One-sided p-value for test of RR = 1 versus RR > 1.
[5]P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative, i.e., upward trend.
[6]Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[7]Calculated for matched study design.
[8]For population control group only, all cases.

*Data not available; ns = not significant.

lists the values of several statistical measures for the effect of spousal smoking by study (see boldface entries in Table 5-6 for details). Their meanings will be described before proceeding to interpretation of the data, even though the concepts discussed may be familiar to most readers. The p-values refer to a test for effect and a test for trend. In the former, the null hypothesis of no association (referred to as "no effect" of ETS exposure on lung cancer risk) is tested against the alternative of a positive association. The test for trend applies to a null hypothesis of no association between RR and exposure level against the alternative of a positive association. When data are available on more than two levels of intensity or duration of ETS exposure, typically in terms of the husband's smoking habit (e.g., cig./day or years of smoking), then a test for trend is a useful supplement in testing for an effect, as well as indicating whether a dose-response relationship is likely.

The entries under "power" in Table 5-9 are calculated for the study's ability to detect a true relative risk of 1.5 and a decision rule to reject the null hypothesis of no effect when $p < 0.05$ (see Dupont and Plummer [1990] for methods to calculate power). The power is the estimated probability that the null hypothesis would be rejected if the true relative risk is 1.5 (i.e., that the

correct decision would result; the power would be larger if the true relative risk exceeds 1.5). If the estimates of power for the U.S. studies in Table 5-9 are used for illustration, it can be seen that the estimated probability that a study would *fail* to detect a true relative risk of 1.5 (equal to 1 – Power, the probability of a Type II error [discussed in the next paragraph] when the true relative risk is 1.5) is as follows: FONT, 0.07; GARF(Coh), 0.08; GARF, 0.40; JANE, 0.56; BUFF, 0.83; CORR, 0.78; WU, 0.79; HUMB, 0.80; KABA, 0.83; BUTL(Coh), 0.82; and BROW, 0.85. Thus, 7 of the 11 U.S. studies have only about a 20% chance of detecting a true relative risk as low as 1.5 when taken alone. Sources of bias effectively alter the power in the same direction as the bias (e.g., a downward bias in RR decreases the power). Of the potential sources of bias discussed by study in Section A.4, the predominant direction of influence on the observed RR, when identifiable, appears to be in the direction of unity, thus affecting power adversely. The RRs already have been reduced to adjust for smoker misclassification, the only systematic source of upward bias that has been established.

Studies of all sizes, large and small, are equally likely to make a false conclusion if ETS is not associated with lung cancer risk (Type I error). However, smaller studies are less likely to detect a real association when there is one (Type II error). This imbalance comes from using the significance level of the test statistic to determine whether to reject the null hypothesis. If the decision rule is to reject the hypothesis when the p-value is smaller than some prescribed value (e.g., 0.05), then the Type I error rate is 0.05, but the Type II error rate increases as study size decreases. When a study with low power fails to reject the null hypothesis of no effect, it is not very informative because that outcome may be nearly as likely when the null hypothesis is false as when it is true. When detection of a small relative risk is consequential, pooling informational content of suitably chosen studies empowers the application of statistical methods.

The heading in Table 5-9 that remains to be addressed is "relative weight," to be referred to simply as "weight." When the estimates of relative risk from selected studies are combined, as for studies within the same country as shown in the table, the logarithms of the RRs are weighted inversely proportional to their variances (see Appendix D and footnote 2 of Table 5-9). These relative weights are expressed as percentages summing to 100 for each country in Table 5-9. Study weight and power are positively associated, which is explained by the significant role of study size to both. Consequently, studies weighted most heavily (because the standard errors of the RRs are low) also tend to be the ones with the highest power (most likely to detect an effect when present).

5.3.2. Analysis of Data by Study and Country

5.3.2.1. *Tests for Association*

The p-values of the test statistics for the hypothesis of no effect (i.e., RR = 1) are shown in Table 5-9. Values of the test statistics (the standardized log odds ratio; see Appendix D) are plotted in Figure 5-1

Figure 5-1. Test statistics for hypothesis RR = 1, all studies.

Figure 5-2. Test statistics for hypothesis RR = 1, USA only.

. Also shown in Figure 5-1 for reference are the points on the horizontal axis corresponding to p-values of 0.5, 0.2, 0.1, 0.05, 0.01, and 0.001. For example, the area under the curve to the right of the vertical line labeled $p = 0.01$ is 0.01 (1%), so it is apparent from Figure 5-1 that three studies had significance levels $p < 0.01$ (more specifically, $0.001 < p < 0.01$). The size of the symbol (inverted triangle) used for a study is proportional in area to the relative weight of that individual study, but of current interest is the location and not the size of the symbol. If the null hypothesis is true, then the plotted values would arise from a standard normal distribution, shown in the figure (points to the left of zero indicate that the RR is less than 1, and points to the right of zero indicate that RR is greater than 1). If the points lie more toward the right side of the normal curve than would be likely to occur by chance alone, then the hypothesis of no effect is rejected in favor of a positive association between ETS exposure and lung cancer. If one constructs five intervals of equal probability (i.e., intervals of equal area under the standard normal curve), the expected number of observations in each interval is six (these five intervals are not shown on Figure 5-1). The observed numbers in these intervals, however, from left to right are 3, 3, 1, 7, and 16, an outcome that is significant at $p < 0.005$, by the chi-square goodness-of-fit test. At the points on the standard normal curve corresponding to p-values 0.5, 0.4, 0.3, 0.2, 0.1, and 0.05, the probability that a number of outcomes as large as that actually observed would occur by chance is less than 0.005 at all points. Consequently, the hypothesis of no effect is rejected on statistical grounds, and that conclusion is not attributable to a few extreme outcomes that might be aberrant in some way.

Figure 5-2 displays the U.S. studies alone (see Appendix D for calculation of the test statistics). Figure 5-3

Figure 5-3. Test statistics for hypothesis RR = 1, by country.

Figure 5-4. Test statistics for hypothesis RR = 1, tiers 1-3 only.

corresponds to Figure 5-1 except that the test statistics for the hypothesis of no effect (i.e., RR = 1) for the significance levels shown apply to a single overall estimate of RR for each country, formed by statistically pooling the outcomes from the studies within each country. The areas of the symbols for countries are also in proportion to statistical weight as given in Table 5-9. It is implicitly assumed that studies within a country, and the subpopulations sampled, are sufficiently homogeneous to warrant combining their statistical results into a single estimate for the country (see Greenland [1987] for a discussion of applications of meta-analysis to epidemiology). The calculational method employed weights the observed RR from each study within a country inversely proportional to its estimated variance (see Appendix D). The relative

study weights are shown in Table 5-9. Each symbol in Figures 5-1, 5-2, 5-3, and 5-4 has been scaled so that its area is proportional to the weight of the outcome represented, relative to all other outcomes shown in the same figure.

Greece, Hong Kong, and Japan, which together comprise a total weight of 39%, are *each* statistically significant at $p < 0.01$ against the null hypothesis of no increase in relative risk (RR = 1). When the United States is included, the total weight is 73%, and *each* of the four countries is significant at $p < 0.02$. The four studies combined into the group called Western Europe are not large. Together they represent 5% of the total weight, and their combined odds ratio (1.17) is slightly above 1 but not statistically significant ($p = 0.21$). In contrast, China is weighted quite high (22%), the p-value is large (0.66), and the odds ratio is less than 1 (0.95), strongly indicating no evidence of an increase in RR due to ETS. This is largely because China is very heavily influenced by WUWI (relative weight of 60% of China), which is a very large case-control study. However, this apparent inconsistency in WUWI may be due to the presence of indoor smoke from cooking and heating, which may mask any effect from passive smoking. A similar but more extreme situation is found in LIU, conducted in a locale where indoor heating with smoky coal (an established risk factor for lung cancer) and inadequate venting are common. Both WUWI and LIU were conducted primarily to assess the hazardous potential of these pollutants. The indoor environments of the populations sampled in WUWI and LIU make detection of any carcinogenic hazard from ETS unlikely, and thus render these studies to be of little value for that purpose (see discussions of WUWI and LIU in Section A.4). Without WUWI or LIU, the combined results of the two remaining studies in China, GAO and GENG, are significant at $p = 0.03$.

Such qualitative considerations about the likely utility of a study to detect an ETS effect, if one exists, are taken into account in Section 5.5. In that section, studies are ranked into one of four tiers based on their likely utility. Studies such as WUWI and LIU would be placed into Tier 4, the grouping with the least likelihood of providing useful information on the effects of ETS. Figure 5-4 is similar to Figure 5-3 displaying the distribution of test statistics for the pooled estimates by country, but includes only the studies in Tiers 1, 2, and 3; it is shown here for comparison purposes (see Section 5.5 for a detailed discussion of the analysis based on tiers).

5.3.2.2. *Confidence Intervals*

Confidence intervals for relative risk are displayed by study and by country in Table 5-9 (see Appendix D for method of calculation). The 90% confidence intervals by country are illustrated in Figure 5-5

Figure 5-5. 90% confidence intervals, by country.

Figure 5-6. 90% confidence intervals, by country, tiers 1-3 only.

. (*Note*: 90% confidence intervals are used for correspondence to a right-

tailed test of the hypothesis of no effect at a 5% level of significance.) The area of the symbol (solid circle) locating the point estimate of relative risk within the confidence interval is proportional to study weight. Symbol size is used as a device to draw attention to the shorter confidence intervals, which tend to be based on more data than the longer ones. The confidence intervals for countries jointly labeled as Western Europe are in Table 5-9, except for Sweden which contains two studies, PERS and SVEN. For those two studies combined, the odds ratio (OR) is 1.19 (90% C.I. = 0.81, 1.74). The confidence intervals for the pooled relative risk estimates by country for studies in Tiers 1, 2, and 3 only (see previous paragraph and Section 5.5) are displayed in Figure 5-6.

In descending order, the relative risks in Figure 5-6 are for Greece, Hong Kong, Japan, the United States, and Western Europe. (China is being excluded from this summary because it contains only one study in Tiers 1-3 [GAO], which is unlikely to be representative of such a vast country. The relative risk estimate for that study, 1.19, is similar to the overall relative risks for the United States and Western Europe.) The estimated relative risks from exposure to spousal smoking differ between countries, with Greece, Hong Kong, and Japan at the high end of the scale and the United States and Western Europe at the low end. These differences suggest that combining studies from different countries should be done with caution. The relative risks pertain only to ETS exposure from spousal smoking, which may be a higher proportion of total ETS exposure in some countries than in others. This also emphasizes the importance of taking into account exposure and background (nonspousal) ETS, which is considered in the estimation of population risk for the United States in Chapter 6.

5.3.3. Analysis of Data by Exposure Level

5.3.3.1. *Introduction*

In Section 5.3.2, analyses are conducted by individual study and by studies pooled within countries, using the dichotomous data on spousal smoking (i.e., any level of spousal smoking versus no spousal smoking) as a surrogate for ETS exposure. This section examines the response data from all of the studies that provide data analysis by exposure-level categories. Exposure level, for these studies, refers to the amount of spousal smoking. In different studies, exposure is measured by intensity (e.g., cig./day smoked by the husband), duration (e.g., number of years married to a smoker), or a combination of both (e.g., number of pack-years--packs per day × years of smoking by the husband). The data are analyzed by calculating RR estimates for the highest exposure groups only (Section 5.3.3.2) and then by testing for an upward trend in RR across exposure groups within studies as ETS exposure increases (Section 5.3.3.3).

An evaluation of the highest exposure group or a test for exposure-related trend may be able to detect an association that would be masked in a test for effect using only dichotomous data. This masking is especially likely to occur when dealing with a weak association or a crude surrogate measure for exposure that is widespread (i.e., greater potential for exposure misclassification), both of which are difficulties in studies of ETS and lung cancer.

As discussed in Chapter 3, ETS is a dilute mixture, and, consequently, any association observed between environmental levels of ETS exposure and lung cancer is likely to be weak (i.e., have a low RR). Furthermore,

questionnaire-based assessment of exposure to ETS is a crude indicator of actual lifetime exposure, and spousal smoking is an incomplete surrogate for exposure because it does not consider ETS from other sources, such as the workplace. Therefore, exposure misclassification in both directions is inevitable. For example, there will be women whose husbands do not smoke but who are exposed to substantial levels of ETS from other sources, and there will be women whose husbands smoke but who are not actually exposed to appreciable levels of ETS. This latter scenario is most likely if the level of spousal smoking is low. Comparing the highest exposure group with the "unexposed" group will help reduce the effect of this latter type of exposure misclassification bias.

In addition, the detection of an exposure-response relationship (trend) across exposure groups increases support for a causal association by diminishing the likelihood that the results can be explained by confounding, because any potential confounder would have to be associated with both lung cancer and ETS exposure in a dose-related manner. However, the potential for exposure misclassification is compounded when the exposed group is further divided into level-of-exposure categories and the sample sizes become small. This is especially problematic in small studies. These inherent difficulties with the ETS database tend to diminish the possibility of detecting exposure-response relationships. Therefore, the inability to demonstrate an exposure-response trend is not considered evidence against causality; rather, if a statistically significant trend can be detected despite these potential obstacles, it provides evidential support for a causal association.

5.3.3.2. *Analysis of High-Exposure Data*

In this section, analyses will be conducted for the highest exposure groups by study and by studies pooled within countries. As described in Section 5.3.3.1, analyzing only the data from the highest exposure group of each study increases the sensitivity for detecting an association and reduces the effects of exposure misclassification. Fractionating the data, however, does decrease the power to observe statistical significance.

The results of statistical inference using only data from the highest exposure categories are displayed in Table 5-10

Table 5-10. Statistical measures for highest exposure categories only[1]

Location	Study	Highest exposure level	Relative weight[2] (%)	Power[3]	P-value Effect[4]	RR[5,6]	Confidence interval[6] 90%
Greece	KALA	(≥41 cig./day)	35	0.06	0.16	1.57	(0.74, 3.32)
Greece	TRIC	(≥21 cig./day)	65	0.11	0.003	2.55	(1.46, 4.42)
Greece	**All**	**High**	**8**		**0.002**	**2.15**	**(1.38, 3.35)**
Hong Kong	KOO	(≥21 cig./day)	36	0.11	0.36	1.18	(0.58, 2.55)
Hong Kong	LAMT	(≥21 cig./day)	64	0.16	0.02	2.05	(1.18, 3.57)
Hong Kong	**All**	**High**	**8**		**0.03**	**1.68**	**(1.08, 2.62)**
Japan	AKIB	(≥30 cig./day)	6	0.10	0.13	2.1	(0.7, 2.5)
Japan	HIRA (Coh)	(≥20 cig./day)	89	0.13	0.00015	1.91	(1.42, 2.56)
Japan	INOU	(≥20 cig./day)	4	*	0.05	3.09	(1.0, 11.8)
Japan	**All**	**High**	**22**		**<0.00004**	**1.96**	**(1.49, 2.60)**
United States	CORR	(≥41 pack-yrs)	8	0.06	0.005	3.20	(1.53, 6.74)
United States	FONT	(≥80 pack-yrs)	14	*	0.21	1.32[7]	(0.75, 2.29)
United States	GARF	(≥20 cig./day)	15	0.21	0.01	2.05	(1.19, 3.49)
United States	GARF (Coh)	(≥20 cig./day)	45	*	0.33	1.09	(0.81, 1.49)
United States	HUMB	(≥21 cig./day)	2	*	0.46	1.09	(0.27, 4.73)
United States	JANE	(≥50 pack-yrs)	8	*	0.50	1.01	(0.50, 2.04)
United States	WU	(≥31 years)	8[8]	*	*	1.87	*
United States	**All**	**High**	**36**		**0.005**	**1.38**	**(1.13, 1.70)**
W. Europe	PERS	(≥16 cig./day)	100	*	0.02	3.11	(1.18, 7.71)
W. Europe	**All**	**High**	**2**		**0.02**	**3.11**	**(1.18, 7.71)**
China	GAO	(≥40 years)	35	0.33	0.02	1.7	(1.09, 2.65)
China	GENG	(≥20 cig./day)	65	*	<0.00001	2.76	(2.02, 3.84)
China	**All**	**High**	**24**		**<0.000001**	**2.32**	**(1.78, 3.03)**
All	**All**	**High**			**<0.000001**	**1.81**	**(1.60, 2.05)**

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Table 5-10. (continued)

[1]Similar to Table 5-9 except entries apply to highest exposure category only in each study. Only studies with data available for categorized measures of exposure are included. Relative risks and confidence bounds are corrected for smoker misclassification.
[2]A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3]*A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4]One-sided p-value for test of RR = 1 versus RR > 1.
[5]Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[6]Values may differ from those of Table 5-11, where confidence intervals are shown as they appear in the source. In Table 5-11, the RR and confidence interval are *not* corrected for smoker misclassification, as in this table, and most of the confidence intervals are 95% instead of 90%.
[7]Value shown is for all cell types with the two control groups combined. For adenocarcinoma cases only, the RR is 1.68 with C.I. = 0.81, 3.46.
[8]Relative weight assumed to be the same as for CORR, based on the outcome in Table 5-9.

*Data not available.

. As indicated in the table, exposure-level data are available in 17 studies. The definitions of highest exposure category, shown next to the study name in the table, vary widely between studies. Crude RR estimates adjusted for smoker misclassification (see Section 5.2 and Appendix B) are used in this section rather than the estimates adjusted for modifying factors within the studies, because the latter are available by exposure level for only a limited number of studies.

Several observations are apparent from Table 5-10. First, every one of the 17 individual studies shows increased risk at the highest exposure level, even after adjusting for smoker misclassification. Second, 9 of the 16 comparisons for which sufficient data are available are statistically significant ($p \leq 0.05$), despite most having very low statistical power. Third, the RR estimates pooled within countries are each statistically significant with $p \leq 0.02$. Although the RR estimates within a country are pooled across different definitions of highest exposure, which somewhat limits their interpretation and practical value, it is apparent that these RRs are considerably higher than the values observed for the dichotomous data (Table 5-9). The RR estimates pooled by country vary from a low of 1.38 ($p = 0.005$) for the United States to a high of 3.11 ($p = 0.02$) for Western Europe, which contains only one study. Finally, the overall pooled estimate of 1.81 for the highest exposure groups from all 17 studies is highly statistically significant ($p < 0.000001$).

These results are consistent with the statistical evidence presented in Section 5.3.2 for an association between ETS exposure and lung cancer. In fact, increased risks are found for the highest exposure groups without exception. Furthermore, the RR estimates pooled within countries are all statistically significant and range from 1.38 to 3.11, even after adjustment for smoker misclassification. The consistency of these highest exposure results cannot be accounted for by chance, and the stronger associations detected for the highest exposure groups across all countries

further reduce the likelihood that bias or confounding could explain the observed relationship between ETS and lung cancer.

In addition, with the exception of Western Europe, which contains only one low-power study in this analysis, the pooled RR estimates from other, more "traditional" countries are all appreciably higher than that from the United States. It is likely that these differences are at least partially a result of higher background (nonspousal) ETS exposures to the allegedly "unexposed" group in the United States. Again, this highlights the importance of accounting for ETS exposures from sources other than spousal smoking. An adjustment for background ETS exposures is made in Chapter 6, for the estimation of population risk for the United States.

5.3.3.3. *Tests for Trend*

In this section, exposure-response data from the studies providing data by exposure level are tested for upward trend. An exposure-response relationship provides strong support for a causal association (see Section 5.3.3.1).

Table 5-11

Table 5-11. Exposure response trends for females

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
AKIB	21	82		1.0		0.03
(cig./day)	29	90	1-19	1.3	(0.7, 2.3)[5]	
	22	54	20-29	1.5	(0.8, 2.8)[5]	
	12	23	≥30	2.1	(0.7, 2.5)[5]	
AKIB	21	82	0	1.0		0.24
(years)	20	30	1-9	2.1	(1.0, 4.3)[5]	
	29	81	20-39	1.5	(0.8, 2.7)[5]	
	22	59	≥40	1.3	(0.7, 2.5)[5]	
CORR	8	72	0	1.00		0.01
(pack-yrs.)	5	38	1-40	1.18	(0.44, 3.20)	
	9	23	≥41	3.52	(1.45, 8.59)	
FONT[6]	*	*	0	1.00		0.07
(years)	*	*	1-15	1.19	(0.88, 1.61)	
	*	*	16-30	1.14	(0.82, 1.59)	
	*	*	>30	1.25	(0.91, 1.72)	
FONT[7]	*	*	0	1.00		0.02
(years)	*	*	1-15	1.33	(0.93, 1.89)	
	*	*	16-30	1.40	(0.96, 2.05)	
	*	*	>30	1.43	(0.99, 2.09)	
FONT[6]	*	*		1.00		0.04
(pack-yrs.)	*	*	0<15	0.96	(0.72, 1.29)	
	*	*	15-39	1.13	(0.81, 1.59)	
	*	*	40-79	1.25	(0.86, 1.81)	
	*	*	≥80	1.33	(0.68, 2.58)	
FONT[7]	*	*		1.00		0.01
(pack-yrs.)	*	*	0<15	1.03	(0.73, 1.46)	
	*	*	15-39	1.26	(0.85, 1.87)	
	*	*	40-79	1.49	(0.98, 2.27)	
	*	*	≥80	1.70	(0.82, 3.49)	
GAO	99	57	0-19	1.0		0.29
(tot. yrs.)[8]	93	63	20-29	1.1	(0.7, 1.8)	
	107	78	30-39	1.3	(0.8, 2.1)	
	76	48	≥40	1.7	(1.0, 2.9)	
GARF	44	157	0	1.00		<0.02
(cig./day)	29	90	1-9	1.15	(0.8, 1.6)	
	17	56	10-19	1.08	(0.8, 1.5)	
	26	44	≥20	2.11	(1.1, 4.0)	
GENG	*	*	0	1.00		<0.05[9]
(cig./day)	*	*	1-9	1.40	(1.1, 1.8)	
	*	*	10-19	1.97	(1.4, 2.7)	
	*	*	≥20	2.76	(1.9, 4.1)	

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Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
GENG	*	*	0	1.00		<0.05[9]
(years)	*	*	<20	1.49	(1.15, 1.94)	
	*	*	20-39	2.23	(1.54, 3.22)	
	*	*	≥40	3.32	(2.11, 5.22)	
HUMB	*	*	0	1.0		ns
(cig./day)	*	*	1-20	1.8	(0.6, 5.6)[5]	
	*	*	≥21	1.2	(0.3, 5.2)[5]	
INOU	*	*	0-4	1.00		<0.03
(cig./day)	*	*	5-19	1.58	(0.4, 5.7)[5]	
	*	*	≥20	3.09	(1.0, 11.8)[5]	
JANE[10]	*	*	0	1.00		*
(pack-yrs.)	*	*	1-24	0.71	(0.37, 1.35)	
	*	*	25-49	0.98	(0.47, 2.05)	
	*	*	≥50	1.10	(0.47, 2.56)	
KALA	26	46	0	1.00		0.08
(cig./day)	34	39	1-20	1.54	(0.88, 2.70)	
	22	22	21-40	1.77	(0.93, 3.35)	
	8	9	41+	1.57	(0.64, 3.85)	
KALA	26	46	0	1.00		0.04
(years)	15	21	<20	1.26	(0.56, 2.87)	
	15	20	20-29	1.33	(0.58, 3.03)	
	17	15	30-39	2.01	(0.86, 4.67)	
	17	16	≥40	1.88	(0.82, 4.33)	
KOO	32	67	0	1.00		0.16
(cig./day)	17	15	1-10	2.33	(0.9, 5.9)	
	25	35	11-20	1.74	(0.8, 3.8)	
	12	19	≥21	1.19	(0.5, 3.0)	
LAMT[6]	84	183	0	1.00		0.01
(cig./day)	22	22	1-10	2.18	(1.14, 4.15)	
	56	66	11-20	1.85	(1.19, 2.87)	
	20	21	≥21	2.07	(1.07, 4.03)	
LAMT[7]	53	92	0	1.00		0.01
(cig./day)	17	12	1-10	2.46	(1.09, 5.54)	
	37	28	11-20	2.29	(1.26, 4.16)	
	15	9	≥21	2.89	(1.18, 7.07)	

(continued on the following page)

Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
PERS[11]	34	*	0	1.0		0.12
(cig./day)	26	*	1-15	1.0	(0.6, 1.8)	
	7	*	≥16	3.2	(1.0, 9.5)	
TRIC[12]	24	109	0	1.00		0.01
(cig./day)	24	56	1-20	1.95	(1.13, 3.36)	
	14	25	≥21	2.55	(1.31, 4.93)	
WU[13]	*	*	0	1.0		*
(years	*	*	1-30	1.2	*	
exposed as	*	*	≥31	2.0	*	
adult)						
GARF(Coh)[14]	65	*	0	1.00		*
(cig./day)	39	*	1-19	1.27	(0.85, 1.89)	
	49	*	≥20	1.10	(0.77, 1.61)	
HIRA(Coh)[15]	37	21,895	0	1.00		0.01
(cig./day)	99	44,184	1-19[16]	1.41	(1.03, 1.94)	
	64	25,461	≥20	1.93	(1.35, 2.74)	

[1]Smoking by spouse unless otherwise specified.
[2]See footnote 6 in Table 5-10.
[3]Confidence intervals are 95% unless noted otherwise.
[4]P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative (i.e., upward trend). Values below 0.01 are shown as 0.01.
[5]90% confidence interval.
[6]All histologies.
[7]Adenocarcinomas only.
[8]Years lived with a smoking husband.
[9]Neither crude data nor a test for trend is included in reference articles. The relative risk at each exposure category is significant alone, however, at $p < 0.05$.
[10]Data are from subject responses in Table 3 of the source.
[11]Low exposure level is for husband smoking up to 15 cigarettes per day or one pack (50 g) of pipe tobacco per week, or smoking any amount during less than 30 years of marriage. High exposure level is for husband smoking more than 15 cigarettes per day or one pack of pipe tobacco per week during 30 years of marriage or more.
[12]Data from Trichopoulos et al. (1983), with RRs corrected (personal communication from Trichopoulos, 1984).
[13]Years of exposure to spousal smoke *plus* years of exposure to workplace smoke; adenocarcinomas only.
[14]Value under "RR" is mortality ratio of observed to expected lung cancer deaths. Value under "Case" is number of observed lung cancer deaths.
[15]Standardized for age of subject (Hirayama, 1984). Values under "case" are numbers of lung cancer deaths; values under "cont." are total population.
[16]Includes former smokers of any exposure level.

*Data not available; ns = not significant.

presents the female exposure-response data and trend test results from the studies of ETS and lung cancer discussed in this report. The p-values reported in the table are for a test of no trend against the one-sided alternative of an upward trend (i.e., increasing RR with increasing exposure). (*Note*: The results for tests of trend are taken from the study reports. Unless the report specified that a one-sided alternative was used, the reported p-value was halved to reflect the outcome for the one-sided alternative of RR increasing with exposure. Where the data are available, the p-values reported by the individual study's authors have been verified here by application of the Mantel, Haenszel test [Mantel, 1963].)

Wu-Williams and Samet (1990) previously reviewed the exposure-response relationships from the epidemiologic studies on ETS then available. They determined that 12 of 15 studies were statistically significant for the trend test for at least one exposure measure. The probability of this proportion of statistically significant results occurring by chance in this number of studies is virtually zero ($p < 10^{-13}$). Intensity of spousal smoking was the most consistent index of ETS exposure for the demonstration of an exposure-response relationship.

Our assessment of the exposure-response data is similar and provides essentially the same results for a slightly different set of studies. Table 5-12

Table 5-12. Reported p-values of trend tests for ETS exposure by study[1]

Study	Trend test results		
	Intensity (cig./day)	Duration (total years)	Cumulative (pack-years)[2]
AKIB	0.03	0.24	*
CORR	*	*	0.01
FONT	* *	0.07[3] <0.02[4]	0.04 <0.01
GAO	*	0.29	*
GARF	<0.02	*	*
GENG	<0.05[5]	<0.05[5]	*
HUMB	ns	*	*
INOU	<0.03	*	*
JANE	*[6]	*	*
KALA	0.08	0.04	*
KOO	0.16	*	*
LAMT	<0.01 <0.01[4]	*	*
PERS	0.12	*	*
TRIC	<0.01	*	*
WU	*	*[6]	*
GARF(Coh)	*[6]	*	*
HIRA(Coh)	<0.01	*	*

[1]Detailed data presented in Table 5-11.
[2]A "pack-year" is equivalent to one pack/day for 1 year.
[3]All cell types.
[4]Adenocarcinoma only.
[5]See footnote 9 in Table 5-11.
[6]Trend results presented without p-values or raw data--see Table 5-11.

*Data not available; ns = not significant.

summarizes the p-values of the trend

tests for the various ETS exposure measures from the studies presented in Table 5-11. The exposure measure most commonly used was intensity of spousal smoking. Eight of the twelve studies that reported exposure-response data based on cigarettes per day showed statistical significance at the $p < 0.05$ level for the trend test. Again, the probability of this many statistically significant results occurring by chance in this number of studies is negligible ($p < 10^{-7}$). The trend test results for the other exposure measures were consistent, in general, with those based on cigarettes per day (three of six studies using total years of exposure were significant, as were two of two studies using pack-years).

Overall, 10 of the 14 studies with sufficient exposure-response data show statistically significant trends for one or more exposure measures. No possible confounder has been hypothesized that could explain the increasing incidence of lung cancer with increasing exposure to ETS in so many independent studies from different countries.

By country, the number of studies with significant results for upward trend is as follows: China, 1 of 2; Greece, 2 of 2; Hong Kong, 1 of 2; Japan, 3 of 3; Sweden, 0 of 1; and United States, 3 of 4. Of particular interest, two of the U.S. studies, GARF and CORR, are statistically significant for a test of trend, providing evidence for an association between ETS exposure and lung cancer even though neither was significant in a test for effect. In both cases, this occurs because the data supporting an increase in RR are largely at the highest exposure level. It appears that relatively high exposure levels are necessary to observe an effect in the United States, as would be expected if spousal smoking is a weaker surrogate for total ETS exposure in this country.

The U.S. study by Fontham et al. (1991), a well-conducted study and the largest case-control study of ETS and lung cancer to date, with the greatest power of all the U.S. studies to detect an effect, was statistically significant with a p-value of 0.04 for the trend test with pack-years as the exposure measure. When the analysis was restricted to adenocarcinomas (the majority of the cases), tests for trend were statistically significant by both years ($p = 0.02$) and pack-years ($p = 0.01$).

5.3.4. Conclusions

Two types of tests have been conducted: (1) a test for effect, wherein subjects must be classified as exposed or unexposed to ETS, generally according to whether the husband is a smoker or not, and (2) a trend test, for which exposed subjects are further categorized by some level of exposure, such as the number of cigarettes smoked per day by the husband, duration of smoking, or total number of packs smoked. Results are summarized in Table 5-13

Table 5-13. P-values of tests for effect and for trend by individual study[1]

Country	Study	Power	Test	P-value[2]
Greece	**KALA**	0.39	**Effect**	**0.02**
			Trend	**0.04**
Greece	**TRIC**	0.45	**Effect**	**<0.01**
			Trend	**<0.01**
Hong Kong	CHAN	0.43	Effect	>0.50
Hong Kong	KOO	0.43	Effect	0.06
			Trend	0.16
Hong Kong	**LAMT**	0.73	**Effect**	**<0.01**
			Trend	**<0.01**
Hong Kong	**LAMW**	0.39	**Effect**	**<0.01**
Japan	**AKIB**	0.42	**Effect**	**0.05**
			Trend	**0.03**
Japan	**HIRA(Coh)**	0.75	**Effect**	**0.04**
			Trend	**<0.01**
Japan	**INOU**	0.17	**Effect**	0.07**(0.05)**[3]
			Trend	**0.03**
Japan	SHIM	0.37	Effect	0.38
Japan	**SOBU**	0.66	**Effect**	**0.01**
United States	BROW	0.15	Effect	0.28
United States	BUFF	0.17	Effect	>0.50
United States	BUTL(Coh)	0.18	Effect	0.17
United States	**CORR**	0.22	**Effect**	0.10**(0.005)**[3]
			Trend	**0.01**
United States	**FONT**	0.93	**Effect**	**0.03**[4]
			Trend	**0.04**[4]
United States	**GARF**	0.60	**Effect**	0.12**(0.01)**[3]
			Trend	**<0.02**
United States	GARF(Coh)	0.92	Effect	0.18

(continued on the following page)

Table 5-13. (continued)

Country	Study	Power	Test	P-value[2]
United States	HUMB	0.20	Effect Trend	0.10 ns
United States	JANE	0.44	Effect	>0.50
United States	KABA	0.17	Effect	>0.50
United States	WU	0.21	Effect	0.29
<u>W. Europe</u>				
Scotland	Hole(Coh)	0.09	Effect	0.26
England	LEE	0.20	Effect	0.50
Sweden	**PERS**	0.45	**Effect** Trend	0.27**(0.02)**[3] 0.12
Sweden	SVEN	0.24	Effect	0.31
China	**GAO**	0.66	**Effect** Trend	0.18**(0.02)**[3] 0.29
China	**GENG**	0.32	**Effect** **Trend**	**0.01** **<0.05**
China	LIU	0.18	Effect	>0.50
China	WUWI	0.89	Effect	>0.50

[1]Test for effect--H_0: no increase in lung cancer incidence in never-smokers exposed to spousal ETS; H_A: an increase. Test for trend--H_0: no increase in lung cancer incidence as exposure to spousal ETS increases; H_A: an increase. P-values less than 0.05 are in boldface.
[2]Smallest p-value is used when there is more than one test for trend; ns = not significant.
[3]P-value in parentheses applies to test for effect at highest exposure only (see text).
[4]For all cell types. P-values for adenocarcinoma alone were smaller.

, with countries in the same order as in Table 5-9. Studies are noted in boldface if the test of effect or the trend

test is significant at 0.05 (one-tailed) or if, as in PERS and GAO, only the odds ratio at the highest exposure is significant. In 8 of the 11 studies in Greece, Hong Kong, or Japan, at least one of the tests is significant at 0.05. For the United States and Western Europe, 4 of the 15 studies are significant at 0.05 for at least one test. For the studies within the first group of countries (Greece, Hong Kong, and Japan), the median power is 0.43, and only 1 of the 10 studies (10%) has power less than 0.25 (INOU). In contrast, the median power for the United States and Western Europe together is 0.21, and 10 of the 15 studies (67%) have power less than 0.25. In a small study, significance is meaningful, but nonsignificance is not very informative because there is little chance of detecting an effect when there is one. Consequently, there are several studies in the United States-Western Europe group that provide very little information. Two of the four studies in China are significant at the 0.05 level for at least one test. The two nonsignificant studies in China (LIU and WUWI) are not very informative on ETS for reasons previously described (see Section 5.3.2.1).

For the U.S. and Western Europe studies, 3 of the 5 with power greater than 0.25 are shown in boldface (FONT, GARF, and PERS), indicating at least suggestive evidence of an association between ETS and lung cancer, compared with only 1 of 10 with power under 0.25 (CORR). All three of the higher power studies are significant for effect (PERS and GARF are significant at the highest exposure only) and two (FONT and GARF) are also significant for trend. CORR is significant for trend and for effect at the highest exposure level. Overall, the evidence of an association in the United States and Western Europe is strengthened by the tests at the highest exposure levels and by the tests for trend.

To summarize, the results of the several different analyses in this section provide substantial evidence that exposure to ETS from spousal smoking is associated with increased lung cancer mortality. The evidence is strongest in Greece, Hong Kong, Japan, and the United States. The evidence for Western Europe appears similar to that in the United States, but there are far fewer studies. (The usefulness of statistical information from studies in China is quite limited, so no conclusions are drawn from the studies there.)

The evidence from the individual studies, without pooling within each country, is also conclusive of an association. Adjustment, on an individual study basis, for potential bias due to smoker misclassification results in slightly lower relative risk estimates but does not affect the overall conclusions. The results based on either the test for effect or the test for trend cannot be attributed to chance alone. Tests for effect, tests at the highest exposure levels, and tests for trend jointly support the conclusion of an association between ETS and lung cancer in never-smokers.

5.4. STUDY RESULTS ON FACTORS THAT MAY AFFECT LUNG CANCER RISK

5.4.1. Introduction

The possibility of chance accounting for the observed associations between ETS and lung cancer has been virtually ruled out by the statistical methods previously applied. Potential sources of bias and confounding must still be considered to determine whether they can explain the observed increases. While the exposure-response

relationships reviewed in Section 5.3.3.3 generally reduce the likelihood of bias and confounding accounting for the observed associations, this section focuses on specific factors that may bias or modify the lung cancer results.

Validity is the most relevant concern for hazard identification. Generalizability of results to the national population (depending on "representativeness" of the sample population, treated in the text) is important for the characterization of population risk, but no more so than validity. As stated by Breslow and Day (1980), "In an analysis, the basic questions to consider are the degree of association between risk for disease and the factors under study, the extent to which the observed associations may result from bias, confounding and/or chance, and the extent to which they may be described as causal."

Whereas Section 5.3 examined the epidemiologic data by individual study and by pooling results by country, this section considers potential sources of bias and confounding and their implications for interpretation of study results. As indicated in the brief review of the meanings of bias and confounding at the end of this section, confounding arises from the characteristics of the sample population, whereas bias is the result of individual study features involving design, data collection, or data analysis. Section 5.4.2 briefly reviews the evidence on non-ETS risk factors and modifiers of lung cancer incidence that appears in the 30 epidemiologic studies (not counting KATA) reviewed for this report. None of the factors has been established as a confounder of ETS, which would require demonstrating that the factor causes lung cancer and is correlated with ETS exposure (specifically, spousal smoking to affect the analysis in this report).

Our objective is to consider the influence of sources of uncertainty on the statistical measures summarized in Table 5-13, although there are limitations to such an endeavor. For example, not controlling for a factor such as age in the statistical analysis, which should be done whether or not the study design is matched on age, may require reanalyzing data not included in the study report. Potential sources of bias are just that--*potential*--and their actual effect may be impossible to evaluate (e.g., selection bias in case-control studies). Although numerous questions of interest cannot be answered unequivocally, or even without a measure of subjective judgment, it is nevertheless worthwhile to consider issues that may affect interpretation of the quantitative results. The issues of concern are largely those of epidemiologic investigations in general that motivate the conscientious investigator to implement sound methodology. Statistical uncertainty aside, the outcomes of studies that fare well under close examination inspire more confidence and thus deserve greater emphasis than those that do poorly.

Preliminary to the next sections, some relevant notes on epidemiologic concepts are excerpted from two IARC volumes entitled *Statistical Methods in Cancer Research* (Breslow and Day, 1980, 1987), dealing with case-control and cohort studies, respectively, which are excellent references. In the interest of brevity, an assortment of relevant passages is simply quoted directly from several locations in the references (page numbers and quotation marks have been omitted to improve readability). Some readers may wish to skip to the next section; those interested in a more fluid, cogent, and thorough presentation are referred to the references.

- <u>Bias and confounding</u>. The concepts of bias and confounding are most easily understood in the context of cohort studies, and how case-control studies relate to them. Confounding is intimately connected to the concept of causality. In a cohort study, if some exposure E is associated with disease status, then

the incidence of the disease varies among the strata defined by different levels of E. If these differences in incidence are caused (partially) by some other factor C, then we say that C has (partially) confounded the association between E and the disease. If C is not causally related to disease, then the differences in incidence cannot be caused by C, thus C does not confound the disease/exposure association.

Confounding in a case-control study has the same basis as in a cohort study . . . and cannot normally be removed by appropriate study design alone. An essential part of the analysis is an examination of possible confounding effects and how they may be controlled.

Bias in a case-control study, by contrast, [generally] arises from the differences in design between case-control and cohort studies. In a cohort study, information is obtained on exposures before disease status is determined, and all cases of disease arising in a given time period should be ascertained. Information on exposure from cases and controls is therefore comparable, and unbiased estimates of the incidence rates in the different subpopulations can be constructed. In case-control studies, however, information on exposure is normally obtained after disease status is established, and the cases and controls represent samples from the total. Biased estimates of incidence ratios will result if the selection processes leading to inclusion of cases and controls in the study are different (selection bias) or if exposure information is not obtained in a comparable manner from the two groups, for example, because of differences in response to a questionnaire (recall bias). Bias is thus a consequence of the study design, and the design should be directed towards eliminating it. The effects of bias are often difficult to control in the analysis, although they will sometimes resemble confounding effects and can be treated accordingly.

To summarize, confounding reflects the causal association between variables in the population under study, and will manifest itself similarly in both cohort and case-control studies. Bias, by contrast, is not a property of the underlying population. It results from inadequacies in the design of case-control studies, either in the selection of cases or controls or from the manner in which the data are acquired.

- <u>On prospective cohort studies</u>. One of the advantages of cohort studies over case-control studies is that information on exposure is obtained before disease status is ascertained. One can therefore have considerable confidence that errors in measurement are the same for individuals who become cases of the disease of interest, and the remainder of the cohort. The complexities possible in retrospective case-control studies because of differences in recall between cases and controls do not apply. [Regarding the success of a cohort study, the] follow-up over time . . . is the essential feature. . . . The success with which the follow-up is achieved is probably the basic measure of the quality of the study. If a substantial proportion of the cohort is lost to follow-up, the validity of the study's conclusions is seriously called into question.

- <u>On case-control studies</u>. Despite its practicality, the case-control study is not simplistic and it cannot be done well without considerable planning. Indeed, a case-control study is perhaps the most challenging to design and conduct in such a way that bias is avoided. Our limited understanding of this difficult study design and its many subtleties should serve as a warning--these studies must be designed and analyzed carefully with a thorough appreciation of their difficulties. This warning should also be heeded by the many critics of the case-control design. General criticisms of the design itself too often reflect a lack of appreciation of the same complexities which make these studies difficult to perform properly.

  The two major areas where a case-control study presents difficulties are in the selection of a control group, and in dealing with confounding and interaction as part of the analysis. . . these studies are highly susceptible to bias, especially selection bias which creates non-comparability between cases and controls. The problem of selection bias is the most serious potential problem in case-control studies. . . . Other kinds of bias, especially that resulting from non-comparable information from cases and controls are also potentially serious; the most common of these is recall . . . bias which may result

Table 5-14. Other risk-related factors for lung cancer evaluated in selected studies

Category	Possible risk factor	Mixed outcome	No evidence
Personal or family history	WU (US) GENG (Ch) LIU (Ch)	SHIM (Jap) GAO (Ch)	
Heat source for cooking or heating	WU (US) WUWI (Ch) GENG (Ch) GAO (Ch) LIU (Ch)	SOBU (Jap)	LAMW (HK)
Cooking with oil	WUWI (Ch) GAO (Ch)		
Diet	WU (US)	KALA (Gr) HIRA (Jap)	SHIM (Jap)
β-carotene			WUWI (Ch) KALA (Gr) GAO (Ch)-harmful
Occupation	WUWI (Ch) SHIM (Jap) GENG (Ch) BUTL (US) BUFF (US)		WU (US) GAO (Ch)

because cases tend to consider more carefully than do controls the questions they are asked or because the cases have been considering what might have caused their cancer.

In addition to standard demographic factors (e.g., age) that are usually controlled for in a study, a number of other variables have been considered as potential risk factors (including risk modifiers) for lung cancer. If a factor increases the risk of lung cancer and its presence is correlated with exposure to spousal ETS, then it could be a confounder of ETS if not controlled for in a study's analysis. In general, factors that may affect risk of lung cancer and also may be correlated with ETS exposure are of interest as possible explanatory variables. Findings from the ETS studies are reviewed for six general categories: (1) personal history of lung disease, (2) family history of lung disease, (3) heat sources, (4) cooking with oil, (5) occupation, and (6) diet. Table 5-14 provides an overview of results in these categories. Two shortcomings are common in the studies where these factors appear: failure to evaluate the correlation of exposure to the factor and to ETS, and then to adjust the analysis accordingly; and failure to adjust significance levels for multiple comparisons. Multiple tests on the same data increase the chance of a false

positive (i.e., outcomes appear to be more significant than warranted due to the multiple comparisons being made on the same data).

5.4.2. History of Lung Disease

Results regarding history of lung disease have been reported in eight of the reviewed ETS studies, but with little consistency. Tuberculosis (TB), for example, is significantly associated with lung cancer in GAO (OR = 1.7; 95% C.I. = 1.1, 2.4) but not in SHIM (OR = 1.1, no other statistics), LIU or WU (no ORs provided). Chronic bronchitis, on the other hand, is nonsignificant in GAO (OR = 1.2; 95% C.I. = 0.8, 1.7), SHIM (OR = 0.8), KABA, and WU, but it is highly significant in LIU (OR = 7.37; 95% C.I. = 2.40, 22.66 for females; OR = 7.32; 95% C.I. = 2.66, 20.18 for males) and mildly so in WUWI (OR = 1.4; 95% C.I. = 1.2, 1.8). (Notably, the populations of WUWI, LIU, and GENG were exposed to non-ETS sources of household smoke.) Consideration of each lung disease separately, as presented, ignores the effect of multiple comparisons described above. For example, GAO looked at five categories of lung disease. If that were taken into account, TB would no longer be significant. No discussion of the multiple comparisons effect was found in any of the references, which might at least be acknowledged.

Broadening our focus to examine the relationship of lung cancer to history of lung disease in general does little to improve consistency. GENG reports an adjusted OR of 2.12 (95% C.I. = 1.23, 3.63) for history of lung disease, GAO's disease-specific findings are consistently positive, and WUWI reports three positive associations out of an unknown number assessed. SHIM and WU, however, consistently found no effect except marginally for silicosis (perhaps better construed as an occupational exposure surrogate) in SHIM and for childhood pneumonia in WU. LIU found a significant association only for chronic bronchitis and KABA only for pneumonia. Interpretation is hampered by the lack of numerical data for factors that were not statistically significant in KABA, LIU, and WU. Even with such data, however, interpretation is hampered by the absence of control for key potential confounders in many of the studies (e.g., age in GENG and LIU). Only one study (WU) attempted to control for a history variable (childhood pneumonia), which reportedly did not alter the ETS results. The importance of prior lung disease as a factor in studies of ETS is thus unclear, but it does not appear to distort results one way or the other.

5.4.3. Family History of Lung Disease

Only a few of the studies addressed family history of lung disease. GAO found no significant association between family history of lung cancer and subjects' disease status (e.g., parental lung cancer OR = 1.1; 95% C.I. = 0.6, 2.3), and positive family histories were very rare (e.g., 1.0% among mothers of either cases or controls). In contrast, WUWI reports a significant association with history of lung cancer in first-degree relatives (OR = 1.8; 95% C.I. = 1.1, 3.0), which occurred in about 4.5% of the cases. The presence of TB in a household member (OR = 1.6; 95% C.I. = 1.2, 2.1) is also significant, even after adjustment for personal smoking and TB status. The rarity of family-linked lung cancer in these populations makes accurate assessment difficult and also reduces the potential impact on results of any effect it may have. Its study in populations where such cancer is more common would be more appropriate.

The household TB outcome may be the result of multiple comparisons and/or confounding, particularly in view of the weaker (nonsignificant) outcome noted for *personal* TB status.

5.4.4. Heat Sources for Cooking or Heating

Household heating and cooking technologies have received considerable attention as potential lung cancer risk factors in Asian ETS studies. Most studies have focused on fuel type. Kerosene was specifically examined in three studies. All three found positive associations--CHAN and LAMW for kerosene cooking, and SHIM for kerosene heating--but none of the associations were statistically significant, and the SHIM relationship held only for adult and not for childhood exposure. Five studies specifically examined coal. GENG evaluated use of coal for cooking and found a significant positive association. Use of coal for household cooking or heating prior to adulthood is significantly associated with lung cancer in WU's study of U.S. residents, but no results for adulthood are mentioned. Recent charcoal stove use showed a positive (OR = 1.7) but not significant association in SHIM. Separate analyses of five coal-burning devices and two non-coal-burning devices by WUWI found positive although not always significant associations for the coal burners. In contrast, SOBU found no association between use of unventilated heating devices--including mostly kerosene and coal-fueled types but also some wood and gas burners--and lung cancer (OR = 0.94 for use at age 15, 1.09 at age 30, 1.07 at present). Results for wood or straw cooking were specifically reported in three studies. SOBU found a significant association for use of wood or straw at age 30 (OR = 1.89; 95% C.I. = 1.16, 3.06) but only a weak relationship at age 15. GAO found no association with current use of wood for cooking (OR = 1.0; 95% C.I. = 0.6, 1.8), and WUWI mentions that years of household heating with wood, central heating, and coal showed nonsignificant trends (negative, negative, and positive, respectively).

Overall, studies that examined heating and cooking fuels generally found evidence of an association with lung cancer for at least one fuel, which was usually but not always statistically significant. Such relationships appeared most consistently for use of coal and most prominently in WUWI and LIU. Neither study found a significant association between ETS and lung cancer, nor did either address whether coal use was associated with ETS exposure. The presence of non-ETS sources of smoke within households, however, may effectively mask detection of any effect due to ETS (as noted by the authors of WUWI). Evidence of effects of other fuel types and devices is more difficult to evaluate, particularly because many studies do not report results for these factors, but kerosene-fueled devices seem worthy of further investigation.

5.4.5. Cooking With Oil

Cooking with oil was examined by GAO and WUWI, both conducted in China, with positive associations for deep-frying (OR ranges of 1.5-1.9 and 1.2-2.1, respectively, both increasing with frequency of cooking with oil). GAO also reports positive findings for stir-frying, boiling (which in this population often entails addition of oil to the water), and smokiness during cooking and found that most of these effects seemed specific for users of rapeseed oil.

These results may apply to other populations where stir-frying and certain other methods of cooking with oil are common. Neither study, however, addressed whether use of cooking with oil is correlated with ETS exposure.

5.4.6. Occupation

Seven studies investigated selected occupational factors, with five reporting positive outcomes for one or more occupational variables. The outcomes, however, are somewhat inconsistent. SHIM found a strong and significant relationship with occupational metal exposure (OR = 4.8) and a nonsignificant one with coal, stone, cement, asbestos, or ceramic exposure, while WUWI found significant positive relationships for metal smelters (OR = 1.5), occupational coal dust (OR = 1.5), and fuel smoke (OR = 1.6) exposure. Textile work is positively associated with lung cancer in KABA and negatively associated with lung cancer in WUWI. BUFF divided occupations into nine categories plus housewife and found eight positive and one negative associations relative to housewives, but only one ("clerical") is significant. GAO, on the other hand, found no association with any of six occupational categories, while GENG found a significant association for an occupational exposure variable that encompassed textiles, asbestos, benzene, and unnamed other substances (OR = 3.1; 95% C.I. = 1.58, 6.02). WU reported "no association between any occupation or occupational category," although there was a nonsignificant excess among cooks and beauticians. Finally, BUTL(Coh) found an increased RR for wives whose husbands worked in blue collar jobs (> 4; never-smoker). HIRA(Coh) did not present findings for husband's occupation as a risk factor independently but reported that adjustment for this factor did not alter the study's ETS results. Few studies attempted to adjust ETS findings for occupational factors--SHIM found only modest effects of such adjustment for occupational metal exposure, despite an apparent strong independent effect for this factor, and GENG found only minimal effect of occupational exposure on active smoking results but did no adjustment of ETS results. Overall, multiple comparisons, other factors (e.g., socioeconomic status, age), and the rarity of most specific occupational exposure sources probably account for the inconsistent role of occupation in these studies.

5.4.7. Dietary Factors

Investigations related to diet have been reported in nine of the ETS studies, with mixed outcomes. The fundamental difficulty lies in obtaining accurate individual values for key nutrients of interest, such as β-carotene. The relatively modest size of most ETS study populations adds further uncertainty in attempts to detect and assess any dietary effect that, if present, is likely to be small. In those studies where dietary data were collected and adjusted for in the analysis of ETS, diet has had no significant effect. Nevertheless, diet has received attention in the literature as a possible explanatory factor in the observed association between ETS exposure and lung cancer occurrence (e.g., Koo, 1988; Koo et al., 1988; Sidney et al., 1989; Butler, 1990, 1991; Marchand et al., 1991); therefore, a more detailed and specific discussion is provided in this section.

Diet is of interest for a potential protective effect against lung cancer. If nonsmokers unexposed to passive smoke have a lower incidence of spontaneous (unrelated to tobacco smoke) lung cancer incidence due to a protective

diet, then the effect would be upward bias in the RR for ETS. However, for diet to *explain* fully the significant association of ETS exposure in Greece, Hong Kong, Japan, and the United States, which differ by diet as well as other lifestyle characteristics, it would need to be shown that in *each* country: (1) there is a diet protective against lung cancer from ETS exposure, (2) diet is inversely associated with ETS exposure, and (3) the association is strong enough to produce the observed relationship between ETS and lung cancer. Diet may modify the magnitude of any lung cancer risk from ETS (conceivably increase or decrease risk, depending on dietary components), but that would not affect whether ETS is a lung carcinogen.

The literature on the effect of diet on lung cancer is not consistent or conclusive, but taken altogether there may be a protective effect from a diet high in β-carotene, vegetables, and possibly fruits. Also, there is some evidence that low consumption of these substances may correlate with increased ETS exposure, although not necessarily for all study areas. The calculations made by Marchand et al. (1991) and Butler (1990, 1991) are largely conjectural, being based only on *assumed* data. Therefore, we examined the passive smoking studies themselves for empirical evidence on the effect of diet and whether it may affect ETS results.

It was found that nine of the studies have data on diet, although only five of them use a form of analysis that assesses the impact of diet on the ETS association. None of those five studies--CORR, HIRA(Coh), KALA, SHIM, and SVEN--found that diet made a significant difference. In the four studies where data on diet were collected but not controlled for in the analysis of ETS, three (GAO, KOO, and WUWI) are from East Asia and one (WU) is from the United States. Koo (1988), who found strong protective effects for a number of foods, has been one of the main proponents of the idea that diet may explain the passive smoking lung cancer effect. To our knowledge, however, she has not published a calculation examining that conjecture in her own study where data were collected on ETS subjects. In WU, a protective effect of β-carotene was found, but the data include a high percentage of smokers (80% of the cases for adenocarcinoma, 86% for squamous cell), and the number of never-smokers is small. In recent correspondence concerning the large FONT study, its authors state that "mean daily intake of beta-carotene does not significantly differ between study subjects whose spouse smoked and those whose spouse never smoked" (Fontham et al., 1992).

The equivocal state of the literature regarding the effect of diet on lung cancer is also apparent in the nine ETS studies that include dietary factors, summarized in Table 5-15

Table 5-15. Dietary effects in passive smoking studies of lung cancer in females

(continued on the following page)

Table 5-15. (continued)

Table 5-15. (continued)

. Note that GAO found an adverse effect from β-carotene. HIRA and KOO found opposite effects from fish while SHIM found no effect. Fruit was found to be protective by KALA and KOO but adverse by SHIM and WUWI. Retinol (based on consumption of eggs and dairy products) was found to be protective by KOO but adverse by GAO and WUWI.

In view of the results summarized in Tables 5-14 and 5-15, the actual data of ETS studies do not support the suspicion that diet introduces a systematic bias in the ETS results. Indeed, it would be difficult to show otherwise. Dietary intake is difficult to assess; dietary habits vary within countries and enormously between countries, making it difficult to attribute any effect on lung cancer to a particular food group; lifestyle characteristics and consumption of food and beverage with possibly an adverse effect may be associated, either positively or negatively, with the food group under consideration. It would, of course, be helpful to identify dietary factors that may affect lung cancer, positively or negatively, because that information could usefully contribute to public health. To affect interpretation of ETS results, however, it would need to be established also that consumption of the dietary factor of interest is highly correlated with ETS exposure in study populations where ETS exposure is linked with increased incidence of lung cancer.

5.4.8. Summary on Potential Modifying Factors

In summary, an examination of six non-ETS factors that may affect lung cancer risk finds none that explains the association between lung cancer and ETS exposure as observed by independent investigators across several countries that vary in social and cultural behavior, diet, and other characteristics. On the other hand, the high levels of indoor air pollution from other sources (e.g., smoky coal) that occur in some parts of China and show statistical associations with lung cancer in the studies of GENG, LIU, and WUWI may mask any ETS effects in those studies.

5.5. ANALYSIS BY TIER AND COUNTRY

In this section, attention is directed to properties of individual studies, including potential sources of bias, that may affect their utility for the assessment of ETS and lung cancer. Studies are assessed based on qualitative as well as statistical evaluation. The studies are qualitatively reviewed in Appendix A and categorized into "tiers" within country. Studies are individually scored according to items in eight categories. Study scores are then implemented in a numerical scheme to classify each study into one of four tiers according to that study's assessed utility for hazard identification of ETS. Tier 1 studies are those of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. Tier 4 is reserved for studies we would exclude from analysis for ETS, for various reasons specified in the text. In the statistical analysis presented in this section, the summary RR for each country is recalculated for studies in Tier 1 alone and for Tiers 1-2, 1-3, and 1-4 (the last category corresponds to the combined analysis shown in Table 5-9) by country. This exercise provides some idea of the extent to which the summary RR for a country depends on the choice of studies.

The assignment of studies to tiers is shown in Table 5-16

Table 5-16. Classification of studies by tier

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
Greece	KALA	X			
Greece	TRIC			X	
Hong Kong	KOO	X			
Hong Kong	LAMT		X		
Hong Kong	LAMW			X	
Hong Kong	CHAN				X
Japan	AKIB		X		
Japan	HIRA(Coh)		X		
Japan	SHIM		X		
Japan	SOBU		X		
Japan	INOU				X
United States	FONT	X			
United States	BUTL(Coh)		X		
United States	GARF		X		
United States	HUMB		X		
United States	JANE		X		
United States	WU		X		
United States	BROW		X		
United States	BUFF			X	
United States	CORR		X		
United States	GARF(Coh)			X	
United States	KABA		X		

(continued on the following page)

Table 5-16. (continued)

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
W. Europe					
Scotland	HOLE(Coh)	X			
Sweden	PERS	X			
Sweden	SVEN		X		
England	LEE		X		
China	GAO			X	
China	GENG				X
China	LIU				X
China	WUWI				X

. Overall, 5 studies are in the highest tier, while 15, 5, and 5 studies are in Tiers 2, 3, and 4, respectively (KATA was not assigned to a tier). Studies in Tier 4 are not recommended for the objectives of this report. The statistical weight for Tiers 1, 2, and 3 pooled together for each country is shown in Table 5-9 as a percentage of the total for corresponding tiers over all countries. Emphasis on studies through Tier 2 or through Tier 3 is somewhat arbitrary. Although studies in Tier 1 are judged to be of the highest utility, exclusive attention to Tier 1 would eliminate considerable epidemiologic data because only 16% of the studies are in Tier 1. Excluding Tier 4 leaves the choices to either all studies through Tier 2 or through Tier 3. GAO is the only study in China that was not placed in Tier 4, but there is little basis to assume that this single study from Shanghai should be representative of a vast country like China.

Table 5-17

Table 5-17.

Table 5-17. (continued)

presents adjusted relative risk estimates, 90% confidence intervals, and significance levels (one-sided) from studies pooled by country and by tier. The pooled relative risks do not decrease as the results from studies in Tier 2 and Tier 3 are combined with those from Tier 1, with two exceptions: In the United States, the pooled estimate changes from 1.28 to 1.22 to 1.19 when Tier 2 and Tier 3 studies are added, respectively, and in Western Europe, the pooled estimate changes from 1.21 to 1.17 when Tier 2 studies are added. The pooled estimates for studies through Tier 2 are statistically significant at $p = 0.02$ (one-tailed) in Greece, Hong Kong, Japan, and the United States; Western Europe is the exception ($p = 0.22$). The same statement holds with Tier 2 replaced by Tier 3, except that China includes one study at $p = 0.18$. The relative risk results from all four Western European studies (RR = 1.17) is virtually the same for all U.S. studies (RR = 1.19), but with less power that value is not significant for Western Europe. The similarity of outcomes is also interesting, however, because Western Europe is probably more similar to the United States than the other countries.

Analysis by tiers provides a methodology for weighting studies according to their utility for hazard identification of ETS. It allows one to emphasize those studies thought to provide better data for analysis of an ETS effect. The addition of studies of lower utility to the analysis, such as inclusion of Tier 3 studies with those from Tiers 1 and 2, has a small effect on the relative risk estimate but both increases its statistical significance and narrows its confidence interval. In view of that outcome and the results and discussion in Section 5.4, this analysis finds little to indicate confounding or bias in studies through Tier 3 (which include all studies in the United States). In summary, it is concluded that the association of ETS and lung cancer observed from

the analysis of 30 epidemiologic studies in eight different countries is not due to chance alone and is not attributable to bias or confounding.

5.6. CONCLUSIONS FOR HAZARD IDENTIFICATION

5.6.1. Criteria for Causality

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

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

As demonstrated in the preceding sections, the overall results observed in the 30 epidemiologic studies are not attributable to chance and the association between ETS and lung cancer is not explained by bias or confounding.

Below, the evidence for a causal association between ETS and lung cancer is evaluated according to seven specific criteria for causality developed by an EPA workshop to supplement the *Guidelines* (U.S. EPA, 1989). These criteria are similar to the original and classical recommendations of Hill (1953, 1965). The seven recommended (but not official) criteria from the EPA workshop, which vary between essential and desirable, are listed below (U.S. EPA, 1989).

> A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of these actually establishes causality; actual proof is rarely attainable when dealing with environmental carcinogens. The absence of any one or even several of the others does not prevent a causal interpretation. Only the first criterion (temporal relationship) is essential to a causal relationship: with that exception, none of the criteria should be considered as either necessary or sufficient in itself. The first six criteria apply to an individual study. The last criterion (coherence) applies to a consideration of all evidence in the entire body of knowledge.
>
> 1. Temporal relationship: The disease occurs within a biologically reasonable timeframe after the initial exposure to account for the specific health effect.
>
> 2. Consistency: When compared to several independent studies of a similar exposure in different populations, the study in question demonstrates a similar association which persists despite differing circumstances. This usually constitutes strong evidence for a causal interpretation (assuming the same bias or confounding is not also duplicated across studies).
>
> 3. Strength of association: The greater the estimate of risk and the more precise, the more credible the causal association.
>
> 4. Dose-response or biologic gradient: An increase in the measure of effect is correlated positively with an increase in the exposure or estimated dose. If present, this characteristic should be weighted heavily in considering causality. However, the absence of a dose-response relationship should not be construed by itself as evidence of a lack of a causal relationship.
>
> 5. Specificity of the association: In the study in question, if a single exposure is associated with an excess risk of one or more cancers also found in other studies, it increases the likelihood of a causal interpretation.
>
> 6. Biological plausibility: The association makes sense in terms of biological knowledge. Information from toxicology, pharmacokinetics, genotoxicity, and in vitro studies should be considered.
>
> 7. Coherence: Coherence exists when a cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease. A proposed association that conflicted with existing knowledge would have to be examined with particular care. (This criterion has been called "collateral evidence" previously.)

5.6.2. Assessment of Causality

We consider the extent to which the criteria for causality are satisfied for the ETS studies. Regarding *temporal relationship*, ETS exposure classification is typically based on the marital history of a subject, which varies, or on the status at the beginning of a prospective cohort study. Very few studies up through Tier 3 considered current exposure status only (see Appendix A), so some history of ETS exposure is largely the rule for ETS-exposed subjects.

Analysis of data by exposure level in Section 5.3.3 indicates increased relative risk with exposure level, which supports the temporal relationship.

If ETS causes lung cancer, then the true relative risk is small for detection by epidemiologic standards and may differ between countries as well. However, by considering the totality of the evidence, it is determined that the large accumulation of epidemiologic evidence from independent sources in different locales and circumstances, under actual exposure conditions, is adequate for conclusiveness. Having accounted for variable study size, adjusted for a possible systematic spousal bias due to smoker misclassification, and considered potential bias, confounding, and other sources of uncertainty on a study-by-study basis, *consistency* of a significant association is clearly evident for the summary statistical measures for Tiers 1 through 2 and 1 through 3 in Greece, Hong Kong, Japan, and the United States. The combined countries from Western Europe are similar in outcome to the United States, although significance is not attained. There is too much obscurity and uncertainty attached to the studies in China for adequate data interpretation.

The relative risks for each country are obtained by pooling estimates from the epidemiologic studies conducted in the country. The *strength of association* is limited by the true value of the relative risk, which is small. Statistical significance is attained, however, for the pooled studies of the United States and most other countries. The data were obtained from actual conditions of environmental exposure; therefore, imprecision is not increased by extrapolation of results from atypically high exposure concentrations, a common situation in risk analysis. Additionally, all studies were individually corrected for systematic bias from smoker misclassification at the outset, and qualitative characteristics of the studies were carefully reviewed to emphasize the results from the studies with higher utility for the objectives of this report. The outcome for the United States is heavily influenced by the large National Cancer Institute study (FONT) that was specifically designed and executed to avoid methodological problems that might undermine the accuracy or precision of the results.

Of the 14 studies reporting a test for upward trend, 10 are statistically significant at 0.05 (see Table 5-12) which would occur by chance alone with probability less than 10^{-9}. This evidence of *dose response* is very supportive of a causal interpretation because it would be an unlikely result of any operative sources of bias or confounding.

Specificity does not apply to ETS. Although ETS has been assessed for the same endpoint (lung cancer) in all studies, the occurrence of lung cancer is not specific to ETS exposure. Data on histological cell type are not conclusive. The study by Fontham and colleagues (1991) suggests that adenocarcinoma may be more strongly related to ETS exposure than other cell types. Adenocarcinoma, however, does not appear to be etiologically specific to ETS.

Biomarkers such as cotinine/creatinine levels clearly indicate that ETS is taken up by the lungs of nonsmokers (see Chapter 3). The similarity of carcinogens identified in sidestream and mainstream smoke, along with the established causal relationship between lung cancer and smoking in humans with high relative risks and dose-response relationships in four different lung cell types down to low exposure levels, provide *biological plausibility* that ETS is also a lung carcinogen (Chapter 4). In addition, animal models and genotoxicity assays provide corroborating evidence for the carcinogenic potential of ETS (Chapter 4). The epidemiologic data provide

independent empirical verification of the anticipated risk of lung cancer from passive smoking and also an estimate of the increased risk of lung cancer to never-smoking women. The *coherence* of results from these three approaches and the lack of significant arguments to the contrary strongly support causality as an explanation of the observed association between ETS exposure and lung cancer.

5.6.3. Conclusion

Based on the assessment of all the evidence considered in Chapters 3, 4, and 5 of this report and in accordance with the EPA *Guidelines* and the causality criteria above for interpretation of human data, this report concludes that ETS is a Group A human carcinogen, the EPA classification "used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer" (U.S. EPA, 1986a).