6. POPULATION RISK OF LUNG CANCER FROM PASSIVE SMOKING

6.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that environmental tobacco smoke (ETS) exposure is causally associated with lung cancer. If an effect is large enough to detect in epidemiologic studies investigating the consequences of ETS exposure at common exposure levels, the individual risk associated with exposure is considered to be high compared with most environmental contaminants assessed. Of course, the number of lung cancer deaths attributable to ETS exposure for a whole population, such as the United States, depends on the number of persons exposed as well as the individual risk. Studies of cotinine/creatinine concentrations in nonsmokers indicate that ETS is virtually ubiquitous. For example, in urinary bioassays of 663 nonsmokers, Cummings et al. (1990) found that over 90% had detectable levels of cotinine. Among the 161 subjects who reported no recent exposure to ETS, the prevalence of detectable cotinine was still about 80%. Although the average cotinine level for all those tested may be below the average for subjects exposed to spousal ETS, as studied in this report, it indicates uptake of ETS to some extent by a large majority of nonsmokers (see also Chapter 3). Consequently, exposure to ETS is a public health issue that needs to be considered from a national perspective.

This chapter derives U.S. lung cancer mortality estimates for female and male never-smokers and long-term (5+ years) former smokers. Section 6.2 discusses prior approaches to estimating U.S. population risk. Section 6.3 presents this report's estimates. First, the parameters and formulae used are defined (Section 6.3.2), and then lung cancer mortality estimates are calculated from two different data sets and confidence and sources of uncertainty in the estimates are discussed. Section 6.3.3 derives estimates based on the combined relative risk estimates of the 11 U.S. studies from Chapter 5. Section 6.3.4 bases its estimates on the data from the single largest U.S. study, that of Fontham et al. (1991). Finally, Section 6.3.5 discusses the sensitivity of the estimates to changes in various parameter values. ETS-attributable lung cancer mortality rates (LCMR) for each of the individual studies from Chapter 5 are presented in Appendix C.

6.2. PRIOR APPROACHES TO ESTIMATION OF POPULATION RISK

Several authors have estimated the population risk of lung cancer from exposure to ETS. Two approaches have been used almost exclusively. One approach analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report; the other estimates a dose-response relationship for ETS exposure extrapolated from active smoking, based on "cigarette-equivalents" determined from a surrogate measure of exposure common to passive and active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

6.2.1. Examples Using Epidemiologic Data

The National Research Council report (NRC, 1986) is a good example of the epidemiologic approach. An overall estimate of relative risk (RR) of lung cancer for never-smokers exposed to both spousal smoking and background ETS versus those exposed only to background ETS is obtained by statistical summary across all available studies. Two "corrections" are then made to the estimate of RR to correct for the two sources of systematic bias. The first correction accounts for expected upward bias from former smokers and current smokers who may be misclassified as never-smokers; this correction results in a decrease in the RR estimate. The second correction is an upward adjustment to the RR taking into account the risk from background exposure to ETS (experienced by a never-smoker whether married to a smoker or not) to obtain estimates of the excess lung cancer risk from all sources of ETS exposure (spousal smoking and background ETS) relative to the risk in an ETS-free environment. Population risk can then be characterized by estimating the annual number of lung cancer deaths among never-smokers attributable to all sources of ETS exposure. This calculation requires the final corrected estimates of RR (one for background ETS only and one for background plus spousal smoking), the annual number of lung cancer deaths (LCDs) from all causes in the population assessed (e.g., never-smokers of age 35 and over), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to some average background level of ETS; although, in fact, the population contains some individuals with high exposure and others with virtually no exposure.

The NRC report combines data for female and male never-smokers to obtain an overall observed RR estimate of 1.34 (95% confidence interval [C.I.] = 1.18, 1.53), but this estimate is most heavily influenced by the abundant female data. (The female data alone generate a combined RR estimate of 1.32 [95% C.I. = 1.18, 1.52], while the male data produce an RR estimate of 1.62 [95% C.I. = 0.99, 2.64].) To adjust for potential misclassification bias, the NRC uses the construct of Wald and coworkers. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. After correcting the overall observed RR estimate of 1.34 downward for an expected positive (upward) bias from smoker misclassification, the NRC concludes that the relative risk is about 1.25, and probably lies between 1.15 and 1.35. Correction for background sources (i.e., nonspousal sources of ETS) increases the NRC estimate of RR for an "exposed" person (i.e., exposed to ETS from spousal smoking) to 1.42 (range of 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS exposure instead of relative to nonspousal sources of ETS. Under this redefinition, the RR for an "unexposed" person (i.e., unexposed to spousal ETS) versus a truly unexposed person (i.e., in a zero-ETS environment) becomes 1.14 (range of 1.08 to 1.21). The NRC report further estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C); these estimates, however, are based on RRs corrected for background ETS but not for smoker misclassification. Applying these percentages to estimates of 6,500 LCDs in never-smoking women and 3,000 LCDs in never-smoking men in 1988 (American Cancer Society, personal communication), the number attributable to ETS exposure is 1,365 and 600, respectively, for a total of about 2,000 LCDs among never-smokers of both sexes.

Robins (NRC, 1986, Appendix D [included in the NRC report but neither endorsed nor rejected by the committee]) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant

assumptions clearly stated. A related article by Robins et al. (1989) contains most of the same information. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: (1) correction of relative risk for background exposure to ETS independent of age, and (2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. In this method, Robins uses a weighted average RR of 1.3. After correcting this RR for background ETS exposure, age-adjusted population-attributable risks are calculated for females and males separately. Adjusting Robins' results to 6,500 annual LCDs in female never-smokers and 3,000 LCDs in male never-smokers, for comparison purposes, yields estimates of 1,870 female LCDs and 470 male LCDs attributable to ETS. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. Again, adjusting Robins' estimates to 6,500 female LCDs and 3,000 male LCDs, the range of excess LCDs attributable to ETS is 1,650 to 2,990 for never-smoking females and 420 to 1,120 for never-smoking males. Method 3 is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

The Centers for Disease Control (CDC) has published an estimate of 3,825 (2,495 female and 1,330 male) deaths in nonsmokers from lung cancer attributable to passive smoking for the year 1988 (CDC, 1991a), with reference to the NRC report of 1986. Those figures are the midrange of values for males and females from method 2 of Robins in Appendix D of the NRC report (NRC, 1986).

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time that the reports of the Surgeon General and NRC appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report, except for omission of one cohort study (Gillis et al., 1984), and inclusion of Wu et al. (1985), the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. = 1.1, 1.5). When the results are combined for high-exposure categories, the overall relative risk estimate is 1.7 (1.4, 2.1).

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and Surgeon General's reports of 1986 (NRC, 1986; U.S. DHHS, 1986). Like the NRC report, the epidemiologic data for both women and men are considered, for which Wells provides separate estimates of overall relative risk and attributable risk. Wells calculates an overall relative risk of 1.44 (95% C.I. = 1.26, 1.66) for females and 2.1 (1.3, 3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ever-smokers is assumed to be 5% (compared to 7% for Wald et al.). Rates are corrected for background exposure to ETS, except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins, NRC, Appendix D). The calculation of population-attributable risk applies to former smokers as well as never-smokers, which is a departure from Wald et al. and the NRC report. The annual number of LCDs attributable to ETS in the United States is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be the best current estimate (Wells, 1988). (In addition to the estimates of ETS-attributable LCDs, Wells uses the

epidemiological approach to derive estimates of ETS-attributable deaths from other cancers--11,000--and from heart disease--32,000.)

Saracci and Riboli (1989), of the International Agency for Research on Cancer (IARC), review the evidence from the 3 cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. with respect to the exclusion of studies, and add only one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (95% C.I. = 1.20, 1.53), is about the same as that reported by the NRC, 1.34 (1.18, 1.53). It is not reported how the overall relative risk was calculated.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. One method is based on epidemiologic data, but, unlike the previous examples, Repace and Lowrey use a study comparing Seventh-Day Adventists (SDAs) (Phillips et al., 1980a,b) with a demographically and educationally matched group of non-SDAs who are also never-smokers to obtain estimates of the relative risk of lung cancer mortality, in what they describe as a "phenomenological" approach. The SDA/non-SDA comparison provides a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the other epidemiologic studies. It also serves as an independent source of data and an alternative approach for comparison. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The basis for comparison of the two groups is the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA group due to differences in lifestyle. Relatively few SDAs smoke, so an SDA never-smoker is probably less likely to be exposed at home by a smoking spouse, in the workplace, or elsewhere, if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. (1980 a,b) reported that the non-SDA cohort experienced an average LCMR equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in LCMR for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million never-smokers in the United States in 1979 to obtain the number of LCDs attributable to ETS annually. The result, 4,665, corresponds to a risk rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1,000 people exposed. The second method described by Repace and Lowrey is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

Wigle et al. (1987) apply the epidemiologic evidence from the SDA/non-SDA study (Phillips et al., 1980a,b) to obtain estimates of the number of LCDs in never-smokers due to ETS in the population of Canada. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and the age-specific rates of death from lung cancer attributable to ETS estimated by Repace and Lowrey (1985). A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually.

6.2.2. Examples Based on Cigarette-Equivalents

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after extrapolation of the curve to lower doses and conversion of ETS exposure into an "equivalent" exposure from active smoking, determined from a surrogate measure of exposure common to passive and active smoking. Relative cotinine concentrations in body fluids (urine, blood, or saliva) of smokers versus nonsmokers and tobacco smoke particulates in sidestream smoke (SS) and mainstream smoke (MS) have commonly been used for this purpose. The lung cancer risk of ETS is assumed to equal the risk from active smoking at the rate determined by the cigarette-equivalents. For example, suppose the average cotinine concentration in exposed never-smokers is 1% of the average value found in people who smoke 30 cigarettes per day. The lung cancer risk for a smoker of $(0.01)30 = 0.3$ cigarettes per day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both. This assumption may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physicochemical properties in general; the lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages. Active and passive smoking also differ in characteristics of intake; for example, intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation, which may affect deposition and systemic distribution of various tobacco smoke components as well (see Sections 3.2 and 3.3.2).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, conclude that "the differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989) states, "Lacking knowledge of which substances are responsible for the well-established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The Surgeon General's report devotes a three-page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. DHHS, 1986). It concludes that "these limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." (On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well characterized. Recent literature raises some questions on this issue [Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a,b; Whittemore, 1988].)

Citing cigarette-equivalents calculated in other sources, Vutuc (1984) assumes a range of 0.1 to 1.0 cigarettes per day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Doll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cigarettes per day give a range in relative risk from 1.03 to 1.36. The author concludes that "as it applies to passive smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. If the number of LCDs among never-smokers in the United States in 1988 is about 6,500 females and 3,000 males (personal communication from the American Cancer Society), then the number of LCDs in never-smokers attributable to ETS is estimated to range from 240 to 2,020 (140 to 1,380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among never-smokers in the United States. These estimates are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as an alternative to their "phenomenological" approach discussed in Section 6.2.1. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-6} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that inhaled tobacco tar poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (never-smokers and former smokers) are attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including former smokers).

Method 3 of Robins (NRC, 1986, Appendix D--again, included in the NRC report but not specifically endorsed by the committee) extrapolates from data on active smoking, along with several assumptions. Applying his results to 6,500 females and 3,000 males, the range of excess LCDs in never-smokers due to ETS is 550 to 2,940 for females and 153 to 1,090 for males.

Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive

to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4,000+ deaths per year due to passive smoking, is for all causes of death, not just LCDs.

Arundel et al. (1987) attributes only five LCDs among female never-smokers to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6,500 females and 3,000 males). The expected lung cancer risk for never-smokers is estimated by downward extrapolation of the lung cancer risk per mg of particulate ETS exposure for current smokers. The authors' premise is that the lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase (e.g., see Wells, 1991).

6.3. THIS REPORT'S ESTIMATES OF LUNG CANCER MORTALITY ATTRIBUTABLE TO ETS IN THE UNITED STATES

6.3.1. Introduction and Background

This report uses the epidemiologic approach because of the abundance of human data from actual environmental exposures. Furthermore, the assumptions are fewer and more valid than for the cigarette-equivalents approach. The report generally follows the epidemiologic methodology used by the NRC (NRC, 1986) and others (Section 6.2.1), with three important differences. The first difference is that the NRC combined the data on females and males for its summary relative risk estimate. This report uses only the data on females because there are likely to be true sex-based differences in relative risk due to differences in exposure to background ETS and differences in background (i.e., non-tobacco-smoke-related) lung cancer risk. Furthermore, the vast majority of the data are for females. The second difference is that the NRC combined study estimates of relative risk across countries for its summary relative risk estimate; this report combines relative risk estimates only within countries, and then bases the U.S. population risk assessment on the U.S. estimate only. As discussed in Chapter 5, there are apparently true differences in the observed relative risk estimates from different countries, which might reflect lifestyle differences, differences in background lung cancer rates in females, exposure to other indoor air pollutants, and differences in exposure to background levels of ETS. Therefore, for the purposes of U.S. population risk assessment, it is appropriate to use the U.S. studies; in addition, far more studies are currently available so there is less need to combine across countries. The third difference is that the NRC corrected its overall estimate of relative risk downward for smoker misclassification bias. In this report, the individual study estimates are corrected for smoker misclassification bias at the outset, i.e., prior to any analysis, using the particular parameters appropriate for each separate study (Appendix B).

The basic NRC model is defined as

$$RR(d_E) = (1 + Z * \beta d_N)/(1 + \beta d_N)$$

where $RR(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS); Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N; and β is the amount of increased risk per unit dose. The equation is only defined for $Z > RR(d_E) > 1$ (see Section 8.3).

The method used here is based on several assumptions: (1) that body cotinine levels in never-smokers are linearly related to ETS exposure; (2) that current ETS exposure is representative of past exposures; and (3) that the excess risk of lung cancer in nonsmokers exposed to ETS is linearly related to the dose absorbed.

Estimates of $RR(d_E)$ for female never-smokers were derived in Chapter 5, where they were corrected for smoker misclassification bias; these are redefined in Section 6.3.2 as RR_2. The relative risk estimates are then adjusted to be applicable to different baseline exposure groups in order to calculate population risks for never-smoking women. In order to extend the analyses to female former smokers and male never- and former smokers, the relative risks are converted to excess or additive risks. The use of additive risks is more appropriate for these groups because of the different baseline lung cancer mortality rates by sex and smoking status (former vs. never).

More specifically, estimates of ETS-attributable population mortality are calculated from female lung cancer mortality rates, which are themselves derived from summary relative risk estimates either from the 11 U.S. studies combined (Section 6.3.3) or from the Fontham et al. (1991) study alone (Section 6.3.4), along with other parameter estimates from prominent sources (Section 6.3.2). The LCMRs in this instance are defined as the number of LCDs in 1985 per 100,000 of the population at risk. The LCMR in U.S. women under age 35 is minuscule, so only persons of age 35 and above are considered at risk. Although these LCMRs are expressed as a mortality rate per 100,000 of the population at risk, as derived they are applicable only to the entire population at risk and not to any fraction thereof that might, for example, have a different average exposure or age distribution.

The LCMR for the subpopulation and exposure scenario to which the epidemiologic studies apply most directly--never-smoking females exposed to spousal ETS--is estimated first. That estimate is then incremented to include exposure to nonspousal ETS for all never-smoking females. For the ETS-attributable population mortality estimates, these LCMRs are applied to never-smoking males and former smokers at risk, as well as to the females at risk for which the rates were specifically derived. The most reliable component of the total estimate constructed for the United States is the estimate for the female never-smokers exposed to spousal ETS. The other components require additional assumptions, which are described. As the number of assumptions increases, so does the uncertainty of the estimates. Thus, the total estimate of lung cancer risk to U.S. nonsmokers of both sexes is composed of component estimates of varying degrees of certainty.

One might argue that smokers are among those most heavily exposed to ETS, since they are in close proximity to sidestream smoke (the main component of ETS) from their own cigarettes and are also more likely than never-smokers to be exposed to ETS from other smokers. The purpose of this report, however, is to address

respiratory health risks from ETS exposure in nonsmokers. In current smokers, the added risk from passive smoking is relatively insignificant compared to the self-inflicted risk from active smoking.

6.3.2. Parameters and Formulae for Attributable Risk

Several parameters and formulae are needed to calculate attributable risk. These are presented in Table 6-1, with the derivations explained below.

The size of the target population, in this case the number of women in the United States of age 35+ in 1985, is denoted by N, with $N = N_1 + N_2$, where N_1 = the number of ever-smokers and N_2 = the number of never-smokers. The total number of LCDs from all sources, T, is apportioned into components from four attributable sources: (1) non-tobacco-smoke-related causes, the background causes that would persist in an environment free of tobacco smoke; (2) background ETS, which refers to all ETS exposure other than that from spousal smoking; (3) spousal ETS; and (4) ever-smoking. The risk from non-tobacco-smoke-related causes (source 1) is a baseline risk (discussed below) assumed to apply equally to the entire target population (never-smokers and ever-smokers alike). The ever-smoking component of attributable risk (source 4) refers to the incremental risk above the baseline in ever-smokers (this report does not partition the incremental risk in ever-smokers further into components due to background ETS and spousal ETS, except for long-term [5+ years] former smokers). The background ETS component (source 2) is the incremental risk above the baseline in all never-smokers from exposure to nonspousal sources of

Table 6-1. Definition and estimates of relative risk of lung cancer for 11 U.S. studies combined for various exposure sources and baselines; population parameter definitions and estimates used to calculate U.S. population-attributable risk estimates for ETS

DENOMINATOR (Baseline)	NUMERATOR of relative risk			
	All persons	Never-smokers ETS exposure		Current and former smokers
Source of exposure	Non-tobacco-smoke sources of exposure [nt]	Background ETS [nt]+[ETS_B]	Background ETS and spousal ETS [nt]+[ETS_B]+[ETS_S]	Active smoking [nt]+[ETS]+[ACT]
[nt]	1	RR_{03} = 1.34	RR_{02} = 1.59[1]	RR_{01} = 13.8
[nt]+[ETS_B]	-	-	RR_2 = 1.19[2]	RR_{11} = 10.3
[nt]+[ETS_B]+[ETS_S]	-	-	-	RR_1 = 9.26[3]

[1]Basic adjustment for background exposure with Z = 1.75.
[2]Pooled value from 11 U.S. studies for never-smoking females.
[3]RR_1 = a weighted average of 11.94 for women active smokers (63.4%) and 4.69 for women former smokers (36.6%) = 9.26.

Definitions and Estimates of Population Parameter Values

N = Total number of women in U.S. (1985) age 35+ = N_1 (ever-smokers) + N_2 (never-smokers) = 25.7 million + 32.3 million = 58 million.
P_1 = Prevalence (proportion) of female ever smokers age 35+ = 0.443.
P_2 = Proportion of NS women exposed to equivalent spousal ETS (plus background ETS) = 0.6.
Z = Ratio of body cotinine levels in (nonsmokers exposed to background ETS plus spousal ETS) to (nonsmokers exposed to background ETS only) = 1.75.
T = Total LCDs in United States in 1985 among women aged 35+ = 38,000.

ETS. The spousal ETS component (source 3) is the additional incremental risk in never-smokers exposed to spousal smoking.

The calculational formulae also require values for the parameters P_1 (prevalence of ever-smokers), P_2 (proportion of never-smokers exposed to spousal smoking), RR_1 (average lung cancer risk for ever-smokers relative to the average risk for never-smokers in the population), and RR_2 (lung cancer risk of never-smokers exposed to spousal ETS relative to never-smokers not exposed to spousal ETS). Additional parameters (RR_{11}, Z, RR_{01}, RR_{02}, and RR_{03}) are introduced or developed below.

The "baseline" risk is defined as the term in the denominator of a risk ratio. For example, in RR_1 the baseline risk is the lung cancer risk in a population of never-smokers with P_2 exposed to spousal ETS and $1 - P_2$ not exposed to spousal ETS. The conversion of RR_1 to the same baseline risk as RR_2 (the risk of never-smokers not exposed to spousal ETS but still exposed to non-tobacco-smoke-related causes and to background ETS), is given by

$$RR_{11} = RR_1(P_2RR_2 + 1 - P_2). \qquad (6\text{-}1)$$

To convert relative risks to the baseline risk of lung cancer from non-tobacco-smoke-related causes only (i.e., excluding background ETS in the baseline) requires some assumptions. Let RR_{02} denote the conversion of RR_2 to this new baseline. It is assumed that: (1) the excess risk of lung cancer from ETS exposure is proportional to ETS exposure; and (2) the ratio of ETS exposure from spousal smoking plus other sources to exposure from other sources alone, denoted by Z, is known and $Z > RR_2 > 1$. (For the values used in this report, this relation is true. See also the discussion in Section 8.3.) Under these assumptions, $RR_{02} = 1 + \beta Z d_N$ (from Section 6.3.1), or

$$RR_{02} = (Z - 1)/(Z/RR_2 - 1). \qquad (6\text{-}2)$$

Determination of a value for Z from data on cotinine concentrations (or cotinine/creatinine) is discussed below. The conversion of RR_1 to the same zero-ETS baseline risk as RR_{02} follows from multiplying expression (6-1) by RR_{02}/RR_2, i.e.,

$$RR_{01} = RR_1(P_2RR_{02} + (1 - P_2)RR_{02}/RR_2). \qquad (6\text{-}3)$$

The terms RR_{01} and RR_{02} are the lung cancer risks for ever-smokers and for never-smokers exposed to spousal ETS, respectively, relative to the risk for never-smokers in a zero-ETS environment. The risk of never-smokers not exposed to spousal ETS (but exposed to background ETS and nonsmoking causes) relative to the zero-ETS baseline risk is

$$RR_{03} = RR_{02}/RR_2. \qquad (6\text{-}4)$$

The population-attributable risk of lung cancer in the total population for a source (risk factor) is a ratio. The numerators of the ratios for sources of tobacco smoke are:

current/former active smoking in ever-smokers,
$P_1(RR_{01} - 1)$; (6-5)

background ETS plus spousal ETS in never-smokers exposed to both,
$(1 - P_1)P_2(RR_{02} - 1)$; and (6-6)

background ETS in never-smokers not exposed to spousal ETS,
$(1 - P_1)(1 - P_2)(RR_{02}/RR_2 - 1)$. (6-7)

The denominator for each term is their sum plus one, i.e.,

$$Ex(6\text{-}5) + Ex(6\text{-}6) + Ex(6\text{-}7) + 1 \quad (6\text{-}8)$$

where Ex(6-5) refers to expression (6-5), etc. The population-attributable risk for remaining causes of lung cancer (non-tobacco-smoke-related background causes) is

$$1/Ex(6\text{-}8). \quad (6\text{-}9)$$

Multiplying the population-attributable risk for a source by the total number of LCDs yields the number of LCDs attributable to that source. An alternative and equivalent derivation of the source-attributable LCD estimates can be performed by first calculating LCMRs. LCMRs are obtained for each source as follows:

non-tobacco-smoke-related causes: $LCMR_{nt} = 10^5 Ex(6\text{-}9)T/N$.
ever-smoking: $LCMR_{nt}(RR_{01} - 1)$.
spousal ETS: $LCMR_{nt}(RR_{02} - RR_{03})$.
background ETS: $LCMR_{nt}(RR_{03} - 1)$.

Then the number of LCDs attributable to a source is estimated by multiplying the LCMR for that source by the total population at risk from that source.

We now consider parameter values for N, T, P_1, P_2, RR_1, and Z to be used with the value 1.19 for RR_2, the pooled estimate of RR_2 from the 11 U.S. studies (Table 5-17), for the population risk assessment in Section 6.3.3. The value used for RR_2 is then changed to 1.28, the estimate from the Fontham et al. (1991) study in the United States, and a new value of Z is constructed from the cotinine data in that study for the alternative population risk assessment calculations in Section 6.3.4. The female population in 1985 of age 18+ years of age is approximately 92 million (U.S. DHHS, 1989, Chapter 3). Detailed census data by age for 1988 indicate that the proportion of women 35+ years of age in the female population of age 18+ is 0.63 (U.S. Bureau of the Census, 1990). Applying that proportion

to the 1985 population gives approximately 58 million women of aged 35+ in 1985, the value used for N. There were approximately 38,000 female LCDs in the United States in 1985 (U.S. DHHS, 1989), which is used as the value for T.

Using figures from the Bureau of the Census and the 1979/80 National Health Interview Survey, Arundel et al. (1987) estimate the number of women of age 35+ by smoking status, obtaining a value of 0.443 as the fraction of ever-smokers. The National Center for Health Statistics (as reported in U.S. DHHS, 1989) provides the proportion of the female population by smoking status (never, former, current) for 1987. When applied to figures from the Bureau of the Census (1990) for the female population by age group available for 1988, the same fractional value (0.443) is obtained. These sources suggest that the proportion of ever-smokers in the female population has been fairly constant between 1980 and 1987, so P_1 will be given the value 0.443. Multiplying N by P_1 gives an estimate of $N_1 = 25.7$ million ever-smokers, leaving $N_2 = 32.3$ million never-smokers.

RR_1 applies to ever-smokers, which consist of current and former smokers. The relative risks of current and former female smokers of age 35+ for the period 1982-1986 are estimated at 11.94 and 4.69, respectively, from data in the American Cancer Society's Cancer Prevention Study II (CPS-II; as reported in U.S. DHHS, 1989). For 1985, the composition of ever-smokers is 63.4% current smokers and 36.6% former smokers (CDC, 1989a). Using those percentages to weight the relative risks for ever-smokers and former smokers gives 9.26, which will be used as the value of RR_1.

The proportion of never-smokers exposed to spousal ETS in epidemiologic studies typically refers to married persons, so we need to consider how to treat unmarried persons as well in order to set a value for P_2. The American Cancer Society's CPS-II (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just never-smokers) are: married, 75.3; divorced, 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female never-smokers, which comprise about 75% of female never-smokers, so it is necessary to consider exposure to ETS in the remaining 25% of unmarried female never-smokers.

Cummings (1990) obtained urinary cotinine levels on a total of 663 self-reported never-smokers and former smokers. The cotinine levels were slightly higher in males than in females (9.6 and 8.2 ng/mL, respectively), and slightly more than one-half of the subjects were females. The average cotinine level was 10.7 ng/mL for married subjects if the spouse smoked and 7.6 ng/mL otherwise. The average cotinine levels reported by marital status are: married, 8.3 ng/mL; never married, 10.3 ng/mL; separated, 11.8 ng/mL; widowed, 10.4 ng/mL; and divorced, 9.2 ng/mL. The study, in which 7% of the subjects were of age 18 to 29, and 47% were of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried never-smoker is probably closer, on average, to a never-smoker married to a smoker (an exposed person) than to a never-smoker married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

The proportion of never-smoking controls exposed to spousal smoking varies among studies in the United States. If we exclude studies of uncertain representativeness, the median value for the remaining studies is 0.6. From

the evidence on ETS exposure to unmarried female never-smokers, it is reasonable to assume that their exposure to ETS, on average, is at least as large as the average background level plus 60% of the average exposure from spousal smoking. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female never-smokers alike in terms of exposure to ETS (i.e., 60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level only). Consequently, the value $P_2 = 0.6$ is assumed to apply equally to married and unmarried female never-smokers.

The NRC report of 1986 uses Z = 3 for the ratio of ETS exposure from spousal smoking plus other sources to ETS exposure from nonspousal sources alone. That value was primarily based on data from Wald and Ritchie (1984), for men in Great Britain, although Lee (1987b) had reported a value of 3.3 for women in Great Britain. The results of Coultas et al. (1987) also were considered, wherein a value of 2.35 was observed for saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. More recent data suggest that a lower value of Z may be more accurate for the United States. The study of 663 volunteers in Buffalo, New York, reported by Cummings et al. (1990), observed a value of 1.55 based on mean urinary cotinine levels among married females (n = 225; Cummings, 1990). A study by Wall et al. (1988) containing 48 nonsmokers observed a ratio of mean cotinine levels of 1.53. A survey of municipal workers at a health fair found a cotinine ratio of 2.48 for the 112 women surveyed, but the comparison is between women who shared living quarters with a smoker and those who did not (Haley et al., 1989). The 10-country collaborative cotinine study conducted by IARC (Riboli et al., 1990) collected urinary cotinine samples from nonsmoking women in four groups totaling about 100 each--married to a smoker (yes, no) and employed (yes, no)--including two locations, Los Angeles and New Orleans, in the continental United States. The ratios of average cotinine/creatinine concentrations for women married to a smoker to women not married to a smoker range from 1.75 to 1.89 in New Orleans, when the percentage of women employed is assumed to be between 25% and 75%. The data from Los Angeles contain an abnormally high mean for women who are employed and also married to a smoker (a mean of 14.6 based on only 13 observations, compared to the other three means for Los Angeles of 2.1, 4.5, and 6.6), so only the two means for unemployed women (married to a smoker and married to a nonsmoker) were used. The resultant ratio of cotinine/creatinine concentrations is 1.45. Data from the Fontham et al. (1991) study of lung cancer and ETS exposure in five U.S. cities yield a Z of 2.0 based on mean urinary cotinine levels in 239 never-smoking women (data provided by Dr. Elizabeth Fontham).

Cotinine data exhibit variability both within and between subjects, as well as between studies due to different experimental designs, protocols, and geographical locations (see also Chapter 3). Most of the Z values from recent U.S. studies range between 1.55 and 2.0. A value of 1.75 for Z appears reasonable based on the available U.S. data and will be used in Section 6.3.3 along with the combined RR estimate from 11 U.S. studies (Chapter 5) to calculate ETS-attributable lung cancer mortality estimates. Z = 2.0 and Z = 2.6, which are based on *median* cotinine levels, will be used in Section 6.3.4 for alternative calculations of lung cancer mortality based on the results of the Fontham et al. (1991) study. The sensitivity of the lung cancer mortality estimates to changes in Z and other parameters is discussed in Section 6.3.5.

6.3.3. U.S. Lung Cancer Mortality Estimates Based on Results of Combined Estimates from 11 U.S. Studies

This section calculates ETS-attributable U.S. lung cancer mortality estimates based on the combined relative risk estimate (RR_2 = 1.19) derived in Chapter 5 for the 11 U.S. studies. Alternatively, the estimate from just the combined Tier 1 and Tier 2 studies (RR_2 = 1.22 from 8 of the 11; see Table 5-17) could have been used because these eight studies were assessed as having the greater utility in terms of evaluating the lung cancer risks from ETS; however, the results would be virtually the same because the relative risk estimates are so similar. It was therefore decided to use the data from all the U.S. studies for the purposes of the population risk assessment.

6.3.3.1. *U.S. Lung Cancer Mortality Estimates for Female Never-Smokers*

The parameter values presented in Section 6.3.2 are assumed along with RR_2 = 1.19. For Z = 1.75, RR_{02} = 1.59 (from expression 6-2, denoted hereafter as Ex(6-2); see also Table 6-1). Given those parameter values, the formulae in Section 6.3.2 yield the estimated lung cancer mortality for U.S. women in 1985 by smoking status (ever-smoker, never-smoker exposed to spousal ETS, and never-smoker not exposed to spousal ETS) and source (non-tobacco-smoke-related causes, background ETS in never-smokers, spousal ETS in never-smokers, and ever-smoking), as displayed in Table 6-2. The LCMR from non-tobacco-smoke-related causes ($LCMR_{nt}$) is estimated to be 9.4 per 100,000 and is assumed to apply equally to all persons in the target population, regardless of smoking status. The excess LCMR in never-smokers from exposure to background ETS is 3.2, with an additional 2.4 if exposed to spousal ETS. The excess LCMR in ever-smokers, which includes whatever effect exposure to ETS has on ever-smokers as well as the effect from active smoking, is 120.8.

In rounded figures, 5,470 (14.4%) of the 38,000 LCDs in U.S. women age 35 and over in 1985 are unrelated to smoking (active or passive). The remaining 32,530 LCDs (85.6% of the total) are attributable to tobacco smoke: 31,030 in 25.7 million ever-smokers and 1,500 in 32.3 million never-smokers. These 1,500 ETS-attributable LCDs in never-smokers account for about one-third of all LCDs in female never-smokers. Of the 1,500 LCDs, about 1,030 (69%) are due to background ETS, and 470 (31%) are from spousal ETS. In summary, the total 38,000 LCDs from all causes is due to non-tobacco-smoke-related causes, 5,470 (14.4%), occurring in ever-smokers and never-smokers; ever-smoking, i.e., the effects of past and current active smoking as well as ETS exposure, 31,030 (81.7%), occurring in ever-smokers; and background ETS, 1,030 (2.7%), and spousal ETS, 470 (1.2%), occurring in never-smokers. In other words, ever-smoking causes about 81.7% of the lung cancers in women age 35 and over; exposure to ETS from all sources accounts for some 3.9%; and causes unrelated to tobacco smoke are responsible for the remaining 14.4%. The LCDs in never-smokers attributable to ETS equal about 5% (1,500/31,030) of the total attributable to ever-smoking. Part of the mortality attributed to ever-smoking here, however, is due to ETS exposure in former smokers, to be taken into account in Section 6.3.3.3.

6.3.3.2. *U.S. Lung Cancer Mortality Estimates for Male Never-Smokers*

There are 11 studies worldwide of exposure to ETS and lung cancer in males. The studies and their respective relative risks are AKIB, 1.8; BROW, 2.2; BUFF, 33+ years' exposure, 1.6; CORR, 2.0; HUMB, 4.2; KABA, 1.0; LEE, 1.3; HIRA(Coh), 2.25; HOLE(Coh), 3.5; plus the data in Kabat (1990), 1.2; and Varela (1987, Table 13 scaled down to 50 years of exposure), 1.2. (Data

Table 6-2. Estimated female lung cancer mortality by attributable sources for United States, 1985, using the pooled relative risk estimate from 11 U.S. studies[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,220 (3.2)	**410** (1.1)			
NS	Yes	19.38	1,830 (4.8)	**620** (1.6)	**470** (1.2)		
ES		25.69	2,420 (6.4)			31,030[5] (81.7)	
Total		58.00	5,470 (14.4)	**1,030** (2.7)	**470** (1.2)	31,030 (81.7)	38,000

[1]Percentage of grand total (38,000) in parentheses.
[2]The nonblank entries in the table are the product of an individual's attributable risk of lung cancer from non-tobacco-smoke-related causes (expression 6-9 (38,000/58,000,000)), the number at risk in column (1), and the following column-specific multiples: Col. (2) 1
Col. (3) $RR_{03} - 1$
Col. (4) $RR_{02} - RR_{03}$
Col. (5) $RR_{01} - 1$
[3]NS = never-smokers; ES = ever-smokers.
[4]Background sources in the absence of tobacco smoke (i.e., in a zero-ETS environment).
[5]This figure attributes all lung cancer in ever-smokers above the background non-tobacco-smoke-related rate to ever-smoking.

for BROW, BUFF, and HUMB were supplied via personal communication from Drs. Brownson, Buffler, and Humble.) A weighted average of the passive smoking risk (RR_2) from these 11 studies is about 1.6. For the seven U.S. studies, BROW, BUFF, CORR, HUMB, KABA, Kabat (1990), and Varela (1987), the weighted average RR is about 1.4, but this value is heavily weighted (about 66%) by the Kabat (1990) and Varela (1987) studies, neither of which was used in the analysis of the female data. The combined risk for the five U.S. studies not including Kabat (1990) and Varela (1987) is about 1.8, but they are all small, low-weight studies. In any case, the observed relative risks for males appear to be at least as great as those for females.

When an attempt is made to correct the observed male risks for smoker misclassification, however, using the procedures outlined in Appendix B and the community survey-based misclassification factors for males (1.6% for current regular smokers, 15% for current occasional smokers, and 5.9% for former smokers), it is found that for most of these cohorts, the number of smokers misclassified as never-smokers either exceeds the relatively small number of observed never-smokers or is so great as to drive the corrected relative risk substantially below unity. This implies that the misclassification factors from the community surveys are too high to accurately correct the risks in the epidemiologic studies. Until better misclassification data on males are available, no real sense can be made of the male passive smoking relative risks.

Given the greater stability of the more extensive database on females, it was decided to apply the incremental LCMRs for spousal and nonspousal ETS exposure in female never-smokers to male never-smokers. The incremental LCMRs were used instead of the relative risk estimates because relative risk depends on the background risk of lung cancer (from non-tobacco-related causes) as well as the risk from ETS, and background lung cancer risk may differ between females and males. From Section 6.3.3.1, the LCMR from spousal ETS exposure was 2.4 per 100,000 at risk, and the LCMR from nonspousal ETS exposure was 3.2 per 100,000. The 1985 male population age 35 and over is 48 million (U.S. DHHS, 1989), of whom 27.2% (private communication from Dr. Ronald W. Wilson of the U.S. National Center for Health Statistics), or 13.06 million, were never-smokers. Of these, 24% (Wells, 1988), or 3.13 million, were spousally exposed. Applying the female ETS LCMRs, 3.13 million × 2.4/100,000 = 80 deaths in males from spousal ETS exposure and 13.06 million × 3.2/100,000 = 420 deaths from nonspousal exposure, for a total of 500 ETS-attributable LCDs among never-smoking males. These estimates based on female LCMRs are believed to be conservatively low because males generally have higher exposure to background ETS than females. This would lead to lower Z values and subsequently higher estimates of deaths attributable to background (nonspousal) ETS sources. In conclusion, confidence in these estimates for male never-smokers is not as high as those for female never-smokers.

6.3.3.3. *U.S. Lung Cancer Mortality Estimates for Long-Term (5+ Years) Former Smokers*

Because the risk of lung cancer from active smoking decreases with the number of years since smoking cessation (Section 4.2.2), passive smoking may be a significant source of lung cancer risk in long-term former smokers. There is, however, a scarcity of data on the relative risks of lung cancer for former smokers exposed to ETS. With former smokers, it is unknown how much of the observed lung cancer mortality is attributable to non-

tobacco-smoke-related causes, how much is due to ETS exposure, and how much is accounted for by prior smoking. Consequently, neither the observational data on the number of lung cancers in the former smokers nor the relative risk data from never-smoking females are utilized. Instead, long-term former smokers are assumed to have the same LCMR from exposure to ETS as never-smoking females, as was assumed above for never-smoking males. In this manner, the lung cancer risk from ETS exposure can be calculated as an additional risk, supplemental to any remaining risk from previous active smoking. There is some uncertainty in the application of this assumption because the additional risk to long-term former smokers from ETS exposure may not, in fact, be the same as the risk to never-smokers. For example, ETS may have a greater promotional effect on former smokers because of their previous exposures to high concentrations of carcinogens from active smoking.

Female ever-smokers comprise about 44.3%, or 25.7 million, of the total U.S. female population age 35 and over of 58 million. Long-term (5+ years) former smokers comprise about 34% of these ever-smokers (U.S. DHHS, 1990b), or about 8.7 million women. Using a 2.2 concordance factor for former smokers married to ever-smokers versus never-smokers married to never-smokers (see Appendix B), it is estimated that about 77% of the former smokers, or about 6.7 million, would be spousally exposed compared with the 60% for the never-smokers. Thus, based on the LCMRs derived for female never-smokers, the expected number of ETS-attributable LCDs for female long-term former smokers would be 6.7 million × 2.40/100,000 = 160 deaths from spousal exposure and 8.7 million × 3.20/100,000 = 280 deaths from nonspousal exposure, for a total of 440.

Male ever-smokers comprise 72.8% of the U.S. male population, age 35 and over, of 48 million, equal to 35 million; of these, about 43% (derived from data in U.S. DHHS, 1990b, page 60, Table 5), or about 15 million, are 5+ year quitters. Of the never-smoking males, 24% were married to smokers (Section 6.3.3.2). Again using a 2.2 concordance factor for former smokers, it is estimated that 41% of the 15 million former smoking males, or 6.2 million, would be married to ever-smokers. Applying the female never-smoker LCMRs from Section 6.3.3.1, 6.2 million × 2.40/100,000 = 150 deaths from spousal ETS exposure and 15 million × 3.20/100,000 = 480 deaths from nonspousal ETS exposure for a total of 630 ETS-attributable LCDs among male long-term former smokers.

Table 6-3 displays the resultant estimates for LCDs attributable to background ETS and spousal ETS by sex for never-smokers and for former smokers who have quit for at least 5 years. The LCMRs for background ETS and spousal ETS, assumed to be independent of smoking status and sex, are the same as derived in Section 6.3.3.1 for female never-smokers (3.2 and 2.4, respectively). Background ETS accounts for about 2,200 (72%) and spousal ETS for 860 (28%) of the total due to ETS. Of the 3,060 ETS-attributable LCDs, about two-thirds are in females (1,930, 63%) and one-third in males (1,130, 37%). More females are estimated to be affected because there are more female than male never-smokers. By smoking status, two-thirds are in never-smokers (2,000, 65%) and one-third in former smokers who have quit for at least 5 years (1,060, 35%).

The numbers shown in Table 6-3 depend, of course, on the parameter values assumed for the calculations. The sensitivity of the totals in Table 6-3 to alternative parameter values is addressed in Section 6.3.5. First, however, tables equivalent to Tables 6-2 and 6-3 are developed based on the FONT study alone for comparison.

6.3.4. U.S. Lung Cancer Mortality Estimates Based on Results of the Fontham et al. (1991) Study (FONT)

The estimate of RR_2 (1.19), the risk of lung cancer to female never-smokers with spousal ETS exposure relative to the risk for female never-smokers without spousal ETS exposure, used in Section 6.3.3, is based on the combined outcomes of the 11 U.S. epidemiologic studies from Chapter 5 (see Table 5-17). In this section, the quantitative population impact assessment is repeated with FONT, the single U.S. study with Tier 1 classification (Section 5.4.4), as the source of the estimates of RR_2 and Z (constructed from urine cotinine measures), with the remaining parameter values left unchanged. While a single study has lower power and larger confidence intervals on the relative risk estimate than can be obtained by combining the various U.S. studies, using the specific data from a single study decreases the uncertainties inherent in combining results from studies that are not fully comparable. **FONT is the only study of passive smoking and lung cancer that collected cotinine measurements, thus providing estimates for RR_2 and Z from a single study population**. The total number of lung cancers attributable to total ETS exposure is particularly sensitive to those two parameters (discussed in Section 6.3.5).

The NCI-funded Fontham et al. study (1991) is a large, well-conducted study designed specifically to investigate lung cancer risks from ETS exposure (see also the critical review in

Table 6-3. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using 11 U.S. studies (never-smokers and former smokers who have quit 5+ years)[1]

				Lung cancer mortality			
			(1)	(2)	(3)	(4)	
Smoking status[2]	Sex	Exposed to spousal ETS	Number at risk (in millions)	Background ETS	Spousal ETS	Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	410		410	1,500 (NS,F)
NS	F	Yes	19.38	620	470	1,090	
NS	M	No	9.93	320		320	500 (NS,M)
NS	M	Yes	3.13	100	80	180	
FS	F	No	2.0	60		60	430 (FS,F)
FS	F	Yes	6.7	210	160	370	
FS	M	No	8.8	280		280	630 (FS,M)
FS	M	Yes	6.2	200	150	350	
Total			69.07	2,200 (71.9)	860 (28.1)	3,060	3,060

[1]Percentage of total ETS-attributable lung cancer deaths (3,060) in parentheses.
[2]NS = never-smokers; FS = former smokers who have quit 5+ years ago.

Appendix A). It addresses some of the methodological issues that have been of concern in the interpretation of results regarding lung cancer and passive smoking: smoker misclassification, use of surrogate respondents, potential recall bias, histopathology of the lung tumors, and possible confounding by other factors (see also Sections 5.3, 5.4.2, and 5.4.3). Cases and controls were drawn from five major cities across the United States (Atlanta, New Orleans, Houston, Los Angeles, and San Francisco) and, hence, should be fairly representative of the general U.S. population, at least of urban areas with moderate climates. Furthermore, the results of the study are consistent across the five cities.

In spite of the care incorporated into the FONT design to avoid smoker misclassification bias, some might still exist; thus, the adjusted relative risk of 1.29 reported in FONT is "corrected" slightly to 1.28 in this report. The parameter P_2, the proportion of never-smokers exposed to spousal ETS, was assigned the value 0.60 in the preceding section. In FONT, the observed proportion of spousal-exposed controls is 0.60 (0.66) for spousal use of cigarettes only (any type of tobacco) among colon-cancer controls and 0.56 (0.63) in population controls. Consequently, the previous value of 0.60 is retained. Of the 669 FONT population controls, whose current cotinine levels are considered the most representative of typical ETS exposure, there were 59 living with a current smoker and 239 whose spouses never smoked. (The other 371 were nonsmoking women who either no longer lived with a smoking spouse or whose spouse was a former smoker.) The *mean* cotinine level for never-smoking women with spouses who are current smokers (n = 59) is 15.90 ± 16.46; the mean level for the other 239 was 7.97 (± 11.03). The ratio is 15.90/7.97, giving Z = 2.0 (data provided by Dr. Elizabeth Fontham). The median is a measure of central tendency that is less sensitive to extremes, so the ratio of *median* cotinine levels is also considered (Z = 11.4/4.4 = 2.6). Results for both values of Z are displayed in Tables 6-4 and 6-5, which correspond to Tables 6-2 and 6-3, respectively, of the previous sections for direct comparison.

The results of Section 6.3.2 are based on $RR_2 = 1.19$ (combined U.S. study results) and Z = 1.75 (from studies on cotinine levels). In this section, RR_2 and Z are both increased (RR_2 to 1.28 and Z to 2.0 and 2.6). Correcting $RR_2 = 1.28$ for background ETS exposure yields estimates of $RR_{02} = 1.78$ (i.e., the relative risk from spousal and background ETS) for Z = 2.0, and $RR_{02} = 1.55$ for Z = 2.6. The relative risk estimate from exposure to background ETS only becomes
$RR_{03} = 1.39$ for Z = 2.0, and $RR_{03} = 1.21$ for Z = 2.6. The change in RR_2, from 1.19 to 1.28, increases the estimated number of LCDs from background and spousal ETS, whereas increasing Z decreases the figure for background ETS and has no effect on the number for spousal ETS (see Tables 6-2 and 6-4). Relative to the total ETS-attributable LCD estimate in the last section

Table 6-4. Female lung cancer mortality estimates by attributable sources for United States, 1985, using both the relative risk estimates and Z values from the Fontham et al. (1991) study[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,120 (2.9) *1,280 (3.4)*	440 (1.2) *270 (0.7)*			
NS	Yes	19.38	1,680 (4.4) *1,920 (5.1)*	660 (1.7) *410 (1.1)*	660 (1.7) *660 (1.7)*		
ES		25.69	2,230 (5.9) *2,550 (6.7)*			31,220[5] (82.2) *30,900[5] (81.3)*	
Total		58.00	5,030 (13.2) *5,760 (15.2)*	1,100 (2.9) *680 (1.8)*	660 (1.7) *660 (1.7)*	31,220 (82.2) *30,900 (81.3)*	38,000

[1]Percentage of grand total (38,000) in parentheses. Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2]See Table 6-2 for formulae for table entries.
[3]NS = never-smokers; ES = ever-smokers.
[4]Baseline lung cancer mortality in the absence of tobacco smoke (i.e., in a zero-ETS environment).
[5]This figure attributes all lung cancer in ever-smokers above the non-tobacco-smoke-related rate to active smoking.

Table 6-5. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using the Fontham et al. (1991) study (never-smokers and former smokers who have quit 5+ years)[1,2]

				Lung cancer mortality			
			(1)	(2)	(3)	(4)	
Smoking status[3]	Sex	Exposed to spousal ETS	Number at risk (in millions)	Background ETS	Spousal ETS	Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	440 *270*		440 *270*	1,760 *1,340* (NS,F)
NS	F	Yes	19.38	660 *410*	660 *660*	1,320 *1,070*	
NS	M	No	9.93	340 *210*		340 *210*	560 *390* (NS,M)
NS	M	Yes	3.13	110 *70*	110 *110*	220 *180*	
FS	F	No	2.0	70 *40*		70 *40*	530 *410* (FS,F)
FS	F	Yes	6.7	230 *140*	230 *230*	460 *370*	
FS	M	No	8.8	300 *190*		300 *190*	720 *530* (FS,M)
FS	M	Yes	6.2	210 *130*	210 *210*	420 *340*	
Total			69.07	2,360 (66.1) *1,460 (54.7)*	1,210 (33.9) *1,210 (45.3)*	3,570 *2,670*	3,570 *2,670*

[1]Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2]Percentage of total ETS-attributable lung cancer deaths (3,570; *2,670*) in parentheses.

[3]NS = never-smokers; FS = former smokers who have quit 5+ years ago.

(3,060), the net effect is an increase of 12% to 3,570 at Z = 2.0, and a decrease of 13% to 2,670 when Z = 2.6. (FONT is the largest study and therefore the dominant influence in the combined relative risk from the 11 U.S. studies [RR_2 = 1.19], so the outcomes being compared here with those in Section 6.3.3 are not independent. Similarly, the Z-value of 1.75 used with RR_2 = 1.19 in the first analysis is subjectively based on the outcomes of several U.S. cotinine studies, including the FONT cotinine results.) Overall, these two analyses support an estimate in the neighborhood of 3,000 total lung cancer deaths in never-smokers and former smokers (quitters of 5+ years) from exposure to ETS in the United States for 1985.

The 3,000 figure is a composite value from estimates of varying degrees of uncertainty. The confidence for the female never-smoker estimates is highest. The lung cancer estimates for never-smoking females from exposure to spousal ETS (470 to 660; from Tables 6-2 and 6-4) are based on the direct evidence from epidemiologic studies and require the fewest assumptions. Adding in a figure for exposure to background ETS in never-smoking females (680 to 1,100) is subject to the assumptions and other uncertainties attached to the estimate of the parameter Z. The relative risk from ETS exposure, which depends on the risk from background sources of lung cancer as well as the risk from ETS, may differ in females and males. Consequently, the absolute risk (LCMR) in never-smoking females was assumed to apply to never-smoking males, adding
390 to 560 to the total (80 to 110 for spousal ETS and 280 to 450 for background ETS; Tables 6-3 and 6-5). Males, however, are thought to have higher background exposures to ETS than females, so this assumption is likely to underestimate the ETS-attributable lung cancer mortality in males.

The confidence in the estimates for former smokers is less than in those for never-smokers. These estimates also are probably low because they assume that ETS-attributable rates in never-smokers and former smokers are the same. Figures for lung cancer mortality from ETS in former smokers, for the same categories as never-smokers (i.e., females and males, background and spousal ETS), account for an additional 940 to 1,250 (totals of 310 to 440 for spousal ETS and 500 to 810 for background ETS, for both sexes). These figures for former smokers are summed from appropriate entries in Tables 6-3 and 6-5 (Tables 6-2 and 6-4 do not make them explicit; they are accounted for in the entry for lung cancer attributable to ever-smoking).

Finally, there is statistical uncertainty in each of the LCD estimates resulting from sampling variations around all of the parameter estimates that were used in the calculations. It is already apparent that the estimate of total lung cancer mortality attributable to ETS is sensitive to the values of Z and RR_2. Uncertainties associated with the parameter values assumed and the sensitivity of the estimated total ETS-attributable LCDs to various parameter values are examined next.

6.3.5. Sensitivity to Parameter Values

The estimates for ETS-attributable lung cancer mortality are clearly sensitive to the studies, methodology, and choice of models used, and previous methodologies have been presented in Section 6.2. Even for this current model, however, estimates will vary with different input values. Specifically, the estimates depend on the parameter values assumed for the total number of lung cancer deaths from all sources (T), the population size (N), the proportion of ever-smokers in the population (P_1), the proportion of never-smokers exposed to spousal ETS (P_2), the risk of ever-smokers relative to never-smokers (RR_1), the risk of never-smokers exposed to spousal ETS relative to unexposed never-smokers (RR_2), and the ratio of ETS exposure from spousal smoking and background (i.e., nonspousal) sources to background sources alone (Z).

The effects of changing several of the parameters is readily discernible. A change in T/N produces a proportional change in the same direction for all estimates of attributable mortality. A change in P_1 creates a proportional change in the same direction in all mortality figures for ever-smokers and a change in the opposite direction proportional to $1 - P_1$ in all estimates for never-smokers. The parameter values assumed for these three parameters are from the sources described in the preceding text and are assumed to be acceptably accurate. The value of P_2 is assumed to be 0.6, but values between 0.5 and 0.7 are easily credible. At either of those extremes, there is a 17% change in the lung cancer mortality due to spousal smoking, which only amounts to 80 for the first analysis (Table 6-2) and 100 for the second one (Table 6-4). The impact of changing RR_1, RR_2, or Z on the total lung cancer mortality attributable to ETS from the first analysis is displayed in Table 6-6 for RR_1 from 8 to 11, for RR_2 between 1.04 and 1.35 (extremes of the 90% confidence intervals for the 11 U.S. studies; Table 5-17), and for Z in the range 1.5 to 3.0.

For RR_1 in the interval (8,11), the total lung cancer mortality from ETS ranges from about 2,600 to 3,500, a 14% change in either direction relative to the comparison total of 3,060. The extremes are much greater over the range of values considered for RR_2 (1.04 to 1.35). At the low end, where the excess relative risk from spousal ETS is only 4%, there is a 77% decrease in the total lung cancer mortality to 700. The percentage change is roughly equivalent in the opposite direction when the excess relative risk is at the maximum value 35%, for a total of 5,190. The total is also highly sensitive to the value of Z. A decrease of only 0.25 from the comparison value of Z = 1.75 increases the total by 36% to 4,160. A 36% decrease in ETS-attributable mortality occurs at Z = 2.5, leaving a corresponding estimate of 1,950. At Z = 3.0, the total drops further to 1,680, a 45% decrease.

Varying more than one parameter value simultaneously may have a compounding or canceling effect on the total lung cancer mortality due to ETS. For example, at the following

Table 6-6. Effect of single parameter changes on lung cancer mortality due to ETS in never-smokers and former smokers who have quit 5+ years

Parameter change		LCM due to ETS			
		Background[1]	Spousal[2]	Total	Percentage of change[3]
None[4]		**2,210**	**850**	**3,060**	**0**
Z =	1.50	3,310	850	4,160	+36
	1.75	**2,210**	**850**	**3,060**	**0**
	2.00	1,660	850	2,510	-18
	2.25	1,320	850	2,170	-29
	2.50	1,100	850	1,950	-36
	2.75	950	850	1,800	-41
	3.00	830	850	1,680	-45
RR_2 =	1.04	510	190	700	-77
	1.05	630	240	870	-72
	1.10	1,220	470	1,690	-45
	1.15	1,780	690	2,470	-19
	1.19	**2,210**	**850**	**3,060**	**0**
	1.20	2,310	890	3,200	+5
	1.25	2,820	1,080	3,900	+27
	1.30	3,290	1,270	4,560	+49
	1.35	3,750	1,440	5,190	+70
RR_1 =	8.00	2,510	970	3,480	+14
	8.50	2,380	920	3,300	+8
	9.00	2,260	870	3,130	+3
	9.26	**2,210**	**850**	**3,060**	**0**
	9.50	2,160	830	2,990	-2
	10.00	2,060	800	2,860	-7
	10.50	2,020	780	2,800	-9
	11.00	1,890	730	2,620	-14

[1]69,100,000 at risk.
[2]35,400,000 at risk.
[3]Percentage of change from total shown in boldface (the outcome from Tables 6-2 and 6-3, using the 11 U.S. studies).
[4]Z = 1.75, RR_2 = 1.19, RR_1 = 9.26.

values of RR_2, the range of percentage changes from the total of 3,060 ETS-attributable lung cancer deaths for values of Z in the interval 1.50 to 3.0 are shown in parentheses: $RR_2 = 1.04$ (-69%, -88%), $RR_2 = 1.15$ (+10%, -56%), $RR_2 = 1.25$ (+73%, -30%), and $RR_2 = 1.35$ (+131%, -7%). The total ETS-attributable LCD estimates range from 380 (at $RR_2 = 1.04$, Z = 3.0) to 7,060 (at $RR_2 = 1.35$, Z = 1.5). Without considering the additional variability that other parameters might add, it is apparent that the estimated lung cancer mortality from ETS is very sensitive to the parameters RR_2 and Z and that the uncertainty in these parameters alone leaves a fairly wide range of possibilities for the true population risk.

While various extreme values of these parameters can lead to the large range of estimates noted, the extremities of this range are less likely possibilities for the true population risk because the parameters RR_2 and Z are not actually independent and would be expected to co-vary in the same direction, not in the opposite direction as expressed by the extreme values. For example, if the contributions of background to total ETS exposure decrease, Z would increase, and the observable relative risk from spousal exposure, RR_2, would be expected to increase as well. In addition, most of the evidence presented in this report suggests that a narrower range of both RR_2 and Z are appropriate. Thus, while substantially higher or lower values are conceivable, this report concludes that the estimate of approximately 3,000 ETS-attributable LCDs based on the 11 U.S. studies is a reasonable one. Furthermore, this estimate is well corroborated by the estimates of 2,700 and 3,600 calculated by analyzing the FONT data alone, the only study dataset from which estimates of both RR_2 and Z are obtainable.

6.4. SUMMARY AND CONCLUSIONS ON POPULATION RISK

Having concluded in the previous chapter that ETS is causally associated with lung cancer in humans and belongs in EPA Group A of known human carcinogens, this chapter assesses the magnitude of that health impact in the U.S. population. The ubiquity of ETS in a typical individual's living environment results in the respiratory uptake of tobacco smoke to some degree in a very high percentage of the adult population, conservatively upwards of 75% based on the outcome of urinary cotinine/creatinine studies in nonsmokers. Compared with observations on active smokers, body cotinine levels in nonsmokers are low, on the order of a few percent, and there is considerable variability in interindividual metabolism of nicotine to cotinine. Some authors have used the relative cotinine levels in active and passive smokers to estimate the probability of lung cancer in nonsmokers by extrapolating downward on a dose-response curve for active smokers. This "cigarette-equivalents" approach requires several assumptions, e.g., that the dose-response curve used for active smokers is reasonably accurate and low-dose extrapolation of risk for active smokers is credible, that cotinine is proportional (and hence a substitute for) whatever is used for "dose" in the dose-response curve, and that the risk calculated in this way applies equally to active and passive smokers with equivalent cotinine measures. The effect of differences in physico-chemical properties of mainstream smoke and sidestream smoke (the principal component of ETS), in lung dosimetry between active and passive smoking, and in exposure patterns (related to concentration and duration of exposure) are not fully understood, but the current state of knowledge casts doubts on the validity of these assumptions.

The remaining approach to population risk extrapolates to the general population from the epidemiologic evidence of increased relative risk of lung cancer in never-smoking women married to smokers. To extrapolate exposure and consequent risk to other sources of ETS exposure, cotinine levels of never-smokers exposed to spousal ETS are compared with those of never-smokers exposed only to other sources of ETS (background), and it is assumed that excess risks of lung cancer from ETS exposures, using cotinine levels as a surrogate measure, are proportional to current ETS exposure levels. (Here, cotinine levels are used to gauge relative levels of *ETS* exposure, not to extrapolate between active and passive smoking as in the "cigarette-equivalents" approach.) The use of current cotinine data to estimate ETS exposure in nonsmokers seems reasonable because cotinine levels correlate quite well with questionnaire response on ETS exposure. However, the total estimate of population risk is sensitive to uncertainty in making these assumptions and variability in the use of cotinine measures.

This report uses the modeling approach based on direct ETS epidemiologic evidence because the assumptions are fewer and more valid than for the "cigarette-equivalents" approach, and the abundance of human data from actual environmental exposures makes this preferred approach feasible. The total number of lung cancer deaths in U.S. females from all causes is partitioned into components attributable to non-tobacco-smoke-related causes (background causes unrelated to active or passive smoking), background ETS (also called nonspousal ETS), spousal ETS, and ever-smoking. Two sets of calculations are made for the U.S. female population age 35 and over in 1985 based on parameter values from national statistics and estimates from the epidemiologic studies on ETS and lung cancer. They differ in the values assumed for two parameters in the formulae for attributable risk: RR_2, the relative risk of lung cancer for never-smokers exposed to spousal smoke, and Z, the ratio of cotinine concentrations in never-smokers exposed to spousal ETS to those exposed to background ETS only. The first analysis uses the pooled estimate of RR_2 from the 11 U.S. studies from Chapter 5, and a subjective value of Z based on the outcomes of independent U.S. cotinine studies ($RR_2 = 1.19$ and $Z = 1.75$). The second analysis uses the estimates of RR_2 and Z from the large, high-quality Fontham et al. study (1991), the sole U.S. study that collected cotinine data for its study population ($RR_2 = 1.28$ with mean $Z = 2.0$ and with median $Z = 2.6$).

The estimated lung cancer mortality in never-smoking women from ETS (background and spousal ETS) is 1,500 in the first analysis and 1,760 (1,340) in the second analysis for Z = 2.0 (2.6). When estimates for never-smoking males and former smokers (5+ year quitters) of both sexes are added, the corresponding totals are 3,060 and 3,570 (2,670). All of these figures are based on calculations in which unknown parameter values are replaced with numerical estimates that are subject to uncertainty, and departures in either direction cannot be precluded as unrealistic possibilities for the correct population risks. Nonetheless, because of the large database utilized and the extensive analysis performed, there is a high degree of confidence in the estimates derived for female never-smokers. The figures for male never-smokers and former smokers of both sexes are subject to more uncertainty because more assumptions were necessary for extrapolation from the epidemiologic results. The estimates for male never-smokers, in particular, may be on the low side because males generally are exposed to higher levels of background ETS than

females. In summary, our analyses support a total of approximately 3,000 as an estimate for the annual U.S. lung cancer deaths in nonsmokers attributable to ETS exposure.

A quantitative estimate of the variance associated with the 3,000 estimate is not possible without many assumptions, both about the model and the accuracy of the parameters used to derive the population estimates. As exhibited in Table 6-6, we believe the largest variability to be associated with RR_2 and Z. Based on the statistical variations, estimates as low as 400 and as high as 7,000 are possible. However, where specific assumptions were made, we believe that they are generally conservative, and we expect that the actual number may be greater than 3,000.

A feature of variability not addressed in the range presented above is the correlation between RR_2 and Z. The greater the correlation, the smaller will be the expected variance of RR_{02}, resulting in a narrower range of lung cancer estimates. Because only one lung cancer study, FONT, allows RR_2 and Z to be jointly estimated, no assessment of this correlation is possible. However, the two point estimates derived from the FONT data--2,700 and 3,600--provide additional reassurance in the 3,000 estimate.

In conclusion, despite some unavoidable uncertainties, we believe these estimates of ETS-attributable lung cancer mortality to be fairly reliable, if not conservatively low, especially with respect to the male nonsmoker component. First, the weight of evidence that ETS is a human lung carcinogen is very strong. Second, the estimates are based on a large amount of data from various studies of human exposures to actual environmental levels of ETS. They do not suffer from a need to extrapolate from an animal species to humans or from high to low exposures, as is nearly always the case in environmental quantitative health risk assessment. Thus, the confidence in these estimates is judged to be medium to high. In summary, the evidence demonstrates that ETS has a very substantial and serious public health impact.