

Appendix D: Risk Assessment—Exposure to Environmental Tobacco Smoke and Lung Cancer

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This authored appendix was prepared by Dr. James Robins of the Harvard University School of Public Health. The material was not considered by the committee largely because of lack of time, nor was it reviewed by the National Research Council. It gives an approach to risk assessment that considers both the epidemiologic data and some measures of exposure to the constituents of ETS. It is included as an addendum of this report and is presented here as one possible way to integrate the data contained in the remainder of the report.

INTRODUCTION

In Chapter 12, the results of 13 epidemiologic studies are summarized. Each study provided an estimate of the ratio of the lung cancer mortality rate among nonsmokers who answered "yes" to a question like "Is your spouse a smoker?" (hereafter called "exposed" individuals) to the mortality rate among nonsmokers who answered "no" to that question (hereafter called "unexposed" individuals). A weighted average of the 13 study-specific rate ratios is roughly 1.3. In this appendix, we assume that a weighted average of 1.3 is causally related to differences in environmental tobacco smoke (ETS) exposure between "exposed" and "unexposed" individuals and not to bias (e.g., misclassification of smokers as nonsmokers—see Chapter 12).

Wald and Ritchie (1984) have shown that "unexposed" individuals have, on average, 8.5 ng/ml of cotinine in their urine. Since virtually the only source of cotinine or nicotine in body fluids is tobacco products, primarily through tobacco smoke exposures, it follows that "unexposed" individuals are exposed to ETS. For this reason, whenever we refer to such "unexposed" subjects, we place the word "unexposed" in quotation marks. If the "unexposed" subjects have, in fact, been exposed to ETS, the observed relative risk of 1.3 would be an underestimate of the true adverse effect of ETS on "exposed" individuals. The correct measure of the adverse effect of ETS on "exposed" individuals would be the ratio of the lung cancer mortality rate in "exposed" individuals to the rate in truly unexposed individuals (which we shall call the true relative risk in the "exposed").

In Section D-1, we use the data collected by Wald and Ritchie (1984) on levels of urinary cotinine in "exposed" and "unexposed" individuals to estimate this true relative risk by two different methods.

In Section D-2, we combine the existing epidemiologic data on active smokers with data on nonsmokers exposed to ETS to estimate the ETS exposure of an average nonsmoker in cigarette-equivalents per day. Additionally, we compare this estimate to independent estimates of ETS exposure based on (1) levels of respirable suspended particulates (RSP), benzo[a]pyrene (BaP), and *N*-nitrodimethylamine (NDMA) in ETS and in mainstream smoke and (2) levels of urinary cotinine and nicotine in active smokers and nonsmokers.

In Section D-3, we compute how many of the lung cancer deaths estimated to occur among (lifelong) nonsmoking persons in 1985 might be attributable to ETS. The estimate is made separately for women and for men.

Many environmental exposures are regulated to a level where the anticipated lifetime risk of death attributable to exposure is less than 1 in 100,000 or 1 in 1,000,000. In Section D-4, we consider whether the lifetime risk of death (from lung cancer) attributable to ETS among nonsmokers with moderate ETS exposure is in excess of 1 in 100,000. (Although we do not estimate the lifetime risk of death attributable to ETS from causes other than lung cancer, this does not imply that we believe that lung cancer is the only cause of mortality influenced by ETS exposure. The decision to restrict the analysis to lung cancer mortality reflects the fact

that the data necessary to perform an adequate quantitative risk assessment for causes of death other than lung cancer do not exist.)

In discussions of the health effects of ETS exposure, one should consider the effect on exsmokers of breathing other people's cigarette smoke, since exsmokers have given up smoking, presumably to protect their health. Therefore, in Section D-4 we estimate, for exsmokers, the lifetime risk of death from lung cancer attributable to breathing other people's cigarette smoke.

The sections D-1 to D-4 give nontechnical expositions of the issues. A separate Technical Discussion Section provides additional technical support and mathematical background.

In order to make quantitative estimates of the lung cancer risk attributable to ETS, numerical values must be chosen for a large number of parameters. When there are either no data or inconsistent data as to the magnitude of an important parameter, results are reported for a range of plausible values (i.e., a sensitivity analysis is performed).

Summary of Main Results Under the Assumption That the Summary Rate Ratio of 1.3 Is Causal

We summarize our main results. We caution the reader that the proper interpretation of these results requires that one read Section D-1 to D-4 and the discussion section that follows.

The estimated true relative risk for "exposed" individuals lies between 1.41 and 1.87. For "unexposed" individuals, the estimated true relative risk lies between 1.09 and 1.45. The number of (actively smoked) cigarettes effectively inhaled by a nonsmoker living with a smoking spouse lies in the range of 0.36-2.79 cigarettes/day. If the spouse is a nonsmoker, however, the estimated number lies between 0.12 and 0.93 cigarettes/day.

Of the roughly 7,000 lung cancer deaths estimated to have occurred among lifelong nonsmoking women in 1985, between 1,770 and 3,220 may be attributable to ETS. Of the roughly 5,200 lung cancer deaths estimated to have occurred among lifelong nonsmoking males in 1985, between 720 and 1,940 may be attributable to ETS.

The estimated lifetime risk of lung cancer attributable to ETS in a nonsmoker with moderate ETS exposure lies between 390 and 990 in 100,000. The estimated lifetime risk of lung cancer attributable to other people's cigarette smoke for an exsmoker who

smoked one pack per day from age 18 to 45 and was moderately exposed to other people's cigarette smoke lies between 520 and 2,030 per 100,000.

D-1 ESTIMATION OF THE TRUE RELATIVE RISK

Method 1

The first method for estimating the true relative risk relies on two assumptions:

- The excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. That is, if an individual's dose of ETS (at all ages) were doubled, his excess relative risk would be doubled.
- At every age, "exposed" subjects have been exposed to ETS at a rate 3 times that of "unexposed" subjects. A factor of 3 was selected to reflect the empirical observation that the concentration of cotinine in the urine of nonsmokers with smoking spouses is about 3 times that of nonsmokers without smoking spouses (Wald and Ritchie, 1984).

These two assumptions imply that the excess (true) relative risk in "exposed" individuals is 3 times that of "unexposed" individuals. Hence, in the absence of bias, the summary rate ratio of 1.3 equals the ratio of the true relative risk in "exposed" individuals to that in "unexposed" individuals. Therefore,

$$1.3 = \frac{1 + 3x}{1 + x},$$

where x and $3x$ are the excess true relative risks in "unexposed" and "exposed" individuals, respectively. Solving for x gives $x = 0.18$ and, thus, the true relative risk in "exposed" and "unexposed" individuals of 1.54 and 1.18, respectively. If we used the summary rate ratio of 1.14 from only the U.S. studies (see Chapter 12), we estimate the true relative risk in "exposed" and "unexposed" individuals to be 1.23 and 1.09, respectively.

It is likely that the second assumption above may be inappropriate (see Remark 4 in the Technical Discussion). For instance, it is unlikely that the ETS exposure in childhood is 3 times greater in subjects who later married smokers, i.e., "exposed" subjects, than in subjects who later married nonsmokers, i.e., "unexposed" subjects. If it is not appropriate, then another approach is necessary. This approach is outlined in Method 2, which follows.

Method 2

Method 2 relies on the following two assumptions:

- Assume that (a) cigarette smoke influences the rates of the first- and fourth-stage cellular events in a five-stage multistage cancer process (Day and Brown, 1980; Brown and Chu, in press); (b) ETS affects the same two stages; and (c) the ratio of the relative magnitude of the effect (on a multiplicative scale) on stage 4 to that on stage 1 is the same for ETS and mainstream smoke. If we let β_1 and β_4 represent the magnitude of the effect on the first and fourth stages, respectively, then (c) implies that β_4/β_1 is the same for ETS and mainstream smoke.

- Assume the observed overall summary rate ratio of 1.3 is the ratio of the true relative risk in "exposed" subjects to that in "unexposed" subjects at age 70 (see Remark 3 in the Technical Discussion).

It is possible to estimate the true relative risk in "exposed" and "unexposed" study subjects, given two additional pieces of information (see Remark 8 in the Technical Discussion).

First, we require an estimate of the ratio β_4/β_1 . An estimate of β_4/β_1 can be obtained by fitting the above multistage cancer model to data on the lung cancer experience of active smokers. In particular, an estimate of 0.0124 is obtained by fitting the multistage model to the continuing smoker data among British physicians given by Doll and Peto (1978). Brown and Chu (in press) obtained an estimate of 1.8, derived by fitting the multistage model to data from a large European case-control study of lung cancer. These two estimates of β_4/β_1 , however, differ from one another by 150-fold. A third estimate of β_4/β_1 was computed, based on the following considerations. The estimate of β_4/β_1 from Doll and Peto (1978) fails to adequately account for the rapid fall off in relative risk in British physicians upon cessation of smoking. Since a larger ratio of β_4/β_1 will be associated with a more rapid fall off of risk when smoking is stopped (especially among smokers of relatively few cigarettes a day), we computed the maximum estimate of β_4/β_1 that was statistically consistent (at the 5% level) with the continuing smoker data in Doll and Peto (1978). This estimate was 0.225. Rather than choose among these estimates, we performed a sensitivity analysis using the three estimates of

β_4/β_1 of 0.0124, 1.8, and 0.225 (see Remark 5 in the Technical Discussion).

Second, we require, at each age, an estimate of the age-specific ETS exposure of "exposed" and "unexposed" study subjects relative to the current ETS exposure of an average adult nonsmoker whose spouse is a nonsmoker. Information does not exist to answer questions such as "How many times greater (or less) was the past ETS exposure in average "exposed" subjects from age 0 to 20 than the current ETS exposure of an average adult nonsmoker with a nonsmoking spouse?" Therefore, a sensitivity analysis was performed using 30 different choices for the lifetime exposure histories of "exposed" and "unexposed" subjects (relative to the current ETS exposure of an adult nonsmoker without a smoking spouse). The choice of exposure histories was influenced by the following general considerations. Smaller differences postulated between the lifetime ETS exposures of "exposed" and "unexposed" individuals will be associated with larger estimates of the true relative risk. (Having an observed rate ratio as large as 1.3 when there is truly only a small difference in dose between the "exposed" and "unexposed" subjects would imply that ETS is a potent carcinogen.) Therefore, we tried to select some exposure histories that would modestly underestimate the true difference in exposures between the "exposed" and "unexposed" study subjects and others that would modestly overestimate this difference. The rationale for our particular choices of the 30 exposure histories is given in Remark 7.

Thirty possible exposure histories are given in Table D-1. Remark 6 in the technical discussion describes how to read the exposure histories from this table.

Table D-2 gives the maximum and minimum estimates of the true relative risk among the "exposed" and "unexposed" for each choice of β_4/β_1 , over the 30 exposure histories. The column denoted "all" gives the overall maximum and minimum as the choice of both β_4/β_1 and exposure history varies.

The most striking finding is that the estimate of the excess (true) relative risk for "exposed" individuals varies only twofold, from 0.41 to 0.87, and includes the estimate, 0.54, obtained with Method 1. All estimates exceed the uncorrected value of 0.30. Estimates of the excess true relative risk in the "unexposed" range from 0.09 to 0.45. Because of the possibility that the 30 exposure histories are not representative of those in Japan and Greece, two

TABLE D-1 Thirty Population Exposure Histories in Various Age Groups^a

Value of a, b, or c	Population Subgroup	Age 0-20 yr			Age 20-55 yr			Age 55-70 yr		
		p_a	f_{1a}	f_{2a}	p_b	f_{1b}	f_{2b}	p_c	f_{1c}	f_{2c}
1	E	0.39	1.53 ^b	0.3	1.0	3.0	—	0.5	3.0	3.0
	\bar{E}	0.25	1.53	0.3	1.0	1.0	—	1.0	1.0	—
2	E	0.44	1.53	0.3	1.0	1.5	—	0.5	3.0	2.0
	\bar{E}	0.18	1.53	0.3	1.0	0.15	—	1.0	1.0	—
3	E	0.44	1.53	0.3	—	—	—	0.5	3.0	1.0
	\bar{E}	0.18	0.75	0.15	—	—	—	1.0	1.0	—
4	E	0.44	0.75	0.15	—	—	—	—	—	—
	\bar{E}	0.18	0.75	0.15	—	—	—	—	—	—
5	E	0.44	1.0	0.6	—	—	—	—	—	—
	\bar{E}	0.18	0.5	0.3	—	—	—	—	—	—

^aIn units of d_0 .

NOTATION: E = "Exposed"; \bar{E} = "Unexposed". Population Exposure History (a, b, c) = (1, 2, 3), has $p_{aE} = 0.39$, $p_{a\bar{E}} = 0.25$, $f_{1aE} = f_{1a\bar{E}} = 1.53$, $f_{2aE} = f_{2a\bar{E}} = 0.3$, $p_{bE} = p_{b\bar{E}} = 1.0$, $f_{1bE} = 1.5$, $f_{1b\bar{E}} = 0.15$, $p_{cE} = 0.5$, $p_{c\bar{E}} = 1.0$, $f_{1cE} = 3$, $f_{2cE} = 1$, $f_{1c\bar{E}} = 1$. The interpretation follows.

INTERPRETATION: 39% of E -individuals were exposed to ETS dose rate 1.53 d_0 and 61% to 0.3 d_0 from ages 0-20. 25% of \bar{E} subjects were exposed to 1.53 d_0 and 75% to 0.3 d_0 . From 20-55, all E -subjects were exposed to 1.5 d_0 , all \bar{E} subjects to 0.15 d_0 . From 55-70, 50% of E -subjects were exposed to 3 d_0 and 50% to 1 d_0 . All \bar{E} -subjects were exposed to 1 d_0 .

TABLE D-2 Estimated Ranges for the True Relative Risks (RR) in "Exposed" and "Unexposed" Subjects

Rate Ratio ^a	Group	β_1/β_0			
		All	0.0124	0.225	1.8
1.3	"Exposed"	1.41-1.67 ^b (321)-(113) ^c	1.41-1.87 ^b (321)-(113)	1.43-1.72 (321)-(113)	1.43-1.64 (321)-(113)
	"Unexposed"	1.09-1.45 (321)-(113)	1.09-1.45 (321)-(113)	1.10-1.34 (321)-(113)	1.11-1.27 (321)-(113)
1.14	"Exposed"	1.19-1.35 (321)-(113)	—	—	—
	"Unexposed"	1.04-1.18 (321)-(113)	—	—	—

^aAssume causal summary rate ratio.

^bRange of RR over 30 exposure histories and three values of β_1/β_0 .

^cRange of RR over 30 exposure histories.

^dExposure histories (a, b, c) at which minimum and maximum, respectively, occur (see Table D-1 for definition of exposure histories (a, b, c)).

of the countries in which epidemiologic studies were conducted, we repeated the analysis using the overall summary rate ratio of 1.14 from the U.S. studies. In this case the overall range in the estimates of the true relative risk was 1.19 to 1.35 in the "exposed" and 1.04 to 1.18 in the "unexposed."

D-2 THE CARCINOGEN-EQUIVALENT NUMBER OF ACTIVELY SMOKED CIGARETTES INHALED DAILY BY PASSIVE SMOKERS: COMPARISONS OF EPIDEMIOLOGIC WITH DOSIMETRIC ESTIMATES

In this section we attempt to estimate the number of cigarettes, d_0 , that would have to be actively smoked to deliver to the lung of the smoker a dose of active carcinogen equal to the daily pulmonary dose of carcinogen (attributable to ETS) of an average adult nonsmoker with a nonsmoking spouse. Roughly speaking, d_0 is the (lung) carcinogen-equivalent number of (actively smoked) cigarettes inhaled daily by an average adult nonsmoker with a non-smoking spouse.

Under the assumptions of Method 2, we saw that knowledge of β_1/β_0 and of the relative exposure histories of "exposed" and "unexposed" study subjects was sufficient to estimate the true

relative risks. If we also have an independent estimate of β_1 , we can estimate d_0 as well (see Remark 8). Each of our three methods of deriving an estimate for β_4/β_1 from data on active smokers also produces an estimate of β_1 . In particular, estimates of β_1 of 2.93, 0.803, and 0.14 are associated with β_4/β_1 of 0.0124, 0.225, and 1.8, respectively.

Some conflicting results need to be resolved, however. For any given level of smoking, the relative risk estimated from the British physicians data (Doll and Peto, 1978) is greater than that estimated from the American Cancer Society's follow-up data on a million Americans (Hammond, 1966) or from the multicenter European case-control lung cancer data (Lubin et al., 1984; Brown and Chu, in press). The relative risks in these latter two studies are consistent with one another and will here be treated as identical. Doll and Peto (1981) suggest that these differences in relative risk may be real differences, attributable in part to the different way cigarettes are smoked in Britain and other countries. To bring the British data in line with the other data, we adjusted our estimates of β_1 from the Doll and Peto data as follows. Separately, for the β_4/β_1 of 0.0124 and 0.225 (both based on the British physicians data), we computed the value of β_1 that would be necessary for an individual smoking 25 cigarettes per day since age twenty to have the same lung cancer incidence at age 65 as would follow if $\beta_4/\beta_1 = 1.8$, $\beta_1 = 0.14$ (based on the European case-control data). This gives adjusted estimates of 1.41 and 0.46 for β_1 , corresponding to values for β_4/β_1 of 0.0124 and 0.225, respectively. These values are approximately half those previously estimated from the British physicians data. In our sensitivity analysis we use both the adjusted and unadjusted estimates of β_1 (see Remark 9).

Estimates of d_0 are given in Table D-3. Under the assumption that the summary rate ratio of 1.3 is causal, estimates of d_0 vary about eightfold from 0.12 to 0.93 cigarettes per day. For a given pair of values of β_1 and β_4/β_1 , the variation in d_0 over the 30 exposure histories is only about twofold. When we use the summary estimate of 1.14 from the U.S. studies in lieu of the summary estimate of 1.3, our estimates of d_0 are diminished accordingly.

We next compare the above estimates of d_0 , which are based on the epidemiologic data, with estimates based on the dosimetric measurements reported in Chapters 2 and 7. Estimates of d_0 based on dosimetric calculations are given in Table D-4. In Table D-4 we

TABLE D-3 Estimated Range for d_0 , the Carcinogen-Equivalent Number of (Actively Smoked) Cigarettes Inhaled Daily by Subjects Without a Smoking Spouse

β_4/β_1 : All	0.0124	1.8	0.225
β_1 : All	2.93	1.41	0.14
Rate ratio			0.803
1.3 ^a	0.12-0.93 ^b (311)-(123) ^c	0.24-0.57 (311)-(123)	0.46-0.89 (311)-(423)
1.14	0.05-0.47 (311)-(123)		0.26-0.53 (311)-(123)

^aAssured causal rate ratio.

^bRange of d_0 in cigarettes/day over 30 exposure histories and all ($\beta_4/\beta_1, \beta_1$).

^cExposure history where maximum and minimum occurred.

^dRange of d_0 over 30 exposure histories.

TABLE D-4 Estimates of d_0 Based on Various Constituents of ETS in Cigarettes/Day

Constituent	Range
NDMA	0.17-3.75
BaP	0.0084-1.89
RSP	0.0001-0.005

give an estimated range for d_0 under the assumptions that the ratio of the pulmonary (tissue) dose of active carcinogen in nonsmokers without smoking spouses to the pulmonary dose in active smokers is equal to the ratio of the pulmonary dose of BaP, NDMA, or RSP in the same populations. The estimates in Table D-4 are based on (1) the dosimetric measurements given in Table D-4 and Chapter 7 and (2) the daily number of hours of self-reported ETS exposure among nonsmokers without smoking spouses (Wald and Ritchie, 1984; Friedman et al., 1983). Details of the calculations used to produce Table D-4 are given in Remark 11 of the Technical Discussion. The dosimetry of the biomarkers nicotine and cotinine is more complicated and is discussed in Remark 12.

There is a serious problem in reconciling the estimate of d_0 (Table D-4) based on BaP with that based on RSP, since RSP is often assumed to be a good surrogate for polycyclic hydrocarbons such as BaP. The estimate derived from the BaP measurements is

several orders of magnitude higher. A possible, although unlikely, explanation is that the measurements of BaP levels in ETS (summarized in Table 2-10) inappropriately reflect total environmental BaP, which includes contributions from cooking, coal burning, and other sources, and that the contribution of BaP from ETS to total BaP is of the order of 2% or less.

The large uncertainty in d_0 seen in Table D-4 restricts the utility of these dosimetric calculations, especially given the lack of knowledge concerning the identity of the active carcinogens in ETS and mainstream smoke. In fact, the limitations of our dosimetric data may be even more serious than Table D-4 would lead one to believe. Specifically:

- the range of values entered in Table D-4 for NDMA could actually be orders of magnitude too high (see step 4 of Remark 11),
- the range of values for RSP and BaP do not reflect differences between the particulate phase of ETS and that of mainstream smoke with regard to deposition sites, clearance rates, and particle size,
- the range of values given for BaP in Table D-4 could be orders of magnitude too high if, as discussed above, the BaP entries in Table 2-10 represent the total environmental BaP inhaled by a nonsmoker, and
- the ratio of urinary nicotine (or cotinine) in nonsmokers to that in active smokers may not reflect, even qualitatively, the ratio of the biologically effective dose of active lung carcinogen absorbed by nonsmokers to the dose absorbed by active smokers (see Remark 12).

D-3 ESTIMATING THE NUMBER OF LUNG CANCER DEATHS IN NONSMOKERS IN 1985 ATTRIBUTABLE TO ETS

An estimate of the total number of lung cancer deaths among lifelong nonsmoking women in 1985 is $\sum_t I_0(t)N(t)$, where $N(t)$ is the number of nonsmoking women at risk at age t in 1985 and $I_0(t)$ is the age-specific lung cancer death rate among nonsmoking women in 1985. Data on $I_0(t)$ are given in Garfinkel (1981) for 1972; thus, this may be somewhat inaccurate for 1985. National Health Interview Survey data on $N(t)$ were made available from

R. Wilson of the National Center for Health Statistics. Using these data, the number of lung cancer deaths was estimated to be 7,000, similar to the estimate obtained by Seidman (personal communication) using a related approach.

The total number of lung cancer deaths among nonsmoking women attributable to ETS in 1985 is

$$AN = \sum_t AF(t)I_0(t)N(t),$$

where $AF(t)$ is the age-specific fraction of lung cancer deaths due to ETS exposure in nonsmoking women. That is, $AF(t)$ is the age-specific average excess true relative risk (i.e., the average relative risk minus 1) divided by the age-specific average relative risk in order to estimate the age-specific average relative risk. In women, we require age-specific estimates of the probability of being married to a smoker (i.e., the probability of being "exposed") and of the true relative risk in "exposed" and "unexposed" subjects. We obtained age-specific estimates of the probability of being "exposed" from the Garfinkel et al. (1985) control population (Garfinkel, personal communication).

We estimated the true relative risk in three different ways. First, we use the estimates derived using Method 1 in Section D-1. Second, we use the estimates based on Method 2 of Section D-1. Third, we completely ignore the epidemiologic data on passive smoking and estimate the true relative risk by combining estimates of β_1 and β_2/β_1 extrapolated from data on active smokers, and estimates of d_0 based on dosimetry (Method 3). In a sensitivity analysis, we allow d_0 to equal 0.01, 0.2, and 2 to crudely represent (approximate) exposures to RSP, BaP, and NDMA, respectively (see Table D-4). The estimates of the attributable number based on Methods 1 and 2 are valid whenever the assumptions justifying those methods hold. For a given choice of d_0 , the estimates of the attributable number based on the third method are valid when the first assumption under Method 2 holds and the choice of d_0 is correct (see Remark 13).

Using the relative risk estimates based on Method 1, we obtained an attributable number of 2,010.

In Table D-5, estimated ranges for the attributable number are reported. $AN(EP)$ represents the estimates based on Method 2. $AN(0.01)$, $AN(0.2)$, and $AN(2)$ represent estimates based on the dosimetry estimates of 0.01, 0.2, and 2. (Since the estimate

of the true relative risk based on Method 2 depends only on β_4/β_1 (and not on β_1), the estimate of $AN(EP)$ also depends only on β_4/β_1 .) Estimates of the attributable number of lung cancer deaths based on Method 2 lie between 1,768 and 3,220. (These estimates are approximately halved when the summary rate ratio of 1.14, from the U.S. studies is used in place of the overall summary rate ratio of 1.3.) If the true value of d_0 were 0.01 cigarettes per day, then 259 lung cancer deaths in nonsmoking women would be attributable to ETS. On the other hand, the maximum estimate of the attributable number based on Method 3 with $d_0 = 0.2$ (3,170 deaths) is in agreement with that based on Method 2 (3,220 deaths). The minimum estimates, however, differ by approximately threefold.

The calculation of the number of lung cancers attributable to ETS in 1985 in nonsmoking males is similar. Garfinkel (1981) and Wilson (personal communication), respectively, give data on $I_0(t)$ and $N(t)$ for nonsmoking males. Since estimates of $I_0(t)$ in males and females are nearly equal and the estimates for females are more stable (Garfinkel, 1981), we use the same estimates of $I_0(t)$ for males as for females. Using these data, the estimated number of lung cancers which occurred in lifelong nonsmoking males in 1985 is 5200. For males, the fraction "exposed" is taken to be 14% (based on the control series from the Correa et al. (1983) study of males). Using relative risk estimates based on Method 1, it is estimated that 820 of the 5,200 lung cancer deaths are attributable to ETS. Estimates of the attributable number in males based on Methods 2 and 3 are given in Table D-5. Overall, the results for men are similar to those for women.

D-4 LIFETIME RISK OF DEATH FROM LUNG CANCER ATTRIBUTABLE TO ETS

Among Lifelong Nonsmokers

Permissible exposure limits to environmental agents are often set at levels low enough to reduce the lifetime risk of death attributable to the agent to 1 in 10^5 or 10^6 . For purposes of comparison with other environmental and occupational standards, we have attempted to estimate the fractions of all deaths among nonsmoking men and women who survive past age 45 that are

attributable to ETS-induced lung cancer. (This fraction is precisely the lifetime risk of lung cancer attributable to ETS exposure among persons surviving to age 45.) Since the risk of lung cancer is nearly 0 before age 45, we have chosen to condition this estimate on survival until that age. (Although years of life lost due to ETS exposure would be more preferable as a public health measure than the attributable fraction of deaths, we restrict our analysis to this latter measure in order to help determine whether, for regulatory purposes, ETS is being treated differently than other environmental exposures.) Because environmental regulations are generally set with the intention of protecting all (or at least almost all) individuals, we chose to estimate the attributable fraction for a representative subject with ETS exposure history of $2d_0$ for ages 0-18 and $4d_0$ for ages greater than 18. Based on data from Wald and Ritchie (1984) and Jarvis et al. (1984), this exposure history represents an exposure to ETS that is slightly greater than the average exposure of a nonsmoker exposed as a child to a smoking mother and as an adult to a smoking spouse. We label this exposure history as M , since it represents a moderately high lifetime exposure to ETS.

The fraction of all deaths subsequent to age t_0 (in our case age 45) attributable to exposure-induced lung cancer is, by definition,

$$AF(M) = \sum_{t>t_0} \gamma_{\text{EXCESS}}(t)S(t|t_0),$$

where $\gamma_{\text{EXCESS}}(t)$ is the excess lung cancer death rate at age t due to exposure history M and $S(t|t_0)$ is the overall probability of surviving to age t , given one has survived to t_0 . Given that the assumptions of Method 2 hold, we can obtain an estimate of $AF(M)$ for each value of β_4/β_1 and each of the 30 exposure histories for the "exposed" and "unexposed" study subjects, provided we have data on the age-specific lung cancer rates in nonsmoking women, $I_0(t)$, and data on the all-cause age-specific mortality rates among nonsmoking women (which we estimated from data given in Hammond (1966) (see Remark 14).)

The maximum and minimum of the $AF(M)$ across all exposure histories for each β_4/β_1 are given in Table D-6 in the "never-smoked" rows for males and females. $AF(M)$ is estimated to be between 390 and 990 in 100,000. A similar calculation, using the

TABLE D-5 Estimates of ETS-Attributable Lung Cancer Deaths Among U.S. Nonsmokers in 1985 (by Sex)

β_4/β_1 :	All	0.0124	0.225	0.0124	0.225	1.80
β_1 :	All	2.93	0.803	1.41	0.461	0.140
Sex						
Rate Ratio = 1.3						
AN (EP)^a						
F	1768-3220 ^b (323)-(113) ^d	1768-3220 (323)-(113)	1820-2800 ^c (321)-(113)	1768-3220 (323)-(113)	1820-2800 (321)-(113)	1939-2492 (323)-(113)
M	721-1942 (321)-(113)	721-1942 (321)-(113)	751-1611 (321)-(113)	721-1942 (321)-(113)	750-1611 (321)-(113)	850-1390 (321)-(113)
AN (0.01)						
F	31-259 (423)-(211)	125-259 (423)-(211)	54-102 (423)-(211)	61-127 (423)-(211)	31-59 (423)-(211)	34-55 (423)-(211)
M	14-137 (423)-(111)	53-137 (423)-(111)	24-50 (423)-(111)	26-67 (423)-(111)	14-29 (423)-(111)	16-25 (423)-(111)
AN (0.2)						
F	585-3174 (423)-(211)	1921-3174 (423)-(211)	978-1695 (423)-(211)	1059-1939 (423)-(211)	585-1052 (423)-(211)	634-988 (423)-(211)
M	265-1890 (423)-(111)	908-1890 (423)-(111)	450-891 (423)-(111)	425-1094 (423)-(111)	265-540 (423)-(111)	305-465 (423)-(111)
AN (2)						
F	3793-6778 (423)-(211)	5992-6778 (423)-(211)	5039-6198 (423)-(211)	4702-5973 (423)-(211)	3793-5163 (423)-(211)	3854-4955 (423)-(211)
M	2016-4803 (423)-(111)	3812-4803 (423)-(111)	2904-4060 (423)-(111)	2758-4057 (423)-(111)	2016-3170 (423)-(111)	2151-2908 (423)-(111)
Rate Ratio = 1.14						
AN (EP)						
F	935-1730 (323)-(113)					
M	360-980 (321)-(113)					

^aAN (EP) is based on epidemiologic data in nonsmokers exposed to ETS.

^bRange of attributable number of lung cancers over 30 exposure histories and five choices of ($\beta_1, \beta_4/\beta_1$).

^cRange of AN of lung cancers over 30 exposure histories in nonsmoking females for $\beta_4/\beta_1 = 0.225, \beta_1 = 0.803$.

^dExposure history where minimum and maximum occurs.

TABLE D-6 Range of Estimated Lung Cancer Deaths Attributable to Breathing Other People's Cigarette Smoke per 10,000 Deaths (All Causes)

Rate	Sex	Smoking Status ^a	β_4/β_1 : All		β_1	β_4	1.8	0.225
			2.93	1.41				
1.3 ^b	M	N	39-99	48-99	45-95 ^d	48-99	45-95	39-77
		Ex	52-197	62-126	74-149	52-106	100-197	62-115
		C	58-307 ^c	78-157	107-209	58-117	159-307	86-158
1.14	F	N	40-99	49-99	45-96	49-99	45-96	40-78
		Ex	54-203	64-130	77-154	54-110	103-203	64-120
		C	62-331	84-169	115-225	62-125	171-331	92-170
1.14	M	N	19-49					
		Ex	26-99					
		C	29-159					
1.14	F	N	21-52					
		Ex	29-109					
		C	33-182					

^aSmoking Status: N = never; Ex = smoked 1 pack per day, age 18-45; C = continuing smoker, 1 pack per day from age 18.

^bAssumed causal rate ratio.

^cRange over 30 exposure histories, S values of $(\beta_1, \beta_4/\beta_1)$.

^dRange over 30 exposure histories.

NOTE: All maxima were associated with exposure history (423); all minima with history (311).

summary risk of 1.14 from the U.S. studies (instead of 1.3), halves our estimates for $AF(M)$.

Among Current and Exsmokers

We now estimate $AF(M)$ for $t_0 = 45$ for current and exsmokers of 20 cigarettes per day. To clarify the approach, consider a female exsmoker (or continuing smoker) who was exposed to exposure history M of ETS from other people's cigarette smoke. (The subject's total ETS exposure is even greater, since it consists of contributions from her own cigarette smoke, as well.) Then $\gamma_{\text{excess}}(t)$ necessary for the calculation of $AF(M)$ is the difference between the lung cancer mortality rate at age t , given her total smoke exposure, and her lung cancer mortality rate at age t , had she had the same active smoking history without exposure to other people's cigarette smoke. We require the same assumptions and information to estimate $AF(M)$ for exsmokers and continuing

smokers as we did for nonsmokers, plus an estimate of β_1 . Estimates of $S(t|t_0)$ are obtained as before, except the exsmoker and continuing smoker all-cause mortality rates given in Hammond (1966) are used (see Remark 15).

In Table D-6 the maximum and minimum of $AF(M)$ for each of five combinations of $(\beta_1, \beta_4/\beta_1)$ and all 30 exposure histories for the "exposed" and "unexposed" are given for continuing smokers and exsmokers of 20 cigarettes per day starting at age 18 and, in the case of exsmokers, stopping at age 45. For exsmokers, the estimate lies between 520 and 2,030 per 100,000. For continuing smokers, it lies between 580 and 3,310 per 100,000. A similar calculation, using the summary rate ratio of 1.14 from the U.S. studies, halves our estimates.

DISCUSSION

Exercises in quantitative risk assessment serve several useful purposes. First, public health decisions must often be made without certainty as to the magnitude of the likely health benefits that would result from implementing the various policy options. Quantitative risk assessment can aid in the decision-making process by quantifying this uncertainty. Second, difficulties encountered in providing precise estimates in quantitative risk assessment highlight areas where scientific knowledge is inadequate. Thus, exercises in risk assessment can serve to help focus future research.

All quantitative assessments of risk rely on assumptions. Interval estimates of quantitative risk are reliable only insofar as (1) the assumptions under which they were derived are valid and (2) the range of parameter values used in the estimation process includes the true value. It follows that no quantitative risk estimates can be guaranteed to be reliable. Nonetheless, some risk estimates are more (or less) reliable than others.

With regard to point (2) above, it should be noted that, in performing the risk assessment presented here, a sensitivity analysis was performed only over those parameters for which there were either inadequate empirical estimates (e.g., the lifetime ETS exposure history of "exposed" and "unexposed" subjects) or grossly inconsistent estimates (e.g., the estimates of β_4/β_1). Thus, the analyses did not account for other sources of uncertainty, such as statistical uncertainty, in estimates of other parameters. If they had, the width of the interval risk estimates may have increased

several-fold. Generally, the more parameters that are varied in a sensitivity analysis, the more information that analysis provides; nonetheless, for simplicity, we chose to vary only those parameters with inadequate or inconsistent estimates. It is inevitable that some readers, often with good justification, will feel that we should have used different values for the parameters we treated as fixed or different ranges for the parameters we varied. (Computer programs are available from Dr. Robins.)

In our risk assessment, the most important assumption was that the observed summary rate ratio of 1.3 was causal. If this assumption is correct (below we discuss the possibility that it is not), we believe that the estimate of the lifetime risk of lung cancer among lifelong nonsmokers attributable to moderate ETS exposure [$AF(M)$] will be accurate to within a factor of 2 to 6. This belief depends on the fact that if the rate ratio of 1.3 is causal, we are not extrapolating outside the range of the data (for example, from high to low dose) in estimating $AF(M)$. (Even though our reported uncertainty in estimating $AF(M)$ in never-smokers (Table D-6) is only twofold, nonetheless, as discussed above, our estimate of overall uncertainty would likely be larger; we have guessed twofold to sixfold). For any reasonably flexible model, such as the multistage model, the data (when ample) will drive the risk estimates provided one does not extrapolate outside the range of the data. For instance, even though our estimates of β_1/β_2 used in the sensitivity analysis differed by 150-fold, the overall variation in the lifetime risk of lung cancer due to ETS in nonsmokers varied only twofold (Table D-6). In contrast, in estimating the lifetime risk of lung cancer due to ETS in exsmokers we were forced to extrapolate outside the range of the data. To do this we used statistical models. We found an uncertainty factor of about fourfold (Table D-6) because of the sensitivity of this extrapolation to the particular coefficients assumed for the multistage model. But even this range of four underestimates the true uncertainty, because we have little assurance that it is appropriate to use the multistage model to extrapolate.

Given that we can know the lifetime risk of ETS-caused lung cancer in nonsmokers within a factor of 2 to 6, is this degree of accuracy sufficient for our purposes? Obviously, it depends on the purpose. If there were a regulatory process through which we wished to ensure that the lifetime risk of lung cancer attributable to ETS among nonsmokers would be no greater than 1 in 100,000 (or even

1 in 1,000), by limiting, if necessary, exposure to environmental tobacco smoke, our risk analysis would appear to be sufficient to drive that process. This is true because, even if the lower estimate of risk of 390 per 100,000 were reduced by factor of 2 or 3 (to take into account additional sources of uncertainty), it would still greatly exceed 1 per 100,000.

In this appendix, we confined our risk estimates to those arising under the assumptions that the causal summary rate ratio from the various epidemiologic studies was either 1.3 or 1.14 (the summary rate ratio from the U.S. studies). In Chapter 12 it was concluded that, considering the evidence as a whole, exposure to ETS increases the rate of lung cancer among nonsmokers. Furthermore, it was concluded that our best overall estimate of the causal summary rate ratio from the 13 studies was about 1.3. In light of this conclusion about causation, for purposes of making public health decisions for the United States, it would seem prudent to operate under the assumption that the true summary rate ratio was most likely 1.3 and at least 1.14 (even though values less than 1.14 cannot be excluded). We therefore did not prepare estimates for values less than 1.14.

We also did not make risk estimates under the assumption that the causal summary rate ratio was greater than 1.3, largely because the estimated lifetime risk of lung cancer at this rate ratio of 1.3 was sufficiently large that it did not seem important to quantify how large the lifetime risk might be if the true causal rate ratio were 1.48 (the 95% upper confidence limit for the summary rate ratio of 1.3). Finally, it would have been helpful to be able to compare estimates of risk derived from the 13 epidemiologic studies of nonsmokers exposed to ETS with independent estimates based on dosimetric measurements made in active and passive smokers. Unfortunately, as discussed in Section D-2, uncertainties in the identity and dose of the active carcinogens in ETS and mainstream smoke effectively preclude this possibility at this time.

TECHNICAL DISCUSSIONS

Estimation of the True Relative Risk

Method 1

The assumptions presented in Section D-1 above are replaced by more formal assumptions:

Assumption 1a We assume that, in the "low-dose" range represented by ETS exposure, the increment in the mortality rate at age t due to an increment of ETS exposure experienced at age u ($u < t$) is uninfluenced by any other increment of ETS exposure (whether received at time u or at any other time u').

The mathematical formulation of Assumption 1a is

$$\gamma(t)\{d(u); u \leq t\} = \gamma_0(t)\{1 + \beta(t) \int_0^t f(t, u)d(u)du\}, \quad (D-1)$$

where $\gamma_0(t)$ is the mortality rate at t in the absence of exposure to ETS, $d(u)$ is the dose at age u of the active carcinogen in ETS, $\gamma(t)\{d(u); u \leq t\}$ is the mortality rate at t given a history of exposure to ETS represented by the curve $\{d(u); u \leq t\}$, $\int_0^t f(t, u)d(u)du$ may be interpreted as a weighted average of an individual's past exposure, and $\beta(t)$ is an age-specific measure of the magnitude (on a ratio scale) of the ETS effect. (For example, if there were a 5-year biologic latency period, $f(t, u) = 0$ for $t - u < 5$).

Remark 1 In the above description of Equation D-1, we have implicitly assumed that $\int_0^t f(t, u)du = 1$ so that $\int_0^t f(t, u)d(u)du$ is a weighted average and $\beta(t)$ is an effect measure. In fact, the restriction

$$\int_0^t f(t, u)du = 1 \quad (D-2)$$

is not in general necessary for Equation D-1 to be meaningful, although some restriction is necessary to identify $\beta(t)$. Nonetheless, Equation D-1 can always be "reparameterized" so that Equation D-2 holds. If, in Equation D-1, $\beta(t) = \beta$ independent of t , we say that we have a linear excess relative risk model. If in Equation D-1, $\beta(t)\gamma_0(t) = \beta'$, independent of t , we have a linear excess absolute risk model. If there exists a function $f(t, u)$ for which Equation D-1 is a linear excess relative (or absolute) risk model, then Equation D-1 generally cannot be "reparameterized" so that simultaneously Equation D-2 holds and $\beta(t) = \beta$ or $\beta(t)\gamma_0(t) = \beta'$.

Remark 2 By extending the argument given by Crump et al. (1976), one can show that sufficient (but not necessary) conditions for Assumption 1a to hold are (1) the dose of ETS to passive smokers at any time u has a very small influence on risk at t and

(2) other risk factors for lung cancer operate through the same mechanism as ETS. Since the true relative risk associated with passive smoking exceeds 1.3, Crump et al.'s argument may not be relevant. In Remark 18, we empirically assess the validity of Assumption 1a under the further assumption that cigarette smoke affects two stages of a five-stage multistage cancer process.

Consider now the subset of the source population of an epidemiologic study that includes "exposed" individuals at risk at age t . Clearly, the exposure at any time u , $u < t$, to ETS, say $d(u)$, will vary among persons in this subset. Let $d_E(u|t)$ be the average pulmonary dose at age u among "exposed" individuals at risk at age t .

In a follow-up study in which the data collected includes age, cause of death, and "exposure" status, we can empirically estimate the age-specific (average) mortality rate among "exposed" individuals, $\gamma(t|E)$, and unexposed individuals, $\gamma(t|E)$. Furthermore, it follows from the linearity of Equation D-1 that

$$\begin{aligned} RR(t|E) &\equiv \gamma(t|E)/\gamma_0(t) \\ &= 1 + \beta(t) \int_0^t f(t, u)d_E(u|t)du, \end{aligned} \quad (D-3)$$

where $RR(t|E)$ is the true relative risk (i.e., the ratio of the mortality rate among "exposed" individuals to that of truly unexposed individuals). Unfortunately, we cannot estimate $\gamma_0(t)$ [and thus $RR(t|E)$] without further assumptions. Similarly, we are unable to estimate $RR(t|E)$, the true relative risk due to ETS in "unexposed" individuals. (Remember, "unexposed" individuals are truly exposed.) But, in the absence of bias, from either prospective or case-control data we can empirically estimate

$$\frac{\gamma(t|E)}{\gamma(t|E)} = \frac{1 + \beta(t) \int_0^t f(t, u)d_E(u|t)du}{1 + \beta(t) \int_0^t f(t, u)d_E(u|t)du} = \frac{RR(t|E)}{RR(t|E)}. \quad (D-4)$$

(In a case-control study the left side of Equation D-4 is the age-specific odds ratio comparing "exposed" to "unexposed" individuals.)

Assumption 1b

$$\frac{d_E(u|t)}{d_E(u|t)} \equiv c(u|t) = c(t), \quad (D-5)$$

where $c(t)$ is a known constant independent of u . Note $c(u|t)$ is a ratio of the average exposure at age u of "exposed" subjects at risk at age t to that of "unexposed" subjects at risk at t . Our main result is:

Lemma 1: If Assumptions 1a and 1b hold then $RR(t|E) = 1 + c(t)x$ and $RR(t|E) = 1 + x$ where

$$x = \frac{\frac{\gamma(t|E)}{\gamma(t|E)} - 1}{\frac{\gamma(t|E)}{\gamma(t|E)} - \frac{\gamma(t|E)}{\gamma(t|E)}}.$$

Proof: Let $\beta(t) \int_0^t f(t, u) d_g(u|t) du = RR(t|E) - 1 \equiv x$. Then $RR(t|E) = 1 + c(t)x$ and $RR(t|E) = 1 + x$. Thus, substituting in Equation D-4,

$$\frac{\gamma(t|E)}{\gamma(t|E)} = \frac{1 + c(t)x}{1 + x}$$

implies:

$$x = \frac{\frac{\gamma(t|E)}{\gamma(t|E)} - 1}{\frac{\gamma(t|E)}{\gamma(t|E)} - \frac{\gamma(t|E)}{\gamma(t|E)}}. \quad (D-6)$$

Example: Suppose $c(70) = 3$ and $\gamma(70|E)/\gamma(70|E) = 1.3$, then $x = 0.18$, $RR(70|E) = 1.18$, $RR(70|E) = 1.54$.

We now show that, under Assumption 1a, if $c(u|t) < 3$ for all u , the previous estimates of $RR(t|E)$ and $RR(t|E)$ must, in fact, be underestimates (although the magnitude of the underestimation cannot itself be assessed without further assumptions such as those given under Method 2). First note that even when Equation D-5 is false, it is still true that, under Assumption 1a, with $x \equiv RR(t|E) - 1$, Equation D-6 holds provided $c(t)$ is replaced by $c^*(t)$, where

$$c^*(t) = \frac{\int_0^t f(t, u) d_g(u) du}{\int_0^t f(t, u) d_g(u) du}.$$

[Note that $c^*(t) > \gamma(t|E)/\gamma(t|E)$.] Furthermore, $RR(t|E)$ is still $1 + x$ (by definition) and $RR(t|E) = 1 + c^*(t)x$.

Now it is straightforward to check that $RR(t|E)$ and $RR(t|E)$ are decreasing functions of $c^*(t)$ reaching respective minima of 1 and $\gamma(t|E)/\gamma(t|E)$ when $c^*(t) \rightarrow \infty$ and maxima of ∞ when

$c^*(t) = \gamma(t|E)/\gamma(t|E)$ is greater than 1. $c^*(t) = \gamma(t|E)/\gamma(t|E)$ is the condition of maximum misclassification between "exposed" and "unexposed" groups in terms of exposure to ETS. On the other hand, when $c^*(t) = \infty$ no "unexposed" individual is exposed to ETS.

Furthermore, it is easy to check that if

$$d_g(u|70)/d_g(u|70) = c(u|70) \leq 3 \quad (D-7)$$

for all $u \leq 70$, then $c^*(t) \leq 3$. It follows that in our previous example, $RR(t|E) = 1.18$ and $RR(t|E) = 1.54$ would, in general, be underestimates of the true $RR(t|E)$ and $RR(t|E)$ if Equation D-7 holds.

Remark 9 Note that the investigators of the 13 epidemiologic studies analyze their results as if their observed rate ratios were not dependent on age, as evidenced by the fact that none of the authors reported age-specific rate ratios. But if the rate ratio varies with age, then the observed rate ratio reported in each study will be a weighted average of varying age-specific rate ratios. Since Garfinkel et al. (1985) found the median age of lung cancer in nonsmoking women in his population was approximately 70 (Garfinkel, personal communication), we would expect that this weighted average approximates the rate ratio at 70. This implies that the second assumption under Method 2 in section D-1 is probably close to correct. To be precise, if, in a case-control study, one-to-one matching on age is employed and a matched pair analysis is performed, the matched pair odds ratio estimator will estimate the following weighted average of the age-specific rate ratios, $\gamma(t|E)/\gamma(t|E)$. The large sample expected value of the odds ratio estimator (OR) is $E[OR] = \int [\gamma(t|E)/\gamma(t|E)] f(t) dt$ where

$$f(t) = \frac{h(t) f_D(t)}{\int h(t') f_D(t') dt'}$$

$$h(t) = \frac{p(E|t)p(E|t)}{[\gamma(t|E)/\gamma(t|E)]p(E|t) + p(E|t)}.$$

$f_D(t)$ is the fraction of all lung cancers in nonsmoking women that occur at age t , and $p(E|t)$ is the fraction of nonsmokers in the study source population of age t who are "unexposed."

Remark 4 We now examine the conditions under which Assumption 1b holds with $c(70) = 3$. We conclude from the following

examination that it is unlikely that Assumption 1b is true, even as an approximation.

Wald and Ritchie (1984) estimate that, in 1982 in England, the urinary cotinine concentration of an average nonsmoking male with a smoking spouse is 3 times that of the average nonsmoking male without a smoking spouse. Urinary nicotine data from Jarvis et al. (1984) and interview data from Friedman et al. (1983) suggest that similar results would be obtained in women. Given these observations, the following six conditions must, in general, be met in order for Assumption 1b to hold with $c(70) = 3$.

Condition 1 The ratio of 3 also applies to exposure to the biologically relevant carcinogen or carcinogens in ETS.

Condition 1 is likely to hold, at least in our approximate sense, in the United States and England. [Olav Axelsson has pointed out a situation in which it would not hold. Suppose that the carcinogenic effect of ETS is largely due to the adsorption of environmental radon onto ETS particles. Then, home exposure to ETS would be of greater importance if, in general, only home ventilation rates are low enough to allow significant accumulation of environmental radon onto ETS particles. Friedman et al. (Table 6, 1983) showed that the number of hours currently-"exposed" women are exposed to ETS at home is 12.7 times the number of hours that currently-"unexposed" individuals are exposed at home. On the other hand, the total number of hours of ETS exposure in currently-"exposed" women is only 3 times that of currently-"unexposed" individuals. Thus, if radon uptake rather than urinary cotinine had been measured, Wald and Ritchie may have found a ratio nearer 12 than 3.]

On the other hand, in Japan and Greece the ratio of urinary cotinine in nonsmoking women with a smoking spouse to that in nonsmoking women without a smoking spouse probably exceeds the value of 3 measured by Wald and Ritchie (1984) in England, since women in those countries are likely to spend less time in contact with cigarette smokers outside the home. It follows that one might expect the observed rate ratio in the Hirayama (1984) and Trichopoulos et al. (1983) studies in Japan and Greece, respectively, to exceed that found in studies in the United States. Table 12-4 bears out this expectation. Thus, we might want to exclude Hirayama's and Trichopoulos et al.'s studies in calculating the overall summary rate ratio. We have seen that the U.S.

studies have an overall summary relative risk of 1.14. Assuming Assumption 1b with $c(70) = 3$ holds for the United States, we would estimate the true relative risk in "exposed" and "unexposed" study subjects in the United States to be 1.225 and 1.075. Nonetheless, since 1.225 is less than the observed rate ratios of 1.45 and 2.01 in the Hirayama and Trichopoulos et al. studies, we must also assume that the ETS exposure of nonsmoking women with smoking spouses in Japan and Greece exceeds that in the United States (if we ignore sampling variability and other sources of bias and interaction). Matsukura et al.'s (1984) data on urinary cotinine suggests this may be the case for spouse-exposed Japanese nonsmokers.

Because 10 of the 13 epidemiologic studies were case-control studies, we concentrate on case-control studies in the following. (Most of our remarks would have to be only slightly modified in order to apply to prospective studies such as Garfinkel (1981) and Hirayama (1981), in which the follow-up is only 10 to 15 years.) To characterize further conditions sufficient to imply that $c(70) = 3$, we shall need to be more precise in our definition of "exposed" and "unexposed" subjects. We define an ever-"exposed" (never-"exposed") subject to be a nonsmoker who, when queried in a case-control study in approximately 1982, answered "yes" ("no") to the question "Did you ever live with a smoking spouse?" We define a currently-"exposed" (currently-"unexposed") subject to be a nonsmoker who, in an epidemiologic study in 1982, answered "yes" ("no") to the question "Do you currently live with a smoking spouse?" Some of the case-control studies compared ever-"exposed" and never-"exposed" individuals (for example, Garfinkel et al., 1985). Approximately half of Garfinkel's ever-"exposed" subjects were currently-"unexposed," with the median time since their spouse stopped smoking of 15 years (Garfinkel, personal communication). Other studies compared currently-"exposed" subjects to never-"exposed" subjects.

Condition 2 Wald and Ritchie's (1984) ratio of 3 is independent of age and thus applicable to 70-year-olds. Sufficient urinary cotinine measurements have not been made on 70-year-olds to provide empirical evidence as to whether this condition holds.

Condition 3 Nearly all 70-year-old currently-"exposed" individuals married smokers at about age 20 in approximately 1932. This is

probably a reasonable approximation, assuming little divorce and remarriage in this population.

Condition 4 If the study compares ever-"exposed" to never-"exposed" subjects, the magnitude of the ETS exposure in the years preceding the study date of ever-"exposed" individuals who are currently-"unexposed" (because their spouses either died or quit smoking on average 15 years ago) is the same as that of currently-"exposed" individuals. For this latter condition to hold (even as an approximation), it is necessary either that only a small proportion of the total ETS exposure in currently-"exposed" individuals is directly from their spouses or that, when the smoking spouse of a nonsmoker either dies or quits smoking, the amount of time the nonsmoker spends with other smokers increases. Our guess, based on Table 6 of Friedman et al. (1983), is that the ETS exposure of an average ever-"exposed" female diminishes by a half or more when her husband either dies or quits. Thus, it is unlikely that Condition 4 holds.

Condition 5 The ratio of 3 applies to the ETS exposure of "exposed" and "unexposed" subjects even during childhood. It seems unlikely that children who grew up to marry smoking spouses would have 3 times the ETS exposure in childhood as children who grew up to marry nonsmoking spouses, although in Remark 7 we consider empirical evidence which suggests it is conceivable that Condition 5 might approximately hold.

Condition 6 Wald and Ritchie (1984) would have found the same ratio of 3 if their study had been performed in any year from 1932 to 1982. Even in those case-control studies that compared currently-"exposed" subjects to never-"exposed" subjects, Condition 6 may well be false. For example, in the 1930s and 1940s, nonsmoking women study subjects (who were then 20 to 30 years old) were presumably less often in contact with smokers outside the home. This would suggest that in the 1930s and 1940s the ratio of ETS exposure in nonsmoking women with smoking spouses compared to nonsmoking women without smoking spouses was closer to 12 than to 3 (provided the results of Friedman et al. (1983) mentioned in the discussion under Condition 1 can be extrapolated to the 1930s).

Remark 5: Estimates of β_4/β_1 . We used three different estimates for β_4/β_1 in our sensitivity analysis. All were obtained from data

on active smokers. To obtain the first, we fit by the method of maximum likelihood a five-stage multistage model, with the first and fourth stages affected, to the data on continuing smokers given in Doll and Peto (1978) (excluding, as did Doll and Peto, the subgroup who smoked more than 40 cigarettes per day). This gave $\beta_4/\beta_1 = 0.0124$ (and $\beta_1 = 2.93$). To be precise, we fit, as did Doll and Peto, the data enclosed in rectangles in their Tables 2 and 3. We used the mean number of cigarettes for each "cigarette-per-day" group given in their Table 2 and assumed, for each "cigarette-per-day" group, a variance that was half the maximum possible variance. We then fit the data in three different ways. First, we used the reported actual mean age of onset of cigarette smoking (19.2 years) as date of onset and the means of the age groups defining the rows in Tables 2 and 3 as the age of the event. Secondly, we used age 22.5 years as date of onset. Thirdly, we used age 19.2 years as date of onset, but subtracted 3.3 years from the means of the age groups defining the age of the event. The first and third methods both gave essentially the estimates reported above, while the second method gave $\beta_4/\beta_1 = 0.014$, $\beta_1 = 3.42$. The estimates based on the second method are not used in this appendix.

For our second estimate we used an estimate of $\beta_4/\beta_1 = 1.8$, given by Brown and Chu (in press), based on fitting this same multistage model to data from a large European case-control study. Brown and Chu found that $\beta_4/\beta_1 = 1.8$ (and $\beta_1 = 0.14$) for individuals who smoked 21-30 cigarettes per day (see Table 3 of Brown and Chu). (Brown and Chu find a ratio of 4 for β_4/β_1 for smokers of 1-10 cigarettes per day. We did not use this estimate due to its presumed lack of stability.) Note that the ratio of 1.8 found by Brown and Chu was 150 times that of Doll and Peto. The low β_4/β_1 ratio in the Doll and Peto continuing smoker data does not appear to adequately account for the rapid decline in risk associated with cessation of cigarette smoking as given in Doll and Peto (1976). This implied that the estimate of 0.0124 was probably too low. Furthermore, the estimate of β_4/β_1 from the Doll and Peto continuing-smoker data was quite imprecise, since the correlation between the estimates of β_1 and β_4 was -0.93 . Based on these considerations, we computed a revised estimate of β_4/β_1 from the Doll and Peto continuing-smoker data by finding the maximum value of β_4/β_1 associated with a point on the 2 log likelihood surface that lay 3.87 (chi-squared units) below the value of the 2 log likelihood

surface at its maximum above. At this point, the ratio of β_4/β_1 had increased 20-fold to 0.225 (and $\beta_1 = 0.803$). In our sensitivity analysis, therefore, we used ratios of β_4/β_1 equal to 0.0124, 0.225, and 1.8.

(One might believe that if the estimate of β_4/β_1 , which one would hope to be a biological constant, can differ by 150-fold across data sets, Method 2 is useless. We actually are not so skeptical. If the sensitivity analysis shows that such large differences in estimates of β_4/β_1 have little influence on our estimate of the true relative risk in "exposed" and "unexposed" study subjects, this will indicate a high degree of robustness (insensitivity) to the actual value of β_4/β_1 for lung cancer risk. Therefore, our confidence in the estimates of the true relative risk may therefore be enhanced. As we shall see, we do indeed find such robustness.)

Remark 6: Reading the Exposure Histories from Table D-1 Each of our exposure histories can be represented by a vector (a, b, c) , where the value of a characterizes five possible population-exposure histories from age 0-20 ($a = 1, \dots, 5$), b characterizes two possible exposure histories from age 20-55 ($b = 1, 2$) and c characterizes three possible exposure histories from ages 55-70 ($c = 1, 2, 3$). Since we can select any of five exposure histories between ages 0 and 20, any of two between ages 20 and 55 and any of three between 55 and 70, we have $5 \times 3 \times 2 = 30$ exposure histories. Each value of c gives an exposure history for "exposed" and "unexposed" subjects between the ages of 55 and 70. The population-exposure history between ages 55 and 70 represented by a particular value of c is described by the (up to) six values entered in Table D-1. As an example of how to read Table D-1, consider the case $c = 3$. Reading Table D-1, we see that $p_{eE} = 0.5$, $f_{1eE} = 3d_0$, $f_{2eE} = 2d_0$, $p_{eS} = 1.0$, $f_{1eS} = 1d_0$, and f_{2eS} is undefined. By definition, p_{eE} gives the fraction of "exposed" individuals exposed at rate f_{1eE} between ages 55 and 70. $1 - p_{eE}$ is the fraction of "exposed" individuals exposed at rate f_{2eE} . Therefore, 50% of "exposed" individuals receive a dose of ETS of $3d_0$ from 55 to 70 and 50% receive $1d_0$. Similarly, 100% of "unexposed" individuals receive a dose of $1d_0$ between ages 55 and 70. (Therefore, f_{2eE} need not be defined.)

Remark 7: Choice of 90 Exposure Histories In choosing the exposure histories, we rely heavily on data from the control series in Garfinkel et al. (1985), because similar detailed information is not available for any other study. We made the following assumptions.

1. All study subjects were age 70 at the time of the study. (In the Garfinkel et al. study (1985), the average age of cases and controls was approximately 70.) The choice of 55 as the upper age cutoff reflects the fact that among controls in Garfinkel et al. who were ever-"exposed" but not currently-"exposed," the median time since their smoking spouses either died or quit was roughly 15 years. Thus, we chose $70 - 15 = 55$ as the age at which ever-"exposed" individuals who are currently-"unexposed" ceased to be exposed to their spouses' cigarette smoke. The choice $c = 2$ represents our best guess as to the actual ETS exposure in the Garfinkel et al. study population between ages 55 and 70. The choice $c = 3$ assumes the ever-"exposed" subjects who are currently "unexposed" receive the same ETS dose, d_0 , from age 55 to 70 as never-"exposed" subjects. Note that $c = 1$ represents a study in which all exposed individuals are currently-"exposed."

2. For exposure histories between ages 20 and 55, we assume that all subjects were married at age 20. $b = 1$ represents a population in which Wald and Ritchie (1984) would have obtained the same urinary cotinine measurements had they performed their study in any year from 1932 to 1982. In contrast, $b = 2$ represents a situation in which from 1932 to 1967 never-"exposed" individuals were exposed to ETS at a rate only 15% of that of currently-"unexposed" individuals in 1982 and ever-"exposed" individuals were exposed at a rate half that of a currently-"exposed" individual in 1982. Thus, $b = 2$ represents an extreme example of the situation discussed under Condition 6 of Remark 4 with $c(30/70) = 10$. The true exposure rates between ages 20 and 55 presumably lie between those represented by $b = 2$ and $b = 1$.

3. We next consider ETS exposures between the ages of 0 and 20. 39% (25%) of "exposed" ("unexposed") individuals in the control series in Garfinkel et al. (1985) reported that they were regularly exposed to ETS in their homes during childhood (presumably because, in the large majority of cases, at least one of their parents was a smoker). These controls, who are on average age 70, had to remember their parents' smoking habits over more than 50 years. Therefore, some misclassification is unavoidable. As a guess, we suppose that the false negative rate for parental smoking was 0.3 and the false positive rate was 0.15, independent of "exposure" status. Define p_{eE} to be the fraction of exposed controls with at least one smoking parent. Then, correcting for misclassification, our best estimates of p_{eE} and p_{eS} are 0.44 and

0.18, respectively (since $0.7 p_{aE} + 0.15(1 - p_{aE}) = 0.39$ implies $p_{aE} = 0.44$).

For the exposure histories represented by $\alpha = 1$, we used the uncorrected estimates 0.39 and 0.25, and otherwise used the corrected estimates. The uncorrected estimates were used in our sensitivity analysis because we do not know the true misclassification rates and, if false-positive and false-negative rates depend on "exposure" status, the true ratio of p_{aE}/p_{aG} may be less than or equal to 0.39/0.25. To develop estimates of f_{1a} and f_{2a} we proceed as follows. Jarvis et al. (1985) give mean salivary cotinine levels in children of 0.44, 1.32, 1.99, 3.39 ng/ml, depending on whether neither parent smoked (269), only father smoked (96), only mother smoked (76), or both parents smoked (128). (The numbers in parentheses give the number of children in each parental smoking category.) Now, Jarvis et al. conjecture that an average active smoker would have a salivary cotinine level of approximately 300 ng/ml. It follows that, as a rough approximation, the exposure to ETS of a child with nonsmoking parents is approximately 0.3 d_0 since Wald and Ritchie (1984) found the urinary cotinine levels of currently-"unexposed" individuals were approximately 1/200 that of an average active smoker and $0.44 \times 200/300 \cong 0.3$. (This result obviously depends on unverified assumptions about the comparability of nicotine metabolism in adults and children.) Furthermore, the ratio of ETS exposure in an average child with a smoking parent to an average child without a smoking parent is $[(1.32)(96) + 1.99(76) + 3.39(128)]/(96 + 76 + 128) = 5.1$ (which is a dose of $1.53d_0 = 5.1(0.3)d_0$). Similar data from a study of Coultas et al. (1986) give a ratio of 3.07 rather than 5.1, under the assumption that the fraction of children with two smoking parents among children with at least one smoking parent is $128/(76 + 56 + 128)$, as in the Jarvis study. These results motivated the choice of f_{1a} and f_{2a} for α equal to 1 and 2.

One would expect that in the 1920s children living in homes with no parents smoking might well have less ETS exposure than such children currently have (since in the 1920s fewer caretakers, who were almost exclusively female, smoked). On the other hand, among children who lived in a home with a smoking parent, presumably a higher percentage had only a father who smoked. (Data on this question was not available from the Garfinkel et al. (1985) control population.) Thus, the ETS exposure in the 1920s

of an average child with a smoking parent would also be less than that of a similar child in the 1980s. These observations led to our choice of f_{1a} and f_{2a} for $\alpha = 4$. On the other hand, it is likely that, conditional on having had a smoking parent in childhood, "exposed" individuals are more likely than "unexposed" individuals to have had a mother who smoked. Furthermore, it may well be that "exposed" individuals without a smoking parent had, on average, higher exposures in childhood than "unexposed" individuals without a smoking parent. (Recall that a higher percentage of "exposed" individuals are known to report having at least one smoking parent.) These observations led to our choice of the exposure histories characterized by $\alpha = 3$. The final choice, $\alpha = 5$, reflects the ratio of 3.07 found by Coultas et al. and the possibility that in the 1920s, when few women smoked, this ratio was even less. The maximum value for the ratio of the childhood ETS exposure of "exposed" compared to "unexposed" subjects is 3.17 occurring when $\alpha = 3$.

All 30 exposure histories presume that the ratio of ETS exposure in the 1970s and 1980s in currently-"exposed" subjects to that in currently-"unexposed" subjects is 3, as found by Wald and Ritchie. Thus, the sensitivity analysis may not be applicable to studies carried out in Greece and Japan, for reasons discussed above (although it is possible that in recent years the exposure of Japanese nonsmoking women outside the home has increased to United States' and British levels). Thus, one might wish to use both 1.3 and 1.14 as the summary observed rate ratio in a sensitivity analysis.

Remark 3: Estimating the True Relative Risk Under Assumptions for Method 2 Above Consider a group of individuals (i.e., the "exposed" individuals or the "unexposed" individuals in Garfinkel et al.'s (1985) study) such that each individual i has a constant exposure to ETS, d_{1i} , from age 0 to t_0 , exposure d_{2i} from age t_0 to t_1 , and exposure d_{3i} from age t_1 to t . The d_{1i}, d_{2i}, d_{3i} may vary between individuals in the group. Then, the true relative risk at age t for the group compared to a completely unexposed group, when exposure affects the first and fourth stages of a five-stage multistage model, is:

$$RR(t) = 1 + \beta_1 d_0 [H_1] + \beta_4 d_0 [H_2] + \beta_1 \beta_4 d_0^2 [H_{12}],$$

where β_1 and β_4 are unknown constants (reflecting the magnitude, on a ratio scale, of the exposure effect on the first and fourth stage, respectively), d_0 is as defined in Section D-2 and

$$\begin{aligned}
 H_1(t) &= (t^4 d_0)^{-1} [E(d_1)t^4 + |E(d_2) - E(d_1)|(t - t_0)^4 \\
 &\quad + |E(d_3) - E(d_2)|(t - t_s)^4] \\
 H_2(t) &= (t^4 d_0)^{-1} [E(d_3)t^4 + |E(d_2) - E(d_3)|t_s^4 \\
 &\quad + |E(d_1) - E(d_2)|t_0^4] \\
 F_{12}(t) &= (t^4 d_0^2)^{-1} \{ [E(d_1)]^2 t_0^4 (1 + m^2(d_1)) \\
 &\quad + E(d_1)E(d_2) [1 + p(d_1, d_2)m(d_1)m(d_2)](t_s^4 - t_0^4 - (t_s - t_0)^4) \\
 &\quad + |E(d_2)|^2 (t_s - t_0)^4 [1 + m^2(d_2)] \\
 &\quad + E(d_1)E(d_3) [1 + p(d_1, d_3)m(d_1)m(d_3)](t_s^4 - t_s^4 - (t_s - t_0)^4) \\
 &\quad + (t_s - t_0)^4 \} \\
 &\quad + |E(d_3)|^2 (t - t_s)^4 [1 + m^2(d_3)] \\
 &\quad + [1 + p(d_3, d_2)m(d_3)m(d_2)](t - t_0)^4 - (t_s - t_0)^4 \\
 &\quad - (t - t_s)^4 |E(d_2)E(d_3)|
 \end{aligned}$$

here $E(d_1)$ is the average of d_1 , $m(d_1) = \sqrt{\text{Var}(d_1)}/E(d_1)$, and d_1, d_2 is the correlation between d_1 and d_2 . For simplicity, we all assume that all correlations are 0. This will have little effect on our analysis.

Now define

$$F_1(t) = H_1(t) + (\beta_4/\beta_1)H_2(t) \text{ and } F_{12}(t) = (\beta_4/\beta_1)H_{12}(t).$$

Then we have:

$$RR(t) = 1 + \beta_1 d_0 F_1(t) + (\beta_1 d_0)^2 F_{12}(t). \quad (D-9)$$

Now with $t_0 = 20$, $t_s = 55$, and $t = 70$, for any given choice for β_4/β_1 and for the exposure vector (a, b, c) , we can compute $F_1(70)$, $F_{12}(70)$ both "exposed" and "unexposed" groups. Since 1.3 is assumed to be the ratio of the true relative risk in "exposed" subjects to that in "unexposed" subjects at age 70, we have

$$1.3 = \frac{1 + (\beta_1 d_0) F_{1E}(70) + (\beta_1 d_0)^2 F_{12E}(70)}{1 + (\beta_1 d_0) F_{1E}(70) + (\beta_1 d_0)^2 F_{12E}(70)}. \quad (D-10)$$

Equation D-10 is a quadratic equation in $\beta_1 d_0$. Thus, we can solve for $\beta_1 d_0$ even though we do not know β_1 or d_0 separately. We

then substitute this value of $\beta_1 d_0$ along with the values of $F_{1E}(70)$ and $F_{12E}(70)$ into Equation D-9 to give an exposure-history- β_4/β_1 -specific estimate of the true relative risk at age seventy in "exposed" individuals. If we substitute $F_{1E}(70)$ and $F_{12E}(70)$ instead, we get an estimate of the true relative risk at age 70 in "unexposed" individuals. Note that if we had an independent estimate of β_1 , we could also estimate d_0 . Given β_4/β_1 and (a, b, c) (and thus $\beta_1 d_0$ by Equation D-10), our estimate of d_0 is inversely proportional to our estimate of β_1 .

Estimation of d_0

Remark β : Interpretation of β_1 and d_0 β_1 , when estimated from data on active smokers, is the fractional increase in the rate of the first cellular event per actively smoked cigarette. Since cigarettes differ in carcinogenic potency, neither β_1 nor d_0 are biological constants. Therefore, we must specify the type of cigarette to which we want our estimate of β_1 to refer. In this Appendix, we shall let β_1 be the increase in the rate of the first cellular event associated with one current nonfilter U.S. cigarette containing 20 mg tar as smoked by an average U.S. citizen. In Section D-2 we adjusted our estimates of β_1 from the Doll and Peto data (1978) with this definition of β_1 in mind. Even after adjustment, β_1 will still be defined in terms of the cigarettes smoked by the study subjects in the American Cancer Society (Hammond, 1966) and European case-control studies (Lubin, 1984), which, on average, contained more than 30 mg of tar (since most of the cigarette exposure in these studies occurred before the adoption of low-tar cigarettes). Thus, if we wanted to define β_1 in terms of actively smoked unfiltered cigarettes with a tar content of 20 mg, one might further divide all estimates of β_1 (and multiply all estimates of d_0) by a factor of 1.5 to 2, although we have not chosen to do so. One must still consider the possibility that the lower relative risk found in the European and ACS data compared to the British data is a consequence of the fact that there was less misclassification of smokers as nonsmokers among the British doctors than among the ACS or European case-control study populations. Since, presumably, doctors are accurate reporters, such an assumption may not be unrealistic. If so, the baseline rate among nonsmokers from the ACS study would be falsely inflated upwards and the values of β_1 of 2.93 and 0.803, as originally estimated for the British doctors,

would be the more appropriate values to use. For these reasons, we report results for all five of the combinations of β_4/β_1 and β_1 given in Table D-3.

Remark 10: Adjusting for the ETS Exposure of Active Smokers In estimating β_1 and β_4 from active-smoker data neither we nor Brown and Chu (in press) took account of the fact that in those studies active smokers (and the comparison groups of nonsmokers) were themselves breathing other peoples' cigarette smoke. If $3d_0$ is of the order of 3 or more cigarettes per day (as in Table D-3), a proper analysis (and thus proper estimates of β_1, β_4 , and d_0) would require refitting the active-smoking data taking account of ETS exposure. We have not done so here. We expect that the effect on our estimates of the true relative risk in "exposed" and "unexposed" subjects using Method 2 would not be great (because of the insensitivity of these estimates to uncertainty in β_1/β_4). On the other hand, the effect on our estimates of d_0 may be more pronounced. Further study is required.

Remark 11: Estimation of d_0 from Dosimetry The estimates of d_0 given in Table D-4 are obtained in step 5 of the following sequence of calculations.

1. For the ETS constituents BaP and NDMA we estimated the weight of each constituent inhaled directly by an active smoker from the mainstream smoke of a single cigarette by using the midpoint of the range given in the mainstream weight column in Table 2-10 (i.e., 25 and 30 ng for NDMA and BaP, respectively). (The weights entered in the mainstream weight column of Table 2-10 are averages based on cigarettes whose mainstream-smoke tar content, as measured by a smoking machine, varied between 16 and 30 milligrams.)

2. We estimated the weight of each of the above constituents inhaled daily by a nonsmoker with a nonsmoking spouse by multiplying by 1.07 the range of values given under the ETS weight column in Table 2-10. (1.07 is our estimate of the average number of hours of daily ETS exposure occurring in nonsmokers with nonsmoking spouses. Nonsmokers without smoking spouses report that they are exposed, on average, to ETS between 5 (Table 6, Friedman et al., 1983) and 10 hours a week (Wald and Ritchie, 1984). Our value of 7.5 hours/week (= 1.07 hours/day) is the average of the above estimates. We could have chosen to multiply

the value of 1.07 by a factor of up to 2, since most components of ETS decay with a half-life of approximately 1 hour when smoking ceases, assuming approximately one air change per hour and little plating out onto surfaces.)

3. For each constituent we divided the endpoints of the weight ranges calculated in Step 2 by the weight estimated in Step 1. The resulting range of values is, for each constituent, an estimate of the number of cigarettes that would have to be actively smoked in order that the weight of the constituent in the directly inhaled mainstream smoke would equal the weight of the constituent (attributable to ETS) inhaled daily by an average nonsmoker with a nonsmoking spouse. We shall call this number I_{0m} .

4. We next estimated for each constituent the number of cigarettes whose mainstream smoke would have to be directly inhaled by an active smoker to deliver to the lungs a dose of the constituent equal to the daily (biologically effective) pulmonary dose (attributable to ETS) of a nonsmoker with a nonsmoking spouse. We refer to this number as d_{0m} . For BaP we multiplied the endpoints of the range for I_{0m} by one-seventh. This reflects the fact that BaP is in the particulate phase and, as discussed in Chapter 7, a rough estimate of the deposition rates for particulates in ETS and in mainstream smoke is 10% and 70%, respectively. [This calculation ignores important differences between the ETS and mainstream particulate phases in terms of deposition site, clearance rates, and particle size. Thus, even if BaP were the active carcinogen in ETS and mainstream smoke, d_{0m} , as calculated above, could conceivably be quite different from the true value of d_{0m} defined in terms of the biologically effective dose for producing lung cancer.]

For NDMA we assumed $d_{0m} = I_{0m}$. The rationale for this decision is that NDMA is in the vapor phase in both ETS and mainstream smoke. We therefore assumed that the pulmonary absorption of NDMA per nanogram inhaled was the same for mainstream smoke and ETS. (This assumption may be inadequate, since NDMA is water soluble and thus will dissolve in mucous membranes before reaching the lungs. Therefore, the fraction of inhaled NDMA that reaches the lungs may well be up to several orders of magnitude greater in active smokers (whose intake is via deep inhalations taken through the mouth) than in nonsmokers (whose intake is largely via shallow inhalations taken through the nose). If so, our estimate of d_{0m} would need to be reduced by

the appropriate factor. We have not made any such adjustment here. d_{0m} for RSP was calculated as follows. In Chapter 7 it was calculated that the amount of tar deposited in the lungs after 8 hours of ETS exposure would be about 0.005%-0.26% of that deposited in the lungs of an active smoker of 20 cigarettes containing 14 mg tar each. Thus, the upper limit of the range for d_{0m} (in terms of 20 mg tar cigarettes) equals $(14/20) \times 0.26 \times 10^{-2} \times 20 \times 1.07/8 = 8.2 \times 10^{-5} = 0.005$. The total range is $0.0001 - 0.005$.

5. In what follows we estimate for each of the constituents NDMA, BaP, and RSP the number of cigarettes that would have to be actively smoked to deliver to the smoker a

pulmonary dose of the constituent equal to the daily pulmonary dose (attributable to ETS) of a nonsmoker married to a nonsmoking spouse. This number we will call d_0^* . The * as symbol serves to distinguish this definition of d_0 from that in Section D-2. d_0^* for a given constituent is equivalent to d_0 as defined in Section D-2 if, as assumed in Table D-4, the constituent is the active lung carcinogen in ETS and mainstream smoke or, more generally, if d_0^* for the constituent is equal to d_0 for the unknown active carcinogen.

For the constituents RSP, BaP, and NDMA we first estimated the difference between the total pulmonary dose attributable to a single actively smoked nonfilter cigarette and the fraction of that pulmonary dose attributable to the directly inhaled mainstream smoke. This difference includes contributions from the plume of mainstream smoke, the plume of exhaled mainstream smoke, and the ETS subsequently derived from the plumes of sidestream and inhaled mainstream smoke. We shall call this difference the non-mainstream (pulmonary) dose of the constituent. How does the magnitude of the nonmainstream (pulmonary) dose to a smoker compare to the pulmonary dose of the constituent absorbed by a nonsmoker without a smoking spouse in the Wald and Ritchie study (1984) during that nonsmoker's 1.07 hours of daily exposure? We have no empirical data that directly bear on this question. Nonetheless, we shall assume that the ratio, f , of the dose to a nonsmoker from the nonmainstream smoke of a single cigarette to the daily dose (attributable to ETS) to a nonsmoker with a non-smoking spouse is between 0.1 and 2. We believe the ratio could be as high as 2 because the active smoker is much more likely to directly inhale the highly concentrated plumes of sidestream and inhaled mainstream smoke. (In fact, the ratio could possibly be a

good deal higher than 2.) This ratio could be as low as 0.1 if active smokers rarely directly inhale the plumes of smoke and during the hour in which a nonsmoker with a nonsmoking spouse is exposed to ETS, the average smoker density is 4, with each smoker smoking 2.5 cigarettes per hour. (This is a rather high smoker density and 0.1 may therefore be somewhat too low an estimate.) It is a straightforward algebraic exercise to show that the relationship between d_0^* and d_{0m} is

$$d_0^* = \frac{1}{(1/d_{0m}) + f}$$

The minimum of the range of d_0 (equivalently, d_0^*) values given in Table D-4 (for each constituent) was computed by plugging into the above formula the minimum of the range of d_{0m} estimated in step 4, and $f = 2$. The maximum of the d_0 range in Table D-4 was computed by plugging in the maximum of d_{0m} and $f = 0.1$. The ranges calculated for d_0^* essentially equal those for d_{0m} , with the exception that both endpoints of the d_{0m} range for NDMA were reduced by approximately 40% and the upper endpoint for BaP was reduced 25%.

Remark 18: Dosimetry Based on Urinary Nicotine or Cotinine In this remark we consider whether it is reasonable to take the ratio of urinary nicotine (or cotinine) in nonsmokers to that in active smokers as a proxy for the ratio of the biologically effective dose (attributable to ETS) of the active lung carcinogen in nonsmokers to the biologically effective dose in active smokers.

In aged ETS, nicotine is largely in the vapor phase. Nicotine is water soluble. Thus, presumably most of the nicotine in aged ETS dissolves in the mucous membranes of the upper airways and diffuses directly into the bloodstream. Thus, little of the inhaled nicotine from aged ETS reaches the lower respiratory tract. Therefore, urinary and blood nicotine in nonsmokers should roughly reflect the total amount of inhaled nicotine. In contrast, nicotine in mainstream and sidestream smoke and in fresh ETS is largely in the particulate phase. Therefore, most of the nicotine directly inhaled in mainstream smoke by a smoker reaches the lower respiratory tract (and from there the bloodstream) since the deposition fraction for particulates in mainstream smoke is 70% with most deposition occurring in the lower respiratory tract.

Therefore, if (1) the true carcinogen is in the vapor phase in both ETS and mainstream smoke, (2) the true carcinogen is in the particulate phase in both ETS and mainstream smoke, or (3) the true carcinogen is in the particulate phase in mainstream smoke, the vapor phase in ETS, and is, in addition, water soluble (so that the total dose of the carcinogen from ETS greatly exceeds the pulmonary dose), then serious questions must be raised about the appropriateness of using the ratio of urinary nicotine (or cotinine) in nonsmokers to that in active smokers to approximate the ratio of the biologically effective lung dose of the active carcinogens in nonsmokers to the lung dose in active smokers.

Remark 13: Estimating Lung Cancer Deaths Attributable to ETS Among Lifelong Nonsmokers in 1985 As in the Garfinkel et al. (1985) study, we use "exposed" to mean ever-"exposed", since one cannot calculate a population attributable number from case-control studies in which individuals who are ever-"exposed" but not currently-"exposed" are excluded. If we assume that Assumption 1a and Equation D-5 hold with $c(70) = 3$, then $RR(70|E)$ and $RR(70|E)$ are 1.54 and 1.18, respectively, based on a summary rate ratio of 1.3. We would then need to assume, for example, that $RR(t|E)$ and $RR(t|E)$ do not depend on t . Using this approach we obtain an attributable number of 2,010 in nonsmoking women. In contrast, the naive approach, which ignores the ETS exposure of "unexposed" individuals by assuming $RR(70|E) = 1.3$ and $RR(70|E) = 1.0$, gives an attributable number of 1,150.

The second approach supposes that assumptions of Method 2 in Section D-2 hold. We then choose a value for exposure history (a, b, c) and β_4/β_1 which, given that $\gamma(70|E)/\gamma(70|E) = 1.3$, allows us to calculate $\beta_1 d_0$ from Equation D-10. Knowledge of $\beta_1 d_0$, then, allows us to calculate, from equation D-9, $RR(t|E)$ and $RR(t|E)$ for all t (not just $t = 70$).

The third approach is to assume that the first assumptions under Method 2 concerning the multistage cancer model hold but not to assume that $RR(70|E)/RR(70|E) = 1.3$. We then must select a value of β_1 and d_0 in order to estimate $\beta_1 d_0$ and, given (a, b, c) and β_4/β_1 , $RR(t|E)$.

Remark 14: Estimating the Lifetime Risk of Lung Cancer Due to ETS $S(t|t_0) = \prod_{u=t_0}^t [1 - \lambda(u)]$ where $\lambda(u)$ is the all-cause mortality rate in 1985 among nonsmoking women of age u (and we are following the standard convention of using current, i.e. 1985, mortality

rates). We estimated $\lambda(u)$ for female nonsmokers by multiplying the all-cause age-specific mortality rates (for female nonsmokers) given in Hammond (1966) by the ratio of the overall U.S. age-specific female death rates in 1985 (all smoking categories) to those rates in 1962. Furthermore, $\gamma_{\text{Rexcess}}(t) = \gamma_0(t)/R_{\text{Rexcess}}(t)$, where $\gamma_0(t)$ is the incidence of lung cancer death at t in the absence of all exposure, and $R_{\text{Rexcess}}(t)$ is the excess relative risk for lung cancer due to exposure history M . $\gamma_0(t) = [1 - AF(t)]I_0(t)$ where $AF(t)$ and $I_0(t)$ are as defined above.

From Equation D-9 we can obtain an estimate of $R_{\text{Rexcess}}(t) = RR(t) - 1$ for given values of $\beta_1 d_0$ and β_4/β_1 and choice of exposure history M . It follows that, under the assumption that the observed rate ratio of 1.3 is causal, we can then obtain an estimate of $AF(M)$ for $t_0 = 45$ for each choice of exposure history (a, b, c) and value of β_4/β_1 , since, using Equation D-10, we obtain an estimate of $\beta_1 d_0$ from which, in turn, we obtain an estimate of $AF(t)$ and $R_{\text{Rexcess}}(t)$.

Remark 15 In estimating $AF(M)$ in ex- and current smokers, $R_{\text{Rexcess}}(t)$ can be estimated from Equation D-9 for a given value of exposure history (a, b, c) , β_4/β_1 , and β_1 under the assumption that the rate ratio of 1.3 is causal. (Knowledge of β_1 is necessary so that we can estimate from Equation D-10 the value of d_0 rather than simply $\beta_1 d_0$.) $\gamma_0(t)$ is estimated as for nonsmokers. To estimate the all-cause mortality rate among exsmokers and continuing smokers we used the data in Hammond (1966) as described for nonsmokers, except for smokers of 20 cigarettes per day we used an average of the age-specific all-cause mortality rates in Hammond for smokers of 1-19 and >19 cigarettes per day; and for exsmokers we used both their smoking rates while smoking and the number of years since quitting (as a time-dependent covariate) to enter Hammond's table at the proper place. Missing values in Hammond's table were filled in by linear interpolation or extrapolation.

Remark 16 Under Assumption 1a, $R_{\text{Rexcess}}(t)$ would be the same for exsmokers and nonsmokers who had the same history of exposure to other people's cigarette smoke. But if we assume that cigarette smoke affects two stages of a multistage cancer model, then, for an exsmoker, the quadratic terms in Equation D-9 cannot be ignored. As such, a small increment in dose due to breathing other people's cigarette smoke will have a larger absolute effect

on the age-specific-mortality rate of the exsmoker than of the nonsmoker.

Effects of Bias

We now consider the following three questions. In deriving our summary estimates of 1.3 we amalgamated studies that compared ever-"exposed" to never-"exposed" subjects with studies that compared currently-"exposed" to never-"exposed" subjects. Does this introduce an important bias? In Remark 17 below, we show that it does not. Second, under the assumption that our multistage model is correct, Assumption 1a is false, since Equation D-8 has a quadratic dose term. Nonetheless, for calculating the true relative risk in "exposed" and "unexposed" subjects, is Assumption 1a an adequate approximation? Third, should case-control studies of the relationship between childhood ETS exposure and lung cancer have greater power to detect an ETS effect than case-control studies of adult ETS exposure? In particular, does the failure of Garfinkel et al. (1985) to find an effect of childhood exposure cast doubt on the validity of our 13 epidemiologic studies of adult ETS exposure? We will show in Remark 19 that when one takes into account the inevitable misclassification of childhood ETS exposure occurring some 60 years previously, the observed relative risk expected from a case-control study of childhood ETS exposure could be as low as 1.01 and would be no greater than 1.3. Thus, it is not surprising Garfinkel et al. found no effect of childhood exposure.

Remark 17 It is clear that the same causal parameter is not being estimated in studies in which the "exposed" group is ever-"exposed" as in studies in which the exposed group is currently-"exposed" individuals. Yet, our summary value of 1.3 was based on amalgamating estimates of $RR(t|E)/RR(t|E)$ from these two different types of studies. To estimate the magnitude of the bias associated with this amalgamation, we proceeded as follows. Consider studies with exposure history of the form $(a, b, 1)$. For each choice of (a, b) and β_4/β_1 we obtain, from Equation D-10, an estimate of $\beta_1 d_0$, say, $\beta_1 d_0(a, b, \beta_4/\beta_1)$, if we can assume $RR(t|E)/RR(t|E)$ is 1.3 for such studies. For each $\beta_1 d_0(a, b, \beta_4/\beta_1)$ we estimated, using Equation D-10, $RR(t|E)/RR(t|E)$ for a study with exposure history $(a, b, 3)$. The maximum value of $RR(t|E)/RR(t|E)$ estimated in

this way for studies with exposure history $(a, b, 3)$ was 1.39 (associated with $\beta_4/\beta_1 = 1.8$, of course). Given the confidence interval of (1.12, 1.49) reported in Chapter 12 for the amalgamated parameter $RR(t|E)/RR(t|E)$, it follows that any bias due to improperly amalgamating these two types of studies will be small compared to sampling error.

Remark 18 Conditional on the assumption that our multistage model holds for lung cancer, we can test the adequacy of Assumption 1a. Let $\beta_1 d_0'$ and $RR'(70|E)$ be the estimates of $\beta_1 d_0$ and $RR(70|E)$ obtained by removing the quadratic term (in $\beta_1 d_0$) from the numerator and denominator of Equation D-10. Now, since Equation D-9, modified so that the quadratic term in $\beta_1 d_0$ is eliminated, is a linear excess relative risk model, it follows that Assumption 1a is an adequate approximation if the estimates $\beta_1 d_0'$ and $RR'(70|E)$ do not differ greatly from the estimates $\beta_1 d_0$ and $RR(70|E)$, based on the unmodified Equation D-10. We therefore estimated $\max[RR'(70|E) - RR(70|E)]$ as (a, b, c) and β_4/β_1 varied. The maximum was 0.05. Thus, the linear approximation of Assumption 1a is probably adequate.

Remark 19 We now estimate the maximum and minimum relative risk (at age 70) we would expect to observe in a case-control study of ETS exposure in childhood (controlling for ETS exposure in adult life) under the assumption that our multistage model for lung cancer is correct. To do so, we perform a sensitivity analysis over the possible exposure histories of the "exposed" and "unexposed" study subjects in such a case-control study. In particular, we assume that (1) for all study subjects the exposure rate from ages 20 to 70 years was $2d_0$; (2) the false-positive and false-negative rates for the exposure "at least one parent smoked" were 0.15 and 0.3, respectively; and (3) exposure rate from 0 to 20 in the truly "exposed" (i.e., among those who did have a smoking parent) to the truly "unexposed" was, in units of d_0 , one of the following: 1.53 to 0.3, 0.75 to 0.15, 1.0 to 0.6, or 1.0 to 0.05. It only remains necessary to choose values for β_4/β_1 and $\beta_1 d_0$. For each of our three choices to choose values for β_4/β_1 and $\beta_1 d_0$. For each of our previously (using Equation D-10) as (a, b, c) varied.

The maximum relative risk was 1.26, which occurred with exposure rates of 1.53 and 0.3 d_0 in the exposed and unexposed, respectively, $\beta_4/\beta_1 = 0.0124$, and the value of $\beta_1 d_0$ (computed using Equation D-10) based on $(a, b, c) = (1, 2, 3)$. The minimum relative

risk was 1.01. Even when we unrealistically assumed that both the false-positive and false-negative rates for exposure misclassification were 0, the maximum relative risk was only 1.51. Thus, it is not surprising that Garfinkel et al. (1985) failed to detect an effect of childhood exposure in his case-control study.

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