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THE EFFECTIVE NUMBER OF CIGARETTES INHALED DAILY BY PASSIVE SMOKERS: ARE EPIDEMIOLOGIC AND DOSIMETRIC ESTIMATES CONSISTENT?

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Summary

Since the early 1980's, a number of epidemiologic studies have implicated environmental tobacco smoke (ETS) as a cause of lung cancer among non-smokers passively exposed to other people's tobacco smoke. A recent National Academy of Science Report on environmental tobacco smoke (NAS, 1986) summarized 13 such studies. Each study provided an estimate of the ratio of the lung cancer mortality rate among non-smokers with smoking spouses to the mortality rate among those with non-smoking spouses. The weighted average of the 13 study-specific rate ratios was roughly 1.3. In this paper, we show that if this summary rate ratio is causally related to ETS and not to bias then the estimated number of lung cancer deaths attributable to ETS exposure occurring in U.S. non-smokers in 1985 lies in the range 2500–5000. Further, we examine whether the summary rate ratio of 1.3 is consistent with the existing epidemiologic data on active smokers and the dosimetric measurements that have been made on mainstream and environmental tobacco smoke. If consistent with this other data, the hypothesis that the rate ratio of 1.3 is causally related to ETS exposure will be strengthened.

1. Introduction

Since the early 1980's, a number of epidemiologic studies have implicated environmental tobacco smoke as a cause of lung cancer among non-smokers passively exposed to other people's tobacco smoke. A recent National Academy of Science Report on environmental tobacco smoke (ETS) [1] summarized 13 such studies. Each study provided an estimate of the ratio of the lung cancer mortality rate among non-smokers who answered "yes" to the question "Is your spouse a smoker?" (hereafter called "exposed" individuals) to the mortality rate among non-smokers who answered "no" to that question (hereafter called "unexposed" individuals). The weighted average of the 13 study-specific rate ratios was roughly 1.3. If the summary rate ratio of 1.3 from the 13 epidemiologic studies of ETS exposure is causally related to differences in environmental tobacco smoke exposure between "exposed" and "unexposed" in-

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dividuals and not to bias then (1) the estimated number of lung cancer deaths attributable to ETS exposure occurring in U.S. non-smokers in 1985 lies in the range 2500–5000 (see Appendix D of [1]) and (2) intervention to reduce ETS exposure is critical. In this paper we examine whether this summary rate ratio of 1.3 is consistent with both the existing epidemiologic data on active smokers and the dosimetric measurements that have been made on mainstream and environmental tobacco smoke. If consistent with this other data, the hypothesis that the rate ratio of 1.3 is causally related to differences in ETS exposure will be strengthend.

Active smokers of one pack of cigarettes per day have, depending on the study, lung cancer mortality rates 4–20 fold those of non-smokers [2–4]. In this paper, we shall combine the existing epidemiologic data on active smokers with the data on non-smokers exposed to ETS to estimate the ETS-exposure of passive smokers in cigarette-equivalents per day. That is, we estimate the number of cigarettes d_0 that would have to be smoked to deliver to the lungs (of an active smoker) a dose of carcinogen equal to the average daily pulmonary dose of carcinogen (attributable to ETS) of a non-smoker passively exposed to ETS. d_0 is the carcinogen-equivalent number of actively smoked cigarettes inhaled daily by passive smokers.

We also obtain independent estimates of d_0 from dosimetric measurements made on mainstream and environmental tobacco smoke. Although our dosimetric estimates of d_0 do not rely on epidemiologic data, they are sensitive to our assumptions about the identity of the active lung carcinogens in ETS and in mainstream smoke. Therefore, as a form of *sensitivity analysis*, we make dosimetric estimates of d_0 first under the assumption that the active carcinogen in mainstream smoke and ETS is tar (i.e., respirable suspended particulates – RSP), second under the assumption that the active carcinogen is benzo(a)pyrene (BaP), and finally under the assumption that the active carcinogen is *N*-nitrosodimethylamine (NDMA).

If our epidemiologic and dosimetric estimates of d_0 are consistent with one another, this will lend credibility to the hypothesis that the summary rate ratio of 1.3, based on the epidemiology data, is causally related to differences in exposure to environmental tobacco smoke between "exposed" and "unexposed" individuals, and not to bias. If our epidemiologic and dosimetric estimates of d_0 are in conflict, then we would have to consider the possibility that (1) our epidemiologic studies are biased, (2) the methods we used to combine the epidemiologic data on active smokers with that on non-smokers exposed to ETS to estimate d_0 are flawed, (3) we failed to identify the active lung carcinogen, (4) the active lung carcinogen in ETS differs from that in mainstream smoke, and/or (5) our estimates of the dose of RSP, BaP, or NDMA to either actively or passively exposed individuals are flawed. We defer further discussion of these five possibilities until the discussion section of the paper. In the final section of the paper, we provide a quantitative risk assessment of the effect of environmental tobacco smoke on lung cancer.

2. The true relative risk in the "exposed"

Wald and Ritchie [5] have shown that "unexposed" individuals (i.e., non-smokers with non-smoking spouses) 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 exposure, it follows that individuals classified as "unexposed" in epidemiologic studies of ETS are actually exposed to ETS. For this reason, whenever we refer to "unexposed" subjects, we place the word "unexposed" in quotation marks. In contrast, "exposed" subjects (i.e., non-smokers with smoking spouses) have roughly three times as much cotinine in their urine as "unexposed" subjects. Since "unexposed" subjects have, in fact, been exposed to ETS, the observed epidemiologic relative risk of 1.3 is 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").

3. Estimates of d_0 based on epidemiologic data

We formally define d_0 to be the number of cigarettes that would have to be actively smoked to deliver to the lung of the smoker a dose of active lung carcinogen equal to the daily pulmonary dose of carcinogen (attributable to ETS) of an *average non-smoker with a non-smoking spouse* (i.e., an average "unexposed" subject). It follows that $3d_0$ is the carcinogen-equivalent number of actively-smoked cigarettes inhaled daily by an "exposed" subject.

In this section we use the following two assumptions to combine the epidemiologic data on active smokers and on non-smokers exposed to ETS to derive an estimate of d_0.

(1) Assume that (a) cigarette smoke influences the rates of the first- and fourth-stage cellular events in a five-stage multistage cancer process [6,7]; (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 stage, respectively, then (c) implies that β_4/β_1 is the same for ETS and mainstream smoke.

(2) 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 1 in the Appendix).

The plausibility of Assumption (1) is considered in the discussion section of the paper.

In order to estimate d_0 based on these two assumptions, we begin by estimating the true relative risk in the "exposed" and the "unexposed" study sub-

jects. It is possible to estimate the true relative risk in "exposed" and "unexposed" study subjects, given two additional pieces of information (see Remark 3 in the Appendix).

First, 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 non-smoker whose spouse is a non-smoker. Information does not exist to answer questions such as "How many times greater (or less) was the ETS exposure in average "exposed" subjects from age 0 to 20 than the current ETS exposure of an average adult non-smoker with a non-smoking 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 non-smoker without a smoking spouse). The choice of exposure histories was influenced by the following general considerations. Small postulated differences between the lifetime ETS exposures of "exposed" and "unexposed" individuals will be associated with large estimates of the true relative risk. (Having an observed rate ratio as large as 1.30 when there is truly only a small difference in dose between the "exposed" and "unexposed" subjects implies 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 30 exposure histories is given in Remark 7 of the technical discussion section of Appendix D of [1]. The thirty possible exposure histories are characterized in Table 1.

Second, we require an estimate of the ratio β_4/β_1. An estimate of β_4/β_1 can be obtained fitting the above multistage cancer model to data on the lung cancer experience of active smokers. In particular, an estimate of 0.0124 for β_4/β_1 is obtained by fitting the multistage model to the continuing smoker data among British physicians given by Doll and Peto [2]. Brown and Chu [7] 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 [2] 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 [2]. This estimate was 0.225. Rather than choose among these estimates, we performed a sensitivity analysis using the three estimates of $\beta_4\beta_1$ of 0.0124, 1.8, and 0.225 (see Remark 2 in the Appendix).

TABLE 1

Thirty population exposure histories in various age groups[a]

Value of a, b or c	Population subgroup	Age 0–20 y a			Age 20–55 y b			Age 55–70 y c		
		p_a	f_{1a}	f_{2a}	p_b	f_{1b}	f_{2b}	p_c	f_{1c}	f_{2c}
1	E	0.39	1.53[a]	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						

[a]In units of d_0.

Notation: E = "Exposed"; $\bar{E}$ = "Unexposed".

Each of the 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 ($a \in 1,...,5$), b characterizes two possible exposure histories from age 20–55 ($b \in 1,2$), and c characterizes three possible exposure histories from ages 55–70 ($c \in 1,2,3$). 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 1. As an example, consider the case $c = 3$. Reading Table 1, we see that $p_{cE} = 0.5, f_{1cE} = 3d_0$, $f_{2cE} = 2d_0, p_{c\bar{E}} = 1.0, f_{1c\bar{E}} = 1d_0, f_{2c\bar{E}}$ is undefined. By definition, p_{cE} gives the fraction of "exposed" individuals exposed at rate f_{1cE} between ages 55 and 70. $1 - p_{cE}$ is the fraction of "exposed" individuals exposed at rate f_{2cE}. 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, $f_{2C\bar{E}}$ need not be defined.)

Thus, Population exposure history $(a,b,c) = (1,2,3)$, has $p_{aE} = 0.39, p_{a\bar{E}} = 0.25, f_{1aE} = f_{1a\bar{E}} = 1.53$, $f_{2aE} = f_{2a\bar{E}} = 0.3, p_{bE} = p_{b\bar{E}} = 1.0, f_{1bE} = 1.5, f_{1b\bar{E}} = 0.15, p_{cE} = 0.5, p_{c\bar{E}} = 1.0, f_{1cE} = 3, f_{2cE} = 1, f_{1c\bar{E}} = 1$.

Therefore, 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 20–55y, all E-subjects were exposed to 1.5 d_0, all $\bar{E}$ subjects to 0.15 d_0. From 55–70y, 50% of E-subjects were exposed to 3 d_0 and 50% to 1 d_0. All $\bar{E}$-subjects were exposed to $1d_0$.

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

If, in addition we also have an independent estimate of β_1, we can estimate d_0 as well (see Remark 3 of the Appendix). Each of our three methods of deriving an estimate for β_4/β_1 from data on active smokers also produces an

TABLE 2

Estimated ranges for the true relative risks (RR) in "exposed" and "unexposed"subjects

Rate ratio[a]	Group	β_4/β_1			
		All	0.0124	0.225	1.8
1.3	"Exposed"	1.41-1.87[b] (321)-(113)[d]	1.41-1.87[c] (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)-(13)
1.14	"Exposed"	1.19-1.35 (321)-(113)	–	–	–
	"Unexposed"	1.04-1.18 (321)-(113)	–	–	–

[a]Assume causal summary rate ratio.
[b]Range of RR over 30 exposure histories and three values of β_4/β_1.
[c]Range of RR over 30 exposure histories.
[d]Exposure histories (a,b,c) at which minimum and maximum, respectively, occur (see Table 1 for definition of exposure histories (a,b,c)).

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 physician data [2] is greater than that estimated from the American Cancer Society's follow-up data on one million Americans [3] or from the multicenter European case-control lung cancer data [4,7]. The relative risks in these latter two studies are consistent with one another and will here be treated as identical. Doll and Peto [8] 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 4 of the Appendix).

Estimates of d_0 are given in Table 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 vari-

TABLE 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	0.803	0.46
Rate ratio						
1.3[a]	0.12–0.93[b] (311)-(123)[c]	0.12–0.27[d] (311)-(123)	0.24–0.57 (311)-(123)	0.48–0.89 (311)-(423)	0.26–0.53 (311)-(123)	0.46–0.93 (311)-(123)
1.14	0.05–0.47 (311)-(123)					

[a]Assumed causal rate ratio.
[b]Range of d_0 in cigarettes/day over 30 exposure histories and all $(\beta_4/\beta_1,\beta_1)$.
[c]Exposure history where maximum and minimum occurred.
[d]Range of d_0 over 30 exposure histories.

TABLE 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

ation in d_0 over the thirty exposure histories is only about twofold. The summary rate ratio for the subset of the 13 studies (considered in the NAS Report) that were conducted in the U.S. was only 1.14. 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.

4. Estimates of d_0 based on disometric measurements

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 of the NAS report [1]. Estimates of d_0 based on dosimetric calculations are given in Table 4. In Table 4 we give a range of estimates for d_0 under the assumptions that the ratio of the pulmonary dose of active carcinogen in non-smokers 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 4 are based on (1) the dosimetric measurements in Table 3-10 and Chapter 7 of the NAS report and (2) the daily number of hours of self-reported ETS exposure among non-smokers

without smoking spouses [5,9]. We now give details of the calculations used to produce Table 4.

The estimates of d_0 given in Table 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 3-10 of the NAS report (i.e., 25 and 30 ng per cigarette for NDMA and BaP, respectively). (The weights entered in the mainstream weight column of Table 3-10 are averages based on cigarettes whose mainstream-smoke tar content, as measured by a smoking machine, varied between 16 and 30 ng per cigarette).

2. We estimated the weight of each of the above constituents inhaled daily by a non-smoker with a non-smoking spouse by multiplying by 1.07 the range of values given under the ETS weight column in Table 3-10 of the NAS report. (1.07 is our estimate of the average number of hours of daily ETS exposure occurring in non-smokers with non-smoking spouses. Non-smokers without smoking spouses report that they are exposed, on average, to ETS between 5 (Table 6, Friedman et al. [9], and 10 hours a week (Wald and Ritchie, [5]). 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 non-smoker with a non-smoking 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 non-smoker with a non-smoking 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 of the NAS report, 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 rate, 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 non-smokers (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. In Chapter 7 of the NAS report, 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 $(14/20) \times 0.26 \times 10^{-2} \times 20 \times 1.07/8 = 0.005$. 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 non-smoker married to a non-smoking spouse. This number we will call d_0*. The * as a symbol serves to distinguish this definition of d_0 from that in Section 2. d_0* for a given constituent is equivalent to d_0 as defined in Section 2 if, as assumed in Table 4, the constituent is the active lung carcinogen in ETS and mainstream smoke or, more generally, d_0* for the constituent to 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 non-filter cigarette and the fraction of that pulmonary dose attributable to the directly inhaled mainstream smoke. This difference includes contributions from the plume of sidestream smoke, the plume of exhaled mainstream smoke, and the ETS subsequently derived from the plumes of sidestream and exhaled mainstream smoke. We shall call this difference the non-mainstream (pulmonary) dose of the constituent. How does the magnitude of the non-mainstream (pulmonary) dose to a smoker compare to the pulmonary dose of the constituent absorbed by a non-smoker without a smoking spouse in the Wald and Ritchie study [5] 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 the smoker from the non-mainstream smoke of a single cigarette to the daily dose (attributable to ETS) to a non-smoker 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 exhaled 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 non-smoker with a non-smoking 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

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

The minimum of the range of d_0 (equivalent, $d_0{}^*$) values given in Table 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 setting $f = 2$. The maximum of the d_0 range in Table 4 was computed by plugging in the maximum of d_{0m} and setting $f = 0.1$. 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 by 25%.

There is a serious problem in reconciling the estimate of d_0 based on BaP with that based on RSP (Table 4), 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 3-10 of the NAS report) inappropriately reflect total environmental BaP, which includes contributions from cooking, coal burning, and other sources, and 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 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, as discussed above, the limitations of our dosimetric data are actually much worse than even Table 4 would lead one to believe. To reiterate:

- the range of values entered in Table 4 for NDMA could actually be orders of magnitude too high. This would be the case if the fraction of inhaled NDMA which reaches the lungs is several orders of magnitude greater in active smokers (whose intake is via deep inhalation taken through the mouth) than in non-smokers (whose intake is largely via shallow inhalation taken through the nose). (Because NDMA is water soluble, it may dissolve in the mucous membranes of nose-breathers before reaching the lungs.);
- the range of values given 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 4 could be orders of magnitude too high if, as discussed above, the BaP entries in Table 3-10 of the NAS report represent the total environmental BaP inhaled by a non-smoker.

In contrast with our Table 4, Repace and Lowrey [10] effectively assumed that d_0, based on RSP, is in the range of 0.025–0.25. How is it possible that their estimate of d_0 for RSP is 5 to 50 times greater than our maximum estimate? To begin with, Repace and Lowrey failed to take into account the differential pulmonary deposition rates of RSP in ETS and in mainstream smoke. Since the data reviewed in the NAS report suggest the deposition rate in mainstream smoke is sevenfold greater than in ETS, Repace and Lowrey's estimates of d_0 need to be decreased by a factor of seven. The remaining discrepancy between their estimates and estimates based on the NAS report reflect different assumptions about (1) how much tar non-smokers are exposed to on an average day, and (2) how much tar an average smoker inhales.

4.1 Estimates of d_0 *based on urinary nicotine or cotinine*

Some authors suggest that one may estimate d_0 from the ratio of urinary nicotine (or cotinine) in non-smokers to that in active smokers. We now argue that this ratio may not reflect, even qualitatively, the ratio of the biologically effective dose of the active lung carcinogens absorbed by non-smokers to the dose adsorbed by active smokers. In aged ETS, nicotine is largely in the vapor phase. Nicotine is highly 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 non-smokers 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 blood stream) 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 non-smokers to that in active smokers to approximate the ratio of the biologically effective lung dose of the active carcinogens in non-smokers to that in active smokers.

5. Discussion

Our interval estimates of d_0 based on the epidemiologic data 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. With regard to point (2) above, it should be noted that 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 our interval estimates for d_0 in Table 3 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.)

We were able to combine the existing epidemiologic data on active and passive smokers to estimate of d_0 only by assuming that: (a) cigarette smoke influences the rates of the first- and fourth-stage cellular events in a five-stage multistage cancer process [6,7]; (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. Although this version of the multistage model reproduces the qualitative shape of the dose–response curve in active smokers fairly well, there is no compelling reason to believe that the model can accurately predict the lung cancer rate of groups, such as passive smokers, exposed to low levels of carcinogen. It follows that our estimates of d_0 could be badly biased if the above multistage model fails to actually describe the dose–response curve at low levels of exposure. *Unfortunately it is impossible to develop a "model free" estimate of* d_0 *from the epidemiologic data.*

Furthermore, there may be more than one active lung carcinogen in mainstream smoke and ETS. If so, even if both carcinogens affect the first and fourth stages of a five-stage multistage cancer process, nonetheless, if their carcinogenetic potency differs and if the relative proportion of the two carcinogens in ETS differs from that in mainstream smoke, our estimate of d_0 will be biased. Unfortunately, it seems plausible that the single most active carcinogen in ETS would differ from that in mainstream smoke.

Additionally, our epidemiologic estimate of d_0 depends critically upon the assumption that the summary rate ratio 1.3 (in the 13 epidemiologic studies of ETS exposure) is causally related to differences in environmental tobacco smoke exposure between "exposed" and "unexposed" individuals and not to bias,. Lee et al. [11] suggest that the observed increase in risk in epidemiologic studies of ETS exposure is wholly attributable to bias resulting from the mis-

classification of smokers as non-smokers. Nonetheless, in Chapter 12 of the NAS Report, the potential for bias due to misclassification of smokers as non-smokers is considered in detail. There it is concluded the magnitude of this bias is likely small.

Lastly, in estimating β_1 and β_4 from active-smoker data, we took no account of the fact that in those studies active smokers (and the comparison groups of non-smokers) were themselves breathing other peoples' cigarette smoke. If $3d_0$ were of the order of 3 or more cigarettes per day (see Table 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. If, as is more likely, $3d_0$ is less than 1.5 cigarettes per day, little bias should be introduced by failing to account for the ETS exposure of active smokers.

The uncertainties in the dosimetric estimates of d_0 described in Section 4 are, if anything, even greater that the uncertainties in the epidemiologic estimates. The uncertainty in the dosimetric estimates of d_0 stem from two separate sources. The first source of uncertainty is our inability to identify the active carcinogen or carcinogens in mainstream smoke and in ETS. The second source of uncertainty derives from our inadequate knowledge of the doses of the known carcinogens (or carcinogen surrogates) NDMA, BaP, and RSP to which average active and passive smokers are exposed. This latter source of uncertainty could be quickly resolved by careful dosimetric measurement. If, for example, careful measurements of the NDMA and BaP exposure of passively exposed individuals showed that the maximal estimates of d_0 based on NDMA and BaP in Table 3 were 100-fold too high, one would have to seriously question whether the observed summary rate ratio of 1.3 could be causal.

Therefore, we conclude that presently available dosimetric data are not adequate to resolve the question of whether the summary rate ratio of 1.3 based on studies of non-smokers exposed to ETS, is compatible with the epidemiologic data on active smokers. We recommend careful measurements of the carcinogenic exposures of passive and active smokers.

5.1 Risk assessment

We begin by summarizing the main results from our risk assessment. We then show how these results were derived. All estimates given in the summary below were made under the assumption that the summary ratio of 1.3 described in the introduction was causally related to exposure to environmental tobacco smoke.

Of the roughly 7000 lung cancer deaths estimated to have occurred among lifelong non-smoking women in 1985, between 1,770 and 3,220 may be attributable to ETS. Of the roughly 5,200 lung cancer deaths occurring in non-smoking 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 non-smoker 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.

5.2 Estimating the number of lung cancer deaths in non-smokers in 1985 attributable to ETS

An estimate of the total number of lung cancer deaths among lifelong non-smoking women in 1985 is $\sum_t I_0(t)N(t)$ where $N(t)$ is the number of non-smoking women at risk at age t in 1985 and $I_0(t)$ is the age-specific lung cancer death rate among non-smoking women in 1985. Data on $I_0(t)$ are given in Garfinkel [12] 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 an estimate obtained by Seidman (personal communication) using a similar approach.

The total number of lung cancers among non-smoking women attributable to ETS in 1985 is

$$AN = \sum_t AF(t)I_0(t)N(t) \tag{2}$$

where $AF(t)$ is the age-specific fraction of lung cancer due to ETS in non-smoking women. That is $AF(t)$ is the age-specific average excess 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 among non-smoking 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 [13] control population (Garfinkel, personal communication).

We estimated the true relative risk in two different ways. In Method 1, we used the estimates given in Table 2. In Method 2, we completely ignore the epidemiologic data on passive smoking and estimate the true relative risk by combining estimates of β_1 and β_4/β_1 extrapolated from data on active smokers, and estimates of d_0 based on dosimetry. In a sensitivity analysis, we allow d_0 to equal 0.01, 0.2, and 2 to crudely represent (approximate) exposure to RSP, BaP, and NDMA, respectively (see Table 4).

In Table 5, estimated ranges for the attributable number are reported. $AN(\text{EP})$ represents the estimates based on Table 2. $AN(0.01)$, $AN(0.2)$, and $AN(2)$ represent estimates based on the dosimetry estimates of 0.01, 0.2, and 2. Estimates of the attributable number of lung cancer deaths based on Table 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 d_0 were 0.01 cigarettes per day,

TABLE 5

Estimates of ETS-attributable lung cancer deaths among U.S. non-smokers in 1985 (by sex: F = female, M = male)

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
Rate Ratio = 1.3						
AN (EP)[a]						
F	1768-3220[b]	1768-3220	1820-2800[c]	1768-3220	1820-2800	1939-2492
	(323)-(113)[d]	(323)-(113)	(321)-(113)	(323)-(113)	(321)-(113)	(323)-(113)
M	721-1942	721-1942	751-1611	721-1942	750-1611	850-1390
	(321)-(113)	(321)-(113)	(321)-(113)	(321)-(113)	(321)-(113)	(321)-(113)
AN (0.01)						
F	31-259	125-259	54-102	61-127	31-59	34-55
	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)
M	14-137	53-137	24-50	26-67	14-29	16-25
	(423)-(111)	(423)-(11)	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)
AN (0.2)						
F	585-3174	1921-3174	978-1695	1059-1939	585-1052	634-988
	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)
M	265-1890	908-1890	450-891	425-1094	265-540	305-465
	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)
AN (2)						
F	3793-6778	5992-6778	5039-6198	4702-5973	3793-5163	3854-4955
	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)	(423)-(211)
M	2016-4803	3812-4803	2904-4060	2758-4057	2016-3170	2151-2908
	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)	(423)-(111)
Rate ratio = 1.14						
AN (EP)						
F	935-1730					
	(323)-(113)					
M	360- 980					
	(321)-(113)					

[a] *An* (EP) is based on epidemiologic data in nonsmokers exposed to ETS.
[b] Range of attributable number of lung cancers over 30 exposure histories and five choices of (β_1, β_4/β_1).
[c] Range of *AN* of lung cancers over 30 exposure histories in non-smoking females for $\beta_4/\beta_1 = 0.225$, $\beta_1 = 0.803$.
[d] Exposure history where minimum and maximum occurs.

only 259 lung cancer deaths in non-smoking women would be attributable to ETS. On the other hand, the maximum estimate of the attributable number based on Method 2 with $d_0 = 0.2$ (3,170 deaths) is in agreement with that based on Method 1 (3,220 deaths). The minimum estimates, however, differ by approximately three-fold.

The calculation of the number of lung cancers attributable to ETS in 1985 in non-smoking males is similar. For details, see page 306 of the NAS report.

5.3 Lifetime risk of death from lung cancer attributable to ETS

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 (Travis et al. [14]). For purposes of comparison with other environmental and occupational standards, we have attempted to estimate the fractions of all deaths among non-smoking 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 on survival until that age. (Although years of life lost due to ETS exposure would be preferable as a public health measure to 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 an 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 [5], and Jarvis et al. [15], this exposure history represents an exposure to ETS that is slightly greater than the average exposure of a non-smoker 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,

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

where $\gamma_{\text{EXCESS}}(t)$ is the excess lung cancer death rate at age t due to exposure history M and $S(t \mid t_0)$ is the overall probability of surviving to age t, given one has survived to t_0. Under our assumptions, 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 non-smoking women, $I_0(t)$, and data on the all-cause age-specific mortality rates among non-smoking women which we estimate from data given in Hammond [3] (see Remark 14 of Appendix D of the NAS report).

The maximum and minimum of the $AF(M)$ across all exposure histories for each β_4/β_1 are given in Table 5 for males and females. $AF(M)$ is estimated to lie between 390 and 990 per 100,000. A similar calculation using the summary risk of 1.14 from the U.S. studies (instead of 1.30) halves our estimated range for $AF(M)$.

Estimates of the effect of ETS on the lung cancer risk of ex-smokers are given in Table D-6 of Appendix D of the NAS report.

In our risk assessment, the most important assumption was the assumption

TABLE 6

Range of estimated lung cancer deaths attributable to breathing other people's cigarette smoke per 10,000 deaths (all causes)

Rate	Sex	β_4/β_1:	ALL	0.0124		1.8	0.225	
		β_1:	ALL	2.93	1.41	0.14	0.803	0.46
1.3[a]	M	39–99		48–99	45–95[c]	48–99	45–95	39–77
	F	40–99		49–99	45–96	49–99	45–96	40–78
1.14	M	19–49						
	F	21–52						

[a]Assumed causal rate ratio.
[b]Range over 30 exposure histories 5 values of (β_1, β_4/β_1).
[c]Range over 30 exposure histories.
Note: All maxima were associated with exposure history (423); all minima with history (311).

that the observed summary rate ratio of 1.30 was causal. If this assumption is correct (below we discuss the possibility that it is not), we believe that our estimate of the lifetime risk of lung cancer among lifelong non-smokers 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 $AF(M)$ 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_4/β_1 used in the sensitivity analysis differed by some 150-fold, the overall variation in the lifetime risk of lung cancer due to ETS in non-smokers still varied only twofold (Table 6). Therefore, our estimate of the lifetime risk of lung cancer among lifelong non-smokers attributable to ETS exposure is much more robust to our assumption of a multistage model than is our estimate of d_0.

Given that we can know the lifetime risk of ETS-caused lung cancer in non-smokers to within a factor of 2 to 6, is this a 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 non-smokers 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 another factor of 2 or 3 (to take into account additional sources of uncertainty), it would still greatly exceed 1 per 100,000.

In this paper, 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 of the NAS report it was concluded that, considering the evidence as a whole, exposure to ETS increases the rate of lung cancer among non-smokers. 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 public health decision making 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 choose to report results 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 non-smokers exposed to ETS with independent estimates based on dosimetric measurements made in active and passive smokers. Unfortunately, as discussed previously, uncertainties in the identity and dose of the active carcinogens in ETS and mainstream smoke effectively preclude this possibility at this time.

Finally, we review estimates of the lung cancer risk associated with ETS exposure made by others. Russel et al. [16] estimate that 300 lung cancer deaths in Great Britain and 1200 lung cancer deaths in the United States attributable to ETS exposure occur each year among non-smokers. Their calculations are based on their own data demonstrating that urinary nicotine levels in average non-smokers are 0.7% of those in smokers. They then assume that the ratio of urinary nicotine in non-smokers to that in active smokers equals the ratio of the biologically effective dose (attributable to ETS) of the active lung carcinogen in non-smokers to the biologically effective dose in active smokers. Their estimate of 1,200 is less than both our midrange estimate of 3,500 lung cancer deaths in non-smokers assuming the causal rate ratio is 1.3 and our mid-range estimate of 2,000 deaths assuming the causal rate ratio is 1.14. In fact, upon examination of our Table 5, one finds that Russell et al.'s estimate is equal to our smallest estimate of $AN(EP)$ based on a rate ratio of 1.14, i.e., 935+360. The reason for the equality is that, by basing their risk assessment on nicotine dosimetry, Russell et al. effectively assume that d_0 (the carcinogen equivalent number of cigarettes/day inhaled by a non-smoker with a non-smoking spouse)

is 0.07. From our Table 3, we see that this estimate of d_0 is quite close to our lowest possible (epidemiologic) estimate of d_0, based on a rate ratio of 1.14.

Wells [17] estimated that approximately 1800 lung cancer deaths attributable to ETS exposure occur in U.S. non-smokers each year. Like us, he estimated excess lung cancer deaths by using non-smokers death rates from the ACS study and data on the fraction of the U.S. population that are non-smokers supplied by R. Wilson. In addition, like us, Wells performed a meta-analysis of published studies of the effect of ETS on lung cancer to determine a causal rate ratio. These published studies did not include all the studies available to the NAS committee. Therefore, his estimates for the causal rate ratio differed from the estimate of 1.3 used in this paper. In fact, his estimate was higher than 1.3 for both females and males. Nonetheless, his estimated number of lung cancer deaths, 1800, was less than our midrange estimate of 3500. This difference can, in part, be explained by the fact that Wells failed to correct for the fact that "unexposed" subjects are truly exposed to ETS.

Lee et al. [11] suggest that there may be no increase in lung cancer risk associated with ETS exposure, and suggest that the observed increase in risk is attributable to bias resulting from the misclassification of smokers as non-smokers. As discussed previously, based on analyses reported in Chapter 12 of the NAS report, we have ignored the possibility that this type of misclassification resulted in important bias.

Repace [10] estimated that 500 to 5,000 lung cancer deaths attributable to ETS occur among non-smokers yearly in the U.S. This estimate was based largely on comparing the daily tar (RSP) exposure in the average non-smoker to that of an average smoker. Repace's results are *quite* surprising in light of our Table 4. Specifically, our maximum estimate of d_0 based on RSP is 0.005. This value of d_0 would translate into approximately 100 lung cancer deaths attributable to ETS occurring among non-smokers. In contrast, Repace needs to assume that d_0, based on RSP, is in the range of 0.025–0.25 in order to predict 500 to 5,000 lung cancer deaths. We previously considered how it is possible that Repace's estimate of d_0 for RSP is 5 to 50 times greater than our maximum estimate.

Appendix

Remark 1

The investigators of the 13 epidemiologic studies reviewed by the NAS 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. [13] found the median age of lung cancer in non-smoking women in his population was approximately 70 (Garfinkel, personal commu-

nication), we would expect that this weighted average approximates the rate ratio at 70. This implies that the second assumption in Section 3 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, $\gamma(t|E)/\gamma(t|\bar{E})$. The large sample expected value of the odds ratio estimator ($\tilde{\mathrm{OR}}$) is $E[\tilde{OR}]=\int[\gamma(t|E)/\gamma(t|\bar{E})]f(t)\mathrm{d}t$, where

$$f(t)=\frac{h(t)f_{\mathrm{D}}(t)}{\int h(t')f_{\mathrm{D}}(t')\mathrm{d}t'}, \tag{3}$$

$$h(t)=\frac{p(E|t)p(\bar{E}|t)}{[\gamma(t|E)/\gamma(t|\bar{E})]p(E|t)+p(\bar{E}|t)} \tag{4}$$

$f_{\mathrm{D}}(t)$ is the fraction of all lung cancers in non-smoking women that occur at age t, and $p(\bar{E}|t)$ is the fraction of non-smokers in the study source population of age t who are "unexposed".

Remark 2

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 [2] (excluding, as did Doll and Peto, the subgroup of smokers of 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 3 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 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 [7], 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 4 of Brown and Chu). (Brown and Chu find a ratio of 4 for β_4/β_1 for smokers of 1–

20 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 [18]. 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. 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, our approach is useless. Actually, we 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 model for lung cancer risk. Therefore, our confidence in the estimation of the true relative risk may therefore be enhanced. As we shall see, we do indeed find such robustness.)

Remark 3

Estimating the true relative risk under the assumptions of Section 3. Consider a group of individuals (i.e., the "exposed" individuals or the "unexposed" individuals in Garfinkel et al. [13]) 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_s, and exposure d_{3i} from age t_s 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

$$RR(t) = 1 + \beta_1 d_0 [H_1] + \beta_4 d_0 [H_2] + \beta_1 \beta_4 d_0{}^2 [H_{12}], \tag{5}$$

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 3, and

$$\begin{aligned} H_1(t) = (t^4 d_0)^{-1} &[E(d_1) t^4 + [E(d_2) - E(d_1)] (t - t_0)^4 \\ &+ [E(d_3) - E(d_2)] (t - t_s)^4], \end{aligned} \tag{6}$$

$$H_2(t) = (t^4 d_0)^{-1}[E(d_3)t^4 + [E(d_2) - E(d_3)]t_s^4 + [E(d_1) - E(d_2)]t_0^4], \text{ and} \tag{7}$$

$$\begin{aligned} H_{12}(t) = {} & (t^4 d_0^2)^{-1}[E(d_1)]^2 t_0^4 (1 + m^2(d_1)) + E(d_1)E(d_2) \\ & \times [1 + p(d_1,d_2)m(d_1)m(d_2)](t_s^4 - t_0^4 - (t_s - t_0)^4) \\ & + [E(d_2)]^2 (t_s - t_0)^4 [1 + m^2(d_2)] + E(d_1)E(d_3) \\ & \times [1 + p(d_1,d_3)m(d_1)m(d_3)][t^4 - t_s^4 - (t - t_0)^4 \\ & + (t_s - t_0)^4] + [E(d_3)]^2 (t - t_s)^4 [1 + m^2(d_3)] \\ & + [1 + p(d_3,d_2)m(d_3)m(d_2)] \\ & \times [(t - t_0)^4 - (t_s - t_0)^4 - (t - t_s)^4] E(d_2)E(d_3), \end{aligned} \tag{8}$$

where $E(d_1)$ is the average of d_1, $m(d_1) = \sqrt{\text{Var}(d_1)}/\text{E}(\text{d}_1)$, and $p(d_1,d_2)$ is the correlation between d_1 and d_2. For simplicity, we shall assume that all correlations are 0. This will have little effect on our analysis.

Now define

$$F_1(t) = H_1(t) + (\beta_4/\beta_1)H_2(t) \text{ and } F_{12}(t) = (\beta_4/\beta_1)H_{12}(t) \tag{9}$$

Then we have

$$RR(t) = 1 + \beta_1 d_0 F_1(t) + (\beta_1 d_0)^2 F_{12}(t). \tag{10}$$

Now with $t_0 = 20$, $t_s = 55$, and $t = 70$, for any five choice for β_4/β_1 and for the exposure vector (a,b,c), we can compute $F_1(70)$, $F_{12}(70)$ for 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

$$1.3 = \frac{1 + (\beta_1 d_0)F_{1E}(70) + (\beta_1 d_0)^2 F_{12E}(70)}{1 + (\beta_1 d_0)F_{1\bar{E}}(70) + (\beta_1 d_0)^2 F_{12\bar{E}}(70)} \tag{11}$$

Equation (11) 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 eqn. (10) to give an exposure-history-β_4/β_1-specific estimate of the true relative risk at age 70 in "exposed" individuals. If we substitute $F_{1\bar{E}}(70)$ and $F_{12\bar{E}}(70)$ 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 eqn.3), our estimate of d_0 is inversely proportional to our estimate of β_1.

Remark 4

Interpretation od 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 non-filter U.S. cigarette containing 20 mg tar as smoked by an average U.S. citizen. In Section 3 we adjusted our estimates of β_1 from the Doll and Peto data [2] 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, [3]) and European case-control studies (Lubin, [4]), 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, as compared to the British data, is a consequence of the fact that there was less misclassification of smokers as non-smokers 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 non-smokers from the ACS study would be falsely inflated upwards and the values of β_1 of 1.93 and 0.803, as originally estimated for the British doctors, would be 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 3.

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