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Mainstream and Environmental Tobacco Smoke

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Environmental tobacco smoke (ETS) is derived from cigarette smoldering and active smoker exhalation. Its composition displays broad quantitative differences and redistributions between gas and respirable suspended particulate (RSP) phases when compared with the mainstream smoke (MSS) that smokers puff. This is because of different generation conditions and because ETS is diluted and ages vastly more than MSS. Such differences prevent a direct comparison of MSS and ETS and their biologic activities. However, even assuming similarities on an equal mass basis, ETS-RSP inhaled doses are estimated to be between 10,000- and 100,000-fold less than estimated average MSS-RSP doses for active smokers. Differences in effective gas phase doses are expected to be of similar magnitude. Thus the average person exposed to ETS would retain an annual dose analogous to the active MSS smoking of considerably less than one cigarette dispersed over a 1-year period. By contrast, consistent epidemiologic data indicate that active smoking of some 4–5 cigarettes *per day* may not be associated with a significantly increased risk of lung cancer. Similar indications also obtain for cardiovascular and respiratory diseases. Since average doses of ETS to nonsmoking subjects in epidemiologic studies are several thousand times less than this reported intake level, the marginal relative risks of lung cancer and other diseases attributed to ETS in some epidemiologic studies are likely to be statistical artifacts, derived from unaccounted confounders and unavoidable bias.

INTRODUCTION

During the last decade, considerable attention has been devoted to the question of whether environmental tobacco smoke (ETS) causes disease in nonsmokers (USSG, 1986; NRC, 1986; EPA, 1990a). Some epidemiologic studies of nonsmokers presumably exposed to ETS have suggested a marginal increase of risk for some diseases previously associated with active mainstream smoking (MSS). These reported risks, however, border on statistical and epidemiologic insignificance, and could easily derive from numerous and documented biases and confounders.

Official reviews have stopped short of implying a causal role of ETS in most of these associations, with a notable exception for lung cancer. This exception has been based not so much on admittedly questionable epidemiology, but on a public health stance of concern driven by perceived—but largely undocumented—compositional similar-

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ities of ETS and MSS, and by the implausible assumption that no dose exists below which risks are nonexistent or imponderable (USSG, 1986; NRC, 1986; IARC, 1987; EPA, 1990a,b).

This study analyzes the scientific literature on the chemical and physical characteristics of MSS and ETS, their reported specific biologic activities, and the mean relative doses of active MSS smokers and ETS-exposed nonsmokers under prevailing real life conditions, and finally considers the epidemiologic projections that these combined influences imply.

PHYSICAL AND CHEMICAL CHARACTERISTICS OF MSS AND ETS

Mainstream smoke is what smokers generate and inhale. Cigarettes smoldering between puffs emit side stream smoke (SSS), which, along with smoke exhaled by active smokers (EMS), becomes environmental tobacco smoke after immediate and progressive dilution, and aging. Both MSS and ETS result from the combustion of the same substrate and lead to exposures to analogous but not necessarily the same components, and certainly in different proportions, under different physical conditions, and at very different doses.

MSS is generated and exists in the well-defined confines of the cigarette and the mouth and the respiratory system of smokers. It is formed under conditions of high relative humidity, results in particulates with mean aerodynamic diameter of about 0.7 μm (Hiller *et al.*, 1982), and is inhaled within a few seconds of its formation with little aging or intervening transformations. All this permits a rather precise definition of its chemical and physical nature (Dube and Green, 1982).

On the other hand, any characterization of ETS must recognize its unstable and variable nature. The immediate dilution of side stream smoke with air begins a chain of physical and chemical transformations that continuously alter the ensuing ETS as it ages over hours. Smoker-exhaled mainstream smoke also contributes to ETS a certain fraction of gases and the small respirable suspended particulates (RSP) that are not retained in the lungs of smokers (Baker and Proctor, 1990). Actual SSS itself is difficult to define because its composition has been shown to vary under different conditions of experimental generation (Brunnemann *et al.*, 1978; Eatough *et al.*, 1990). Moreover, SSS is not indicative of the physical and chemical changes that occur in ETS as it continuously dilutes and ages.

The experimental generation of SSS-ETS in laboratory chambers after the smoldering of a few cigarettes has provided some clues to the composition of ETS (Benner *et al.*, 1989; Eatough *et al.*, 1989; Ingebrethsen *et al.*, 1988; Pritchard *et al.*, 1988; Vu-Duc and Huynh, 1989; Ingebrethsen and Sears, 1985). Better experiments have been attempted in larger chambers where humidity, temperature, ventilation rates, and other variables could be controlled, also leading to a perception of the differential influence of these variables on ETS decay (Eatough *et al.*, 1990; Baker and Proctor, 1990; Tang *et al.*, 1988; Ingebrethsen *et al.*, 1988). However, such data still fail to represent actual life conditions in real environments with a multismoker presence. No comprehensive studies have been published so far under such natural settings. The few available reports have attempted to measure only selected chemicals, sampled over variable but generally short periods of time, making them of dubious relevance to situations of prolonged exposure (Proctor *et al.*, 1989a,b; Lofroth *et al.*, 1988; Carson and Erikson, 1988; Sterling *et al.*, 1988; Oldaker *et al.*, 1987; Stehlik *et al.*, 1982). In the future,

more useful data should come from real-life ambient conditions with smokers being present, where new ETS is continuously generated as aging ETS decays, eventually establishing quasi-steady-state conditions and an "average" chemical and physical composition of ETS. Thus far, only nicotine and RSP concentrations have been measured with some appearance of accuracy under such conditions.

While several thousand MSS components have been identified in the literature, only about 100 components of fresh SSS and EMS have been measured. In addition, only fragmentary information is available for diluted ETS components, most of which appear to be present—if at all—at levels beyond analytical capabilities (Guerin *et al.*, 1987; NRC, 1986; USSG, 1986; EPA, 1990a). Today only a few specific and some general inferences are possible about the differences of MSS and ETS. SSS, from which ETS mainly is derived, is generated under conditions of better oxygenation and contains proportionally less carbon monoxide than MSS. It also contains fewer products of pyrolysis and distillation, and undergoes immediate cooling and vast dilution with air, with the result that ETS-RSP have considerably smaller size than MSS-RSP, with mean aerodynamic diameters on the order of 0.1 μm, or 100 to 200 times smaller in volume than MSS-RSP (Ingebrethsen *et al.*, 1988; Ingebrethsen and Sears, 1985). Smaller particles tend to evaporate faster and more efficiently than larger ones, so that many substances associated with MSS-RSP are more prevalent in the gas phase of ETS. This and the somewhat more alkaline conditions of SSS cause nicotine to appear in the ETS gas phase almost exclusively, while it is mainly associated with particulates in MSS.

As ETS ages, particle concentration and total mass decrease because smaller particles eventually coalesce, while mass is lost to diffusion/evaporation and to electrostatic and gravitational deposition (Hinds, 1978; Benner, 1989). The process continues with dynamics that depend on temperature, pressure and relative humidity, electrostatic conditions, ambient geometry and surface composition (furniture, fabrics, paints, crowding, etc.), ventilation rates, type and number of cigarettes smoked, mode of smoking, and other variables (Baker and Proctor, 1990).

In time, ETS gases and RSP adsorb to ambient surfaces and are disposed of by ventilation, while adsorbed substances may again desorb and recirculate in gas or vapor form, as has been suggested to happen with nicotine. Complex chemical transformations also occur because of interactions among molecules, oxidation, and probably photochemistry when UV radiation is present (Proctor, 1990). These continuous transformations occur at rates peculiar to each environmental situation and therefore result in physical states and chemical compositions that can be substantially different from place to place and from time to time.

In general, the better measures and estimates of ETS pertain to suspended particulates, a complex of substances that is apparently more stable and more measurable than individual substances. MSS-RSP appears to contain the smoke fractions capable of producing certain tumors in experimental animals. However, given that ETS and MSS have substantial differences in component concentration and partitions between gas and particulate phases, the issue of their relative biologic activity cannot be answered beyond some sensible conjecture. Past and also recent laboratory studies indicate that the biologic potencies of MSS-RSP and SSS-RSP seem virtually equivalent, with no detectable potency noted in the semivolatile fractions (Grimmer *et al.*, 1988; Stanton *et al.*, 1972). These data, however, pertain to the relative position of MSS-RSP and SSS-RSP condensates, and their relationship to ETS-RSP condensates has not been resolved. Other studies have reported that the *in vitro* mutagenic activity of MSS and

ETS may be roughly comparable, although the biologic significance of such data is speculative (Claxton *et al.,* 1989).

MEASUREMENT OF EXPOSURE

In the case of MSS the relative ratios of smoke components remain comparatively stable. Based on internal markers, the measurement of exposure and dose intake has been reasonably well defined, especially as pertains to RSP, nicotine, carbon monoxide, and other specific components (Gori, 1990). However, and despite several attempts at definition, selected markers have been rather disappointing surrogates for total ETS intake or exposure estimates.

A reasonable environmental marker should be specific to ETS, be easily detectable, and have a nearly constant ratio to other ETS components (NRC, 1986). Given the variable chemical and physical nature and the extreme dilution of most components of ETS, it is not surprising that a satisfactory marker of exposure has not been identified. For that and other reasons, an internal marker of actual ETS intake or dose has proven to be even more difficult to identify.

Most epidemiologic studies have measured exposure by means of recall questionnaires, with results that are problematic even at qualitative levels. Aside from the inability of virtually all epidemiologic studies to define whether exposure or lack of it was correctly reported—especially with data from proxy respondents—the issues of intensity and duration of exposure have hardly been addressed by questionnaires. Even when problems of subject misclassification, respondent bias, and correction for background ETS exposure could be addressed, questionnaires have produced no more than rough indexes of exposure. The collection of dependable information on actual doses at specific target sites and at different times has not been possible (Wu-Williams and Samet, 1990; Cummings *et al.,* 1989; McCarthy *et al.,* 1987).

Hopes have been placed on nicotine and its metabolite cotinine as possible markers of ETS intake and actual internal dose (Cummings *et al.,* 1990; Jarvis, 1989; Coultas *et al.,* 1987; Jarvis *et al.,* 1985; Hoffmann *et al.,* 1984). Unfortunately ETS-nicotine resides mostly in the gas phase and decays at rates quite different from other ETS components, to which it will have ratios that are variable in time and largely unpredictable (Tang *et al.,* 1988). Plasma cotinine levels suffer from similar and other shortcomings, although they have been shown to correlate with self-reported exposure to ETS (Cummings *et al.,* 1990; Jarvis, 1989). Reports also suggest that physiologic clearance of nicotine and cotinine at low plasma levels may proceed at much slower rates, likely because of slower release from preferential body compartments (Lewis *et al.,* 1990). Until these low-level kinetics are better understood, low plasma levels of nicotine and cotinine are likely to lead to substantial overestimations of intake doses. As such, nicotine and cotinine may provide a dichotomous index of contemporary exposure, but they remain inadequate as quantitative estimators of exposure, actual ETS dose, or their variation over an individual's life.

The ratio of ETS-nicotine to ETS-RSP has been suggested as a possible means to determine RSP intake from plasma nicotine levels, but such ratios appear too variable to be useful (Oldaker *et al.,* 1989). DNA and protein adducts have been proposed as markers of internal ETS dose, even though their specificity to ETS and their relationship to disease, especially to cancer, are in question (Randerath *et al.,* 1989; Harris *et al.,* 1987). Moreover, recent studies have reported no increase in DNA adducts in non-

smokers exposed to ETS (Holz *et al.*, 1990). The reported mutagenicity of urine samples in ETS-exposed nonsmokers also has proven elusive as a marker, largely because results may not be distinguishable from background rates and because of interferences from dietary sources (Scherer *et al.*, 1987, 1989; Mohtashamipur *et al.*, 1987; Sorsa *et al.*, 1985).

There has been great interest in measuring ETS-RSP directly, since its physical properties make for more positive identification and because biologic activity may reside specifically in the particulate phase, both in terms of its components and in terms of its longer residence time and cellular contact in the lungs. However, suspended particulates in air may be derived from many sources, and measurements of ETS-RSP need to be corrected for non-ETS RSP background. Several studies have reported differential values in the same settings under smoking and nonsmoking conditions (Repace and Lowrey, 1980; Weber and Fisher, 1980; Sterling *et al.*, 1987; Miesner, 1988; Kirk *et al.*, 1988a,b; Turner, 1988). It is obviously difficult to duplicate conditions of room occupancy, clothing, human traffic, ventilation, etc., where the only changing variable is smoking or not smoking. These problems have been much discussed, so that greater credibility can be accorded to the latest published studies. According to the more recent measurements of ETS-RSP in homes and workplaces, and allowing for differences of nonsmoking and smoking situations, a liberal estimate of ETS-attributable-RSP mean concentration in ambient air is less than 50 $\mu g/m^3$ (Table 1).

In regard to exposure to ETS gas phase components, it is enlightening to compare the concentrations of representative ETS components with the corresponding threshold limit values (TLVs), as established by the American Conference of Governmental and Industrial Hygienists for workplace safety. Incidentally, such values include considerable safety factors and are usually lower than the permissible exposure levels (PELs) established by the National Institute for Occupational Safety and Health (NIOSH)

TABLE 1

CONCENTRATIONS OF RSP FROM ETS AND OTHER SOURCES IN VARIOUS ENVIRONMENTAL SETTINGS WITH AND WITHOUT SMOKER PRESENCE

Reference	Site	RSP concentration ($\mu g/m^3$)	
		No smoking	Smoking
Coultas *et al.* (1990a)	Homes	NA	17
Sheldon *et al.* (1989)	Homes	22[a]	65[a]
Spengler *et al.* (1981)	Homes	NA	20
Spengler *et al.* (1985)	Offices	39[b]	72[a]
Proctor *et al.* (1989b)	Offices	8[b]	23[b]
Oldaker *et al.* (1990)	Offices	NA	27[b]
Miesner (1988)	Offices	15[a]	36[a]
Sterling *et al.* (1983)	Office buildings	15[a]	29[a]
Coultas *et al.* (1990b)	Workplaces	NA	64[a]
Oldaker *et al.* (1990)	Restaurants	NA	36[b]
Crouse (1988)	Restaurants	NA	34[b]
Proctor (1990)	Public transport	14[b]	36[b]

Note. NA, data not available or not applicable.

[a] Based on total RSP.

[b] Based on UV-RSP portion of total RSP.

and the Occupational Safety and Health Administration (OSHA). Table 2 gives some examples for selected indicator substances representative of related chemical families.

The estimates in Table 2 assume maximum recorded SSS emissions, no ventilation, no surface adsorption, and no intervening decay of any sort. However, official reports give estimates of the range of the ratios of MSS/ETS concentrations for selected components (NRC, 1986). These were found to vary as follows:

	MSS/ETS ratios		
Nicotine	57,333	to	7,200,000
Benzo[*a*]pyrene	68	to	40,740
Acrolein	1,500	to	20,833
Benzene	112	to	7,167
Acetone	240	to	2,000

Such values show the extremes of dilution that ETS has displayed under various conditions, and suggest that the number of cigarettes required to attain TLVs under realistic conditions would be orders of magnitude higher than the conservative estimates listed in Table 2.

ESTIMATING RELATIVE DOSES OF MSS AND ETS RSP

Although certain assumptions are necessary in estimating ETS-RSP doses, they are based on simple facts or on measurements that are fairly well verified. With this in

TABLE 2

ESTIMATED NUMBER OF CIGARETTES REQUIRED TO REACH TLV LEVELS FROM SSS EMISSION OF SELECTED CHEMICALS IN A SEALED AND UNVENTILATED 100-m^3 ENCLOSURE

SSS component	SSS output[a] (mg/cigarette)	TLV[b] (mg/m^3)	Cigarettes required
Methylchloride	0.88	10.30	1,170
Hydroquinone	0.16	2	1,250
Cadmium	0.0007	0.01	1,430
Acetaldehyde	1.26	180	1,430
Acetic acid	1.5	25	1,660
Nitrogen oxides	2.8	50	1,780
Formic acid	0.525	9.4	1,790
Pyridine	0.39	16	4,100
Phenol	0.25	19	7,600
Methylamine	0.1	13	13,000
Benzene	0.24	32	13,300
Catechol	0.14	23	16,500
Nickel	0.0025	1	40,000
Dimethylamine	0.036	18	50,000
Hydrazine	0.00009	0.13	145,000
Acetone	1	1780	178,000
Benzo[*a*]pyrene	0.00009	0.2[c]	222,000
2-Toluidine	0.003	9	300,000
Polonium 210	0.4 pCi	3 pCi/liter[d]	750,000
Toluene	0.000035	375	1,000,000

[a] Data from EPA (1990a), Table C-2, pp. C-19 and 20.
[b] Data from ACGIH (1990).
[c] Based on the TLV for coal tar pitch volatiles.
[d] EPA (1990c).

mind, such estimates seem reasonably realistic and less affected by obvious judgmental considerations. Nevertheless, in comparing RSP doses from ETS and MSS exposures it also seems reasonable to present results in analog form rather than as precise point estimates, in recognition of possible uncertainties.

Assuming a prolonged daily exposure of 10 hr, a typical person would be exposed to a daily ETS-RSP dose of roughly 0.3–0.4 mg after breathing ambient air with a 50 $\mu g/m^3$ ETS-RSP concentration, at the rate of about 0.7 m^3/hr (Crawford-Brown, 1987). This is equivalent to over a 1000-fold reduction compared with the inhaled dose of the average mainstream smoker.[2]

However, an important difference relates to aerodynamic particle size, which tends to reduce lung retention of the smaller and probably less charged ETS-RSP particles (USSG, 1986). Indeed, available studies indicate an 80–90% efficiency of retention of mainstream smoke RSP in the lungs of smokers (Mitchell, 1962; Dalhamn *et al.*, 1969; Hinds *et al.*, 1983), while other studies show that only some 10% of RSP may be retained in the lungs of ETS-exposed subjects (Hiller *et al.*, 1982). This retention differential has been recognized by the EPA (EPA, 1990a), even though reliable studies suggest a substantially greater difference (McAughey *et al.*, 1989, 1990; Crawford and Eckerman, 1983). Therefore, based on mass alone, the average dose of ETS-RSP retained in the lung may be less than 1/10,000 of average MSS-RSP smoker doses.

RSP retention, however, does not equate with tissue or individual cell dose, which is the important issue given that cancer is thought to begin with cellular events. Among other things, cell dose will depend on quantity available per cell, proximity to cell surface, cell surface exposed, cell surface permeability, and duration of contact. Cellular dose is therefore modulated by mucociliary clearance and by the permeability of lung epithelium (Gerde *et al.*, 1991). In this regard, published data indicate that average mucociliary clearance is some threefold greater in nonsmokers than in smokers (Vastag *et al.*, 1985; Foster *et al.*, 1985), while average airway mucosal permeability appears to be about one third as great in nonsmokers as in smokers (Kennedy *et al.*, 1984), probably as the result of a thicker and more viscous mucous layer (Zayas *et al.*, 1990). Although these studies involve a relatively small number of subjects, they indicate that the effective cellular dose in ETS-exposed nonsmokers may be further reduced by close to 90% when compared with active smokers, due to clearance and permeability factors alone.

Together, these considerations suggest that the lung cell doses for average ETS-exposed nonsmokers are probably between 1/10,000 and 1/100,000 of equivalent cell doses for average mainstream active smokers. In practical terms, this implies an annual retained dose of tobacco smoke components equivalent to far less than the dose from the active smoking of one cigarette somehow evenly dispersed over a 1-year period (see Footnote 2).

MSS AND ETS: EPIDEMIOLOGIC COMPARISONS

An annual ETS retained dose equivalent to the active smoking of less than one cigarette over the course of 1 year may be compared with the MSS dose/response associations reported with various health conditions. The limit of statistical significance

[2] The average smoker of 30 cigarettes per day inhales some 30 mg of nicotine (Gori and Lynch, 1985). The sales-weighted average tar/nicotine ratio for the smoke of commercial cigarettes is 15–18 (FTC, 1985). Therefore the average smoker inhales about 500 mg of tar daily.

TABLE 3

MAXIMUM LEVELS OF DAILY CIGARETTE CONSUMPTION AT WHICH LUNG CANCER RISK IN MALE SMOKERS MAY NOT BE SIGNIFICANTLY INCREASED FROM THE RISK OF NONSMOKERS, BASED ON EPIDEMIOLOGIC DATA (SEE FOOTNOTE 3)

Reference	Maximum cigarettes/day
British doctors[a]	6.3
Swedish men[b]	3.9
ACS, 9 states[c]	5.4
ACS, 25 states[b]	0.9
U.S. veterans[c]	0.6
Canadian veterans[c]	1.6
Japanese men[b]	3.1
California men[c]	7.0

[a] From Doll and Peto (1978).
[b] From USSG (1979), pp. 5-13, Table 2.
[c] From USSG (1982), p. 38, Table 6.

for such associations would provide a reasonable index of comparison. For lung cancer, data from independent studies listed in U.S. Surgeon General Reports yield the results in Table 3, after analysis by standard analytical procedures.[3]

Official sources refer to the British doctors study as the most reliable set of data for dose/response analysis (EPA, 1990a). This prospective study appears to be adequately documented and offers a reasonably accurate tracing of subjects (Doll and Peto, 1978). Thus, data in Table 3 indicate that the active smoking of 4–5 cigarettes/day is not likely to be statistically associated with elevated lung cancer risk. This assessment, presented here without undue claim of precision, is in accord with other estimates (Wynder, 1991). It suggests that since ETS retained doses are several thousand times less than MSS doses from this level of cigarette smoking, they appear insufficient to generate elevated risks of lung cancer.

This conclusion is consistent with an increasing body of scientific opinion that MSS may act as a weak promoter rather than as an initiator, supporting the implication of no observable epidemiologic risk at low doses (Albert, 1989; Doll and Peto, 1981;

[3] Individual studies were analyzed separately. Generally, for each study, the relative risk associated with the number of cigarettes consumed daily was listed. The first step in the analysis was to fit the data to a function of the form

$$RR = A_0 + A_1X + A_2X^2,$$

where RR is the relative risk, A_0, A_1, and A_2 are coefficients calculated by the maximum likelihood method, and X is the daily cigarette consumption. Cigarette consumption data are usually expressed in intervals, e.g., 1–9. The midpoint or the mean value of each interval × 1.25 was used in the calculation, justified by studies which indicate an average 30% underreporting of daily cigarette smoking (Hatziandreu *et al.*, 1989; La Vecchia, 1986; Jackson and Beaglehole, 1985). The highest consumption values are generally reported as open-ended, e.g., 40+, and here the midpoint was set at the given value plus 10. For the British doctors study the actual mean values of the intervals were available (Doll and Peto, 1978). The nonsmoker reference data points (0,1) were also entered in the regressions. Although other functions were examined, graphic and statistical analysis shows that the quadratic function provides an exceptionally good fit to the data, with a corrected multiple coefficient of determination close to 1 in each case. Critical values of daily cigarette consumption were calculated as the values at which the lower bound of the 95% confidence interval of the estimated RR was unity.

TABLE 4

MAXIMUM LEVELS OF DAILY CIGARETTE CONSUMPTION AT WHICH RISK FOR CORONARY HEART DISEASE MORTALITY IN MALE SMOKERS MAY NOT BE SIGNIFICANTLY INCREASED FROM THE RISK OF NONSMOKERS, BASED ON EPIDEMIOLOGIC DATA (SEE FOOTNOTE 3)[a]

Reference	Maximum cigarettes/day
U.S. veterans	1.5
ACS, 9 states	2.5
Japanese men	4.0
Canadian veterans	4.5
British physicians	4.5
Swedish men	2.5
California men	3.0
Swiss physicians	3.0

[a] Epidemiologic data from USSG (1983), p. 118.

Doll, 1978). Moreover, epidemiologic studies of MSS categorize exposure by number of cigarettes smoked, report multiannual exposure durations, and provide some evidence of commensurate latency times preceding diagnosis. By contrast, most nonsmokers in households may be exposed to ETS for only a few hours a day, which would further tend to increase the distance between MSS and ETS doses.

The daily levels of cigarette consumption compatible with no significantly increased risk for other diseases associated with active smoking appear to be of the same order as for lung cancer. Tables 4 and 5 report the analogous estimates for cardiovascular and respiratory disease mortality, with the implication that retained doses of ETS are unlikely to be associated with significant risk elevations for such diseases as well.

CLOSING REMARKS

Ordinarily it is extremely difficult to demonstrate the effects of an agent at low dose levels. Rather, after an effect becomes apparent at high doses, the interpretation is

TABLE 5

MAXIMUM LEVELS OF DAILY CIGARETTE CONSUMPTION AT WHICH RISK FOR RESPIRATORY DISEASE MORTALITY IN MALE SMOKERS MAY NOT BE SIGNIFICANTLY INCREASED FROM THE RISK OF NONSMOKERS, BASED ON EPIDEMIOLOGIC DATA (SEE FOOTNOTE 3)[a]

Reference	Maximum cigarettes/day
Chronic bronchitis	
U.S. veterans	5.5
Canadian veterans	2.6
Emphysema	
U.S. veterans	2.2
Canadian veterans	2.7
California men	5.5
Bronchitis and emphysema	
British physicians	3.0
U.S. veterans	

[a] Epidemiologic data from USSG (1984), p. 202.

made that some effect, however small, would obtain at lower levels. Using some dose/response model an estimate of the effects at low doses, often including some statistical confidence intervals, is attempted.

The difficulty with low level determinations is that often the results fail to be significantly different from the null reference. In other words, the confidence limits of the effect would likely include the null reference, and/or the actual estimate of the effect might even be in the direction of protection instead of harm. Indeed, for most substances there is some threshold of tolerance below which the organism can cope without suffering adverse effects. For that matter it is apparent that levels at or below threshold might actually be beneficial in the sense of inducing and stimulating resistance, a process known as hormesis. This is in fact the case for virtually all beneficial and even essential substances, which would produce adverse effects when administered at excessive doses.

The ETS of public health concern is what is presented to average nonsmokers under commonplace environmental conditions and not the exceptional examples that can be created in laboratories. With this stipulation, ETS is a very elusive entity, undergoing continuous transformations at extremes of dilution that make efforts to define its chemical, physical, and biologic characteristics highly difficult. While the components of MSS/SSS may also be present in ETS, it is also clear that with few exceptions they are undetectable by the most sophisticated analytical procedures.

Despite these rarefied dilutions, an ETS hazard has been presumed from a conjectural association with MSS (EPA, 1990a,b; USSG, 1986; NRC, 1986). Central to this conjecture is the presumption of an equivalent chemical and biologic activity of MSS and ETS, and of the absence of low doses below which risk would be null or intangible. However, current understanding of composition alone is not sufficient to compare activities among MSS, SSS, and ETS, and the actual testing in biological systems suffers for two main reasons: the need to utilize concentrated laboratory surrogates that may have little relevance to actual ETS, and the unresolved obstacles to interpreting high-dose-related animal or *in vitro* data in terms of equivalent human responses at extremely low doses.

With this in mind, and even assuming that the biologic activities of MSS and ETS are of similar order, the reality of the extreme dilution of ETS remains. In this regard we have noted that current regulations allow workplace exposures to many ETS gas phase constituents at concentrations between thousands of and a million times higher than can be expected from commonplace ETS.

We also offered evidence that if epidemiologic investigations of MSS and lung cancer had been confined to the effects of exposure to a few cigarettes daily, they would have failed to yield significant risk signals. Similar evidence has been shown to hold for other diseases associated with active MSS smoking. At the same time it is apparent that subjects included in ETS epidemiologic studies were probably exposed to equivalent MSS-RSP doses below even a single cigarette *per year.* Therefore, marginal RR values associated with ETS exposures should be imputed to biases, confounders, and other weaknesses of the investigations, and any judgment that ETS exposure leads to lung cancer and other diseases would flow from argument, not from credible data.

In fact, the majority of epidemiologic studies of ETS suffer from what appear to be irreparable deficiencies. Earlier on we discussed the failure of epidemiologic studies in general to define exposure to ETS in terms of duration and intensity in any satisfactory way. The additional difficulties arising from misclassification of smoking status or ETS exposure have been amply described in the literature. The erroneous classi-

fication of actual smokers or former smokers as nonsmokers would have serious consequences on epidemiologic results, especially because smokers tend to be married to smokers. The National Research Council Committee on Passive Smoking outlined the knowledge that would be necessary to assess the impact of classification bias, namely, the proportion of the sample that was misclassified, the proportion of male and female subjects, the proportion of married couples that have the same smoking habits, and the relative lung cancer risk of misclassified smokers and nonsmokers (NRC, 1986). Although it is self-evident that knowing all this would eliminate classification bias, these variables have not been measured or reported in studies and therefore are subject to conjectures and assumptions that, however educated, have led to very different assessments (NRC, 1986; Lee, 1987a). In this regard it is possible to state only that misclassification bias is difficult to assess but very probable, and its impact could be of sufficient magnitude to explain the marginal lung cancer RRs reported by some ETS studies (Lee, 1987b).

An even greater prejudice to the credibility of ETS epidemiologic studies derives from their failure to account and control for the possible confounding by many independent risk factors. For lung cancer, a selected list of these is given in Table 6.

Since many of the RRs in Table 4 are substantially larger than any reported for the association of lung cancer and ETS, even weak contributions by combinations of these confounders would be cumulative and could be more than sufficient to explain the marginal lung cancer risks that some epidemiologic studies of ETS have reported. In fact it is likely to be so, because these studies have not controlled for the factors of Table 4 in any meaningful or comprehensive way, while other investigations provide evidence that several of those risk factors cluster and selectively segregate in families with smokers (Subar *et al.*, 1990; Morabia and Wynder, 1990; Sidney *et al.*, 1989; Whichelow *et al.*, 1988, 1991; Koo *et al.*, 1988; Pisani *et al.*, 1986; Friedman *et al.*, 1983). For cardiovascular diseases the independent risk factors reported in the literature number over 200, many of which are the same as apparent lung cancer risks (Hopkins and Williams, 1981). For respiratory diseases analogous independent risk factors have been identified, ranging from genetic to sociologic, to dietary and environmental conditions, also likely to cluster in households with smokers (Shilling *et al.*, 1977; Comstock *et al.*, 1981; Morris *et al.*, 1990; Schwartz and Weiss, 1990).

It should be clear that the seemingly insurmountable difficulties in measuring ETS exposures and doses, unresolved classification bias, and the inability to control for numerous independent confounders explain the inconsistency of weak ETS epidemiologic results and speak against scientifically credible conclusions about a risk that, if real at all, remains imponderable.

Indeed, the only justifiable conclusion is that this issue cannot be resolved scientifically on the basis of currently available information. Moreover, exposure and dose considerations alone seem to indicate that ETS is an insignificant entity among the substantial mass of exogenous and endogenous challenges to health that we continually face.

Hypothetical risks from feeble ETS exposures have been postulated only by presuming what is merely possible, even if extremely unlikely, as opposed to what is scientifically demonstrable and probable. Although at times politically tempting, such hypothetical presumptions are not science and should be resisted. If accepted, they are likely to foster irrational fears, not the enlightened prudence that responsible public health policy should cultivate.

TABLE 6

REPORTED INDEPENDENT RISK FACTORS FOR LUNG CANCER

Factor	Reference	Maximum RR reported	95% CI
Family history of lung cancer	Samet *et al.* (1986)	5.3	(2.2–12.8)
	Ooi *et al.* (1986)	2.4	
	Horwitz *et al.* (1988)	2.8	(1.0–7.7)
	Wu *et al.* (1988)	3.9	(2.0–7.6)
Family history of tuberculosis	Wu *et al.* 1988)	10.0	(1.1–90.1)
	Sakurai *et al.* (1989)	6.4	
	Gao *et al.* (1987)	1.7	(1.1–2.4)
	Hinds *et al.* (1982)	8.2	(1.3–54.4)
β-carotene/vitamin A deficiency	Byers *et al.* (1987)	0.3	(P = 0.06 trend)
	Pastorino *et al.* (1987)	0.2	
	Wu *et al.* (1985)	0.4	(0.2–0.9)
	Ziegler *et al.* (1986)	2.2	
Alcohol intake	Pollack *et al.* (1984)	2.19	(1.3–5.0)
Dietary cholesterol/fat	Goodman *et al.* (1988)	2.2	(1.3–3.8)
Dietary fat intake	Wynder *et al.* (1987)	4–6	
Pork meat intake	Mettlin (1989)	2.4	(1.4–4.2)
Vegetable diet	Jain *et al.* (1990)	0.6	(0.4–0.88)
	Le Marchand *et al.* (1989)	0.3	(P = 0.009 trend)
Fruit intake	Koo (1988)	0.4	(0.2–0.9)
Milk intake	Mettlin (1989); Mettlin *et al.* (1990)	2.1	(1.4–3.2)
Hormone therapy in women	Adami *et al.* (1989)	1.3	
Cooking methods	Gao *et al.* (1987)	1.4–2.6	(1.1–5.0)
	Geng *et al.* (1988)	5.6	(3.4–9.1)
	Sobue *et al.* (1990)	1.9	(1.1–3.3)
	Mumford *et al.* (1987)	2–3	
Radon	Edlin *et al.* (1984)	4.3	(1.7–10.6)
	Lees *et al.* (1987)	2.4	(0.8–7.1)
Occupation	Kvale *et al.* (1986)	2.6	
Motor exhaust exposure	Hayes *et al.* (1989)	1.5	(1.2–1.9)
Socioeconomic class	Brown *et al.* (1975)	2.6–3.8	
Ventilatory function	Lange *et al.* (1990)	2–4	
Cardiac anomalies	Tenkanen *et al.* (1987)	2.4	
Physical inactivity	Albanes *et al.* (1989)	1.6	(1.2–3.5)
	Severson *et al.* (1989)	1.4	(1.0–2.1)
Psychosocial traits	Kulessa *et al.* (1989)	2–3	
Urban/rural risk ratio	Shy (1984)	1.2–2.8	

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