

EPIDEMIOLOGIC, BIOLOGIC, AND FACTUAL INCONSISTENCIES
AND AMBIGUITIES OFFER NO SCIENTIFIC BASIS FOR LISTING
ENVIRONMENTAL TOBACCO SMOKE IN THE
9TH ANNUAL REPORT ON CARCINOGENS

Submitted by
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Credentials

I am Gio Batta Gori, director of the Health Policy Center, Bethesda, Maryland, a study group in toxicology, epidemiology, the environment, and related scientific, policy, and regulatory issues. My experience includes directing the Franklin Institute Policy Analysis Center (1980-88), and executive positions at the National Cancer Institute (1968-1980) as Deputy Director of the Division of Cancer Causes and Prevention (1972-80), Director of the Smoking and Health Program (1968-80), Director of the Diet, Nutrition and Cancer Program (1972-80), Acting Associate Director of the Carcinogenesis Program, (1976-78). Earlier I had academic and industrial experiences. My interests have been in environmental carcinogenesis and health, nutrition and health, non-ionizing radiation and health, smoking and health, prevention and public health, and related risk and cost/benefit issues. In 1976 I received the U.S. Public Health Service Superior Service Award. A two term president of the International Society of Regulatory Toxicology and Pharmacology, I am also a charter fellow of the Academy of Toxicological Sciences, member of scientific societies, editor of Nutrition and Cancer, associate editor of Regulatory Toxicology and Pharmacology, and I publish regularly on scientific and policy issues.

The Brown & Williamson Corporation asked that I comment to the Report on Carcinogens Subcommittee of the NTP Board of Scientific Counselors, in regard to the proposed listing of environmental tobacco smoke in the 9th Annual Report on Carcinogens, to be considered at the December 2-3, 1998 meeting of the Subcommittee. The following remarks are my own and do not necessarily represent the position of Brown & Williamson.

Introduction

The National Toxicology Program in its mission statement "Good Science for Good Decisions" asserts that "[t]he overarching motivation of the Program is to use the best science possible in setting priorities, designing and conducting studies and in reporting results in an objective way that best meets the needs of the public and Federal and State health and regulatory agencies." The NTP takes pride in being "recognized as objective and science based" and continues saying that "it is critical that the NTP play a leadership role in providing the necessary science base", also asserting that the Annual Report on Carcinogens (RoC) "is not intended to constitute a risk assessment but that it is a hazard identification document only." (NTP, 1998).

On this basis, the underlying premise is that the Report on Carcinogens Subcommittee is duty bound to consider RoC listings on strictly scientific merits, so that subsequent regulatory actions might count on factual information. In turn, the premise implies that the proposed consideration of environmental tobacco smoke (ETS) for listing in the 9th RoC should proceed based on criteria of factual objectivity and not on claims that are presented as scientific but are not scientifically justified.

The RoC Subcommittee has been presented with a background document that summarizes the ETS risk assessment by the US Environmental Protection Agency (EPA) and the parallel assessment by the California Environmental Protection Agency (CEPA) that essentially followed the previous EPA model (TPMC, 1998; USEPA, 1992b; CEPA, 1997). Both EPA's and CEPA's reports do not rely on scientific methods to assert that ETS is a human lung carcinogen, the latter also adding that it is a human nasal sinus carcinogen. It is apparent that these background reports are also inappropriate and not consonant with the mission statement of the RoC Subcommittee because they are risk assessment exercises and not hazard identification documents. In fact, EPA asserted that its assessment was "...based on the a priori hypothesis that a positive association exists between exposure to ETS and lung cancer." rather than on the standard null hypothesis of science (USEPA, 1992b, p.5-2), which established a preconceived bias that has led to an extraordinary misrepresentation of facts, selective use of data, and arbitrary interpretive conjectures and assumptions. It should also be noted that the EPA reports was recently voided by a Federal Court because of its overt inconsistencies (Osteen, 1998).

Indeed, observers familiar with elementary principles of scientific inquiry should readily understand that the EPA and CEPA reports are not supported by factual scientific considerations. This is so because the minimum requirements of scientifically justifiable statements are that hypotheses should be tested so that variables can be reliably measured, that control and test conditions are materially the same except for the variables being tested, that confounding interferences are identified, measured, and accounted for, and that the outcomes of multiple tests are consistently reproducible. It is apparent that such minimum requirements cannot be met in considering the evidence of whether ETS is or not a human lung or nasal sinus carcinogen:

- ETS itself cannot be adequately defined because under real field conditions most of its components are diluted beyond physical detection and characterization. Concentrations of conjectural ETS components under conditions considered by epidemiologic studies are likely to be over 3 orders of magnitude below TWA and PEL levels officially permitted in workplaces.
- Animal studies are not interpretable because they utilize exposures unrelated to real life ETS, and animal models of unknown and unlikely correspondence to humans.
- Epidemiologic studies are unable to warrant adequate measures of exposure, because unknown ETS conditions preclude establishing standard markers of exposure, and because of recall uncertainties and misclassification bias.
- Epidemiologic studies have found it impossible to control simultaneously for the several known and independent lung cancer risk factors, and cannot warrant that the conditions of control subjects are materially the same as for exposed subjects.
- Virtually all epidemiologic reports fail conventional requirements of statistical significance at the 95% level.
- Even disregarding the absence of conventional statistical significance, the central values of individual epidemiologic reports are inconsistent and oscillate between a light increase and a light decrease of risk.

- Epidemiologic reports are very heterogeneous because of different study designs, methods of execution, and different populations. Their results cannot be justifiably consolidated by meta-analysis.
- Even if inappropriate meta-analysis is performed, summary risks for different groups are inconsistent. They may suggest a slight elevation for spousal exposures, no elevation for occupational exposures, and a slight reduction of risk for the longest exposures that include childhood exposures.

The points above are not a matter of opinion but of fact, and preclude a science-based conclusion about whether ETS is a human lung or nasal sinus carcinogen. Thus the listing of ETS in the 9th RoC could only be based on criteria other than scientific, and therefore contrary to the NTP mission statement.

The nature of ETS

Mainstream smoke (MS) that smokers inhale contains upward of 4000 known components, while only about 100 components have been measured in the more diluted sidestream smoke (SS) that is generated from a lit cigarette while it is not puffed. ETS derives mainly from the dilution of SS as it is dispersed and ages, with added minor contribution from residues of MS that might be exhaled by smokers.

Because of the extreme dilution, only some two dozen ETS components have been identified directly in real-life settings, although a few more might have been detected under controlled laboratory conditions (USEPA, 1992b, p. 3-10). EPA displays ambiguity about this issue, because at times it affirms that ETS *"is a complex mixture of over 4,000 chemicals found in both vapor and particle phases."* (USEPA, 1992b, p 3-15), and at others it recognizes the dearth of analytical data on ETS and ends up concluding that *"[t]he rapid dilution of both [sidestream smoke] and [mainstream smoke] into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions."* (USEPA, 1992b, p. 4-29).

In reality, most components of real-life ETS are far below the sensitivity of current analytical capabilities and cannot be detected (Guerin et al, 1987; Baker and Proctor, 1990). Nominally, ETS and mainstream smoke may share some components, but most of their chemical and physical differences are factually unknown and most likely sub-

stantial. Moreover, even if it were hypothesized that mainstream smoke components end up in ETS, their conjectured concentrations would be several order of magnitude below PEL and TWA levels that are officially permitted in workplaces (Gori and Mantel, 1991).

Measuring ETS exposures relative to active smoking

Major limitations of epidemiologic studies on ETS have been the unreliable estimates of the extent of exposure -- uncertainties that are compounded by the problems in recalling the cumulation of intensity, frequency, and duration of exposures over individual lifetimes, especially when the actual information is obtained from next of kin proxies when the subjects are deceased.

Even a simple dual classification of exposed and non-exposed subjects presents recognized uncertainties, such as those deriving from the misclassification of some smokers as non-smokers (USEPA, 1992b; Lee, 1992, 1993). On grounds that are problematic but comparatively more solid, a range of probable exposures to ETS can be inferred from physical and chemical derivations. These inferences also are insufficient to determine or validate individual cumulative exposures, but raise compelling doubts about the reliability and meaning of epidemiologic estimates.

On the basis of extrapolations from side-stream and mainstream smoke data, the National Academy of Sciences calculated that for nicotine alone the difference in peak inhalation concentrations between smokers and ETS exposed non-smokers should vary between 57,000 and 7,000,000 fold (NAS, 1986). However, dose estimates based on body fluid concentrations of nicotine or cotinine yield much lower differences, but they were found to depend on environmental and pharmacokinetic assumptions of unlikely validity because nicotine adsorbs and desorbs from curtains, carpets, clothing, and the like, even in the absence of ETS. Nicotine may also be ingested from certain vegetables, and is eliminated from the body at progressively slower rates as its blood concentration declines (USEPA, 1992b, at 3.3.1.1; Domino, 1993, Benowitz et al. 1991; Collier et al., 1992; Van Loy et al., 1997, 1998). Thus, nicotine and cotinine cannot be reliable quantitative markers of ETS exposure.

Still, respirable suspended particles (RSP) are the most material component of ETS that can be collected and approximately weighted. Methods have been devised to separate particles that may derive from ETS and from other sources, and EPA itself noted in its report that prevailing concentrations of ETS-RSP are below 50 $\mu\text{g}/\text{m}^3$ in households

with smokers, the environments studied in the epidemiologic studies that the agency has considered in assessing ETS (USEPA, 1992b, p.3-34). More recent and more refined measurements that utilized personally worn collectors of particulates under real life conditions suggest that the average concentration of ETS particulates is probably less than 20 $\mu\text{g}/\text{m}^3$, especially for home exposures. (Gori and Mantel, 1991; Samet, 1992; Steenland, 1992; Haevner et al., 1996; Jenkins at al., 1996; Sterling et al., 1996; Ogden et al., 1997; Phillips et al, 1994 to 1998).

Because ETS particles are some 100 times smaller that MS particles, the EPA itself recognizes that only about 10% of inhaled ETS particles may be retained by non-smokers, compared to nearly 90% for mainstream smoke particles in active smokers (USEPA, 1992b). Table 1 shows that the prevalent dose of ETS particles is minuscule. Although difficult to define, Table 1 shows it could be easily 100,000 times smaller than the dose of active smokers. For the average ETS-exposed individual, this estimate translates into a dose equivalent to less than the active smoking of 1 cigarette evenly dispersed over the period of 1 year -- a conclusion confirmed by more recent studies that employed more precise techniques and different methodologies (Haevner et al., 1996; Jenkins at al., 1996; Sterling et al, 1966; Ogden et al., 1997; Phillips et al., 1994 to 1998).

Table 1. Relative dose estimate of respirable suspended particles (RSP) in typical active smokers and ETS exposed non-smokers.

ACTIVE SMOKER	30 cigarettes per day (*) 15 mg RSP inhaled per cigarette 90% lung retention efficiency (*) DAILY DOSE about 400 mg
ETS EXPOSED NON-SMOKER	0.05 mg RSP/cubic meter of air (*) 1.5 hours per day exposure (**) 0.7 cubic meters per hour inhaled (*) 10% lung retention efficiency (*) DAILY DOSE about 0.00525 mg

CRUDE DOSE RATIO 0.00525 : 400 about 1 : 75,000

Lung surface permeability some 3 times greater in smokers (***)
Lung clearance some 3 times more efficient in smokers (***)
ETS dose distributed over greater surface deeper in lungs (***)

PLAUSIBLE DOSE RATIO AT TARGET TISSUE < 1 : 500,000

(*) USEPA, 1992b.

(**) USOSHA, 1994; Emmons et al., 1992.

(***) Gori and Mantel, 1991.

Such low level of ETS exposure should be considered against the epidemiologic evidence that smoking 3-4 cigarettes par day may not significantly increase the risk of smokers over that of nonsmokers. Indeed, no observable effect levels (NOAEL) for lung cancer in active smokers emerge from all available epidemiologic studies and are reported in Table 2, where the values represent the upper limits of the 95% confidence interval wehere the risk estimate ceases to be significant, according to standard practice in regulatory risk assessment (Gori, 1976; Gori and Mantel, 1991).

To appreciate this argument one should keep in mind that the epidemiology and pathogenesis of lung cancer suggests that smoking acts as a promoter rather than as a

direct carcinogen, and that and promoters are universally regarded as being effective only above certain dose thresholds. Moreover, no-effect observations at comparatively high doses are also routinely reported in experimental animal exposures to whole smoke or its fractions. (Doll, 1978; Doll and Peto, 1978; Klawansky and Fox, 1984; Altshuler, 1989; Albert, 1989).

Table 2. Maximum levels of daily cigarette consumption at which lung cancer risk in male smokers may not be significantly increased from the risk of non-smokers (from Gori and Mantel, 1991).

Reference	Max. Cigarettes/day
British Doctors*	6.3
Swedish Men**	3.9
ACS 9 States***	5.4
ACS 25 States**	0.9
US Veterans***	0.6
Canadian Veterans***	1.6
Japanese Men**	3.1
California Men***	7.0

* Doll and Peto, 1978

** USSG, 1979. page 5-13 table 2.

*** USSG, 1982. page 38 table 6.

The presence of NOAELs for active smoking should have a disposing relevance in the evaluation of claimed ETS risks, to which one should add the evidence that moderate pipe and cigar smoking are not associated with increased risks of lung cancer (USSG, 1964). In this light, prevalent ETS exposures equivalent to less than the active smoking of one cigarette per year are thousands of times below exposures that result in no significant health risks for active smokers.

Epidemiologic reports of ETS and lung cancer

In its ETS risk assessment, EPA relied on epidemiologic studies that compare the incidence of lung cancer in groups of people exposed or unexposed to ETS. Such studies raise many problems because without some reliable measure of exposure, and without ascertaining reasonably well the confounding roles of other causes of lung cancer and of several biases, it may not be possible to reach conclusions about the role of ETS, if any.

These problems do not plague epidemiologic studies of infectious diseases that could not exist without specific bacteria, viruses, and parasites, and that have been spectacularly successful precisely because single and absolutely necessary causes could be identified and controlled. Still, this is usually not the case for the study of conditions that depend on a multitude of risk factors, none of which seems to be a necessary cause.

In the following pages it will become apparent that the assessment and analysis of the possible role of other confounding factors are practically impossible in the case of ETS studies, the upshot being that these studies cannot be executed according to the scientific method. The problem is common to the study of most multifactorial diseases, to the point that Richard Doll, the prominent antismoking epidemiologist, recognized that such "*[e]pidemiological observations...have serious disadvantages... [T]hey can seldom be made according to the strict requirements of experimental science and therefore may be open to a variety of interpretations. A particular factor may be associated with some disease merely because of its association with some other factor that causes the disease, or the association may be an artifact due to some systematic bias in the information collection*". Doll continued to say that "*[i]t is commonly, but mistakenly, supposed that multiple regression, logistic regression, or various forms of standardization can routinely be used to answer the question: 'Is the correlation of exposure (E) with disease (D) due merely to a common correlation of both with some confounding factor (or factors) (C)?... Moreover, it is obvious that multiple regression cannot correct for important variables that have not been recorded at all.*" Doll concluded that "*[t]hese disadvantages limit the value of observations in humans, but...until we know exactly how cancer is caused and how some factors are able to modify the effects of others, the need to observe imaginatively what actually happens to various different categories of people will remain.*" (Doll and Peto, 1981, page 1218). It should be noted that the key word of the closing phrase is "*imaginatively*", which tells of the inevitable subjectivity in interpreting reports of multifactorial epidemiology -- reports that can only raise conjectures subject to multiple and often contrasting interpretations.

Although multifactorial epidemiology could seldom aspire to be a science, its warnings could be more tenable in proportion to its efforts to approximate a truly scientific test: that is if it made a demonstrable effort to account for as many risk factors as are known, to provide a convincing quantitative measure of exposures, to adopt experimental designs that credibly control for biases, statistical procedures directed at uncovering uncertainties rather than at creating a deceptive impression of precision, and a range of interpretations that covered all possible directions that a final analysis of the data might suggest (Gori, 1998a,b).

At first blush these should be the core discriminants of the quality of epidemiologic reports that are to inform public health policy decisions. Instead, epidemiologists have opted for a set of vague guidelines advanced first in the Surgeon General's report on smoking and later formalized by Hill (USSG, 1964; Hill, 1965) They are the now the familiar considerations of strength, consistency, specificity, temporality, response gradient, plausibility, coherence, analogy, experimental evidence, and so forth. In reality, however, none of these criteria addresses the core issues of biases and confounders as obstacles to causal inference, which has prompted some epidemiologists to warn that relative risk values less than a range from 2 to 5, depending on study complexity, could not be used even to infer hypotheses of causality (Breslow and Day, 1980; Rothman, 1982; Wynder, 1987,1990).

None of the ETS studies comes even close to meeting the precarious causality criteria listed above, a problem that has prompted regulators to invent still more elastic ways to enable unjustifiable inferences of causality. This is the "weight of evidence" approach that EPA and CEPA profess to have adopted in compiling their ETS reports (NAS, 1993; USEPA, 1992b; CEPA, 1997). In theory, this approach entails a loose integration of all pros and cons of a situation, but not EPA's selective choice of data supportive of preconceived objectives.

A cornerstone of EPA's and CEPA's weight of evidence approach has been the use of the meta-analysis procedure in consolidating various epidemiologic reports into a single risk estimate. In reality the use of this procedure is not permissible because meta-analysis can only be properly applied to studies that are highly homogeneous in design, method of conduct, subject characteristics, and data handling, according to guidelines endorsed by the National Cancer Institute and other groups (Blair et al., 1995; Shapiro, 1997,1998). In fact, the editors of the Journal of the National Cancer Institute warned that "[b]iased studies entered into a meta-analysis produce biased results." (Weed and Kramer, 1997). Unfortunately, in 1992 the weight of evidence approach did not have the clearly articulated guidelines that ironically were recently spelled out by EPA in its 1996 proposed guidelines for risk assessment. There, the agency states that in weight of evidence judgments the "[e]xistence of temporal relationships, consistent results in independent studies, strong associations, reliable exposure data, presence of dose-related responses, freedom from biases and confounding factors, and high level of statistical significance are among the factors leading to increased confidence in a conclusion of causality." (USEPA, 1996).

These official requirements now on EPA's books would have precluded the 1992 EPA's, and the 1997 CEPA's conclusions on ETS and lung cancer -- preconceived conclusions

that could only be arrived at through a weight of evidence approach woefully open to all sort of assumptions and selectivity.

The ETS risk assessment by the Environmental Protection Agency

In an ETS survey people may be asked whether they are smokers or not and their answers are assumed to be correct, usually without checking for sure. Epidemiologists may rely on vague distant memories of the extent of exposure to ETS, without checking whether people were also touched by other conditions that seem linked causally with lung cancer: such as a family history of disease, hazardous occupations, poor diets, weight problems, unhealthy homes, lack of exercise and the like. Further, the reliability of answers is often complicated when they are obtained from vague recollections of the next of kin of deceased study subjects. All considered, it is inescapable to conclude that epidemiologists collect and measure some information but cannot warrant to have measured what they say to have measured, a situation that is absolutely incompatible with a scientific interest in objectivity.

The extent of measurement uncertainties that plague epidemiologic reports of passive smoking and lung cancer will be immediately evident in the tables that follow, listing the studies available to EPA in 1992. As a first example of the agency's selectivity, three sets of data were available in 1992: one dealing with nonsmoking wives exposed to the ETS of their smoking husbands (known as spousal studies), one dealing with ETS exposures in workplaces (workplace studies), and one dealing with ETS exposures in childhood (childhood studies). The last two sets did not show an overall elevation of risk and were ignored by EPA on the specious grounds that ETS exposure in these groups could not be well measured, while the agency selected the spousal studies with equally groundless justification that exposure in these studies was adequately measured.

Table 3 lists the spousal studies utilized by EPA in 1992. The range of values in the last column shows the irregular 90% confidence interval adopted by EPA to produce the misleading impression of a nonexistent precision, even though the agency requires 95% statistics in all its official transactions. Table 3 shows that 10 of the 11 studies are still not significant at the 90% level, when all would have been not significant at the 95% level.

Table 3. Passive smoking and lung cancer in neversmoking US females married to smokers.

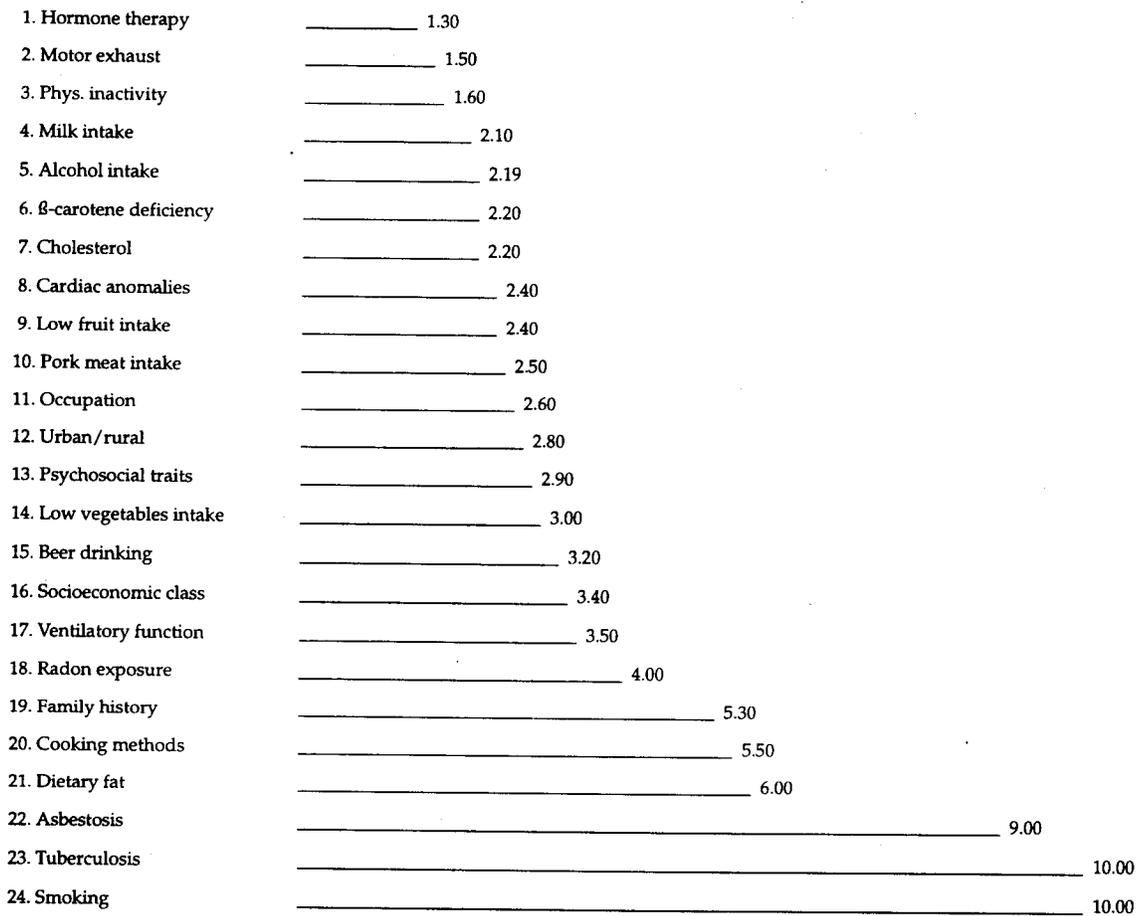
AUTHOR	YEAR PUBLISHED	CANCERS CASES	RELATIVE RISK & 90% CONFIDENCE INTERVAL	
Brownson	1987	19	1.52	0.49-4.79
Buffler	1984	41	0.81	0.39-1.66
Butler	1988	8	2.02	0.48-8.56
Correa	1983	22	2.07	0.94-4.52
Fontham	1991	420	1.29	1.03-1.62
Garfinkel 1	1981	153	1.17	0.85-1.61
Garfinkel 2	1985	134	1.31	0.93-1.85
Humble	1987	20	2.20	0.90-5.50
Janerich	1990	191	0.86	0.57-1.29
Kabat 1	1984	24	0.79	0.30-2.04
Wu	1985	29	1.41	0.63-3.15

(Data from USEPA, 1992b, Table 5-5)

The EPA dismissed the need of checking and adjusting for confounders.

The absence of statistical significance is only one of the uncertainties plaguing these studies, but there is more. In assessing the possible role of ETS it is necessary to find out whether other reported risk factors for lung cancer might be present to confound the situation and to impute to passive smoking a role it doesn't have. Figure 1 summarizes and ranks the major risk factors reported in the literature as being associated with lung cancer.

Figure 1. Rank order of reported lung cancer risk factors.



Adapted from Gori and Mantel, 1991

From a stance that is both scientific and common sense, to inquire about the actual causal significance of any one of these factors requires to know what the individual significance of all others might be -- a task that in practice cannot be carried out without confusion. That is why these factors are confounders in epidemiologic studies of smoking and lung cancer. Doll again had to admit that "...[active] smoking seems to act synergistically with other aetiological agents such as consumption of alcohol; various aspects of the diet; levels of blood pressure, blood lipids, or other cardiovascular risk factors; or exposure to asbestos, radon, or possibly some infective factors. The quantitative effect of smoking will, therefore, vary with variation in the prevalence of these other factors." (Doll et al., 1994). What Doll did not say is that the

prevalence of those other factors is not known, nor could it be known without first understanding the quantitative significance of smoking.

Clearly, then, if the quantitative assessment of the effects of active smoking requires an accurate account of confounders, such an account is even more necessary when investigating the possible effects of ETS that would have to be very much weaker. Therefore, the strength of the lung cancer risks listed in Figure 1 makes it imperative that their potential influence be carefully investigated. It is clear that even a slight imbalance of their prevalence between exposed and non-exposed subjects could invalidate a risk assessment for passive smoking. Such imbalances are in fact certain, because several studies have shown that smokers in general display lifestyles that include peculiar risk factors other than smoking: for instance they may exercise less, consume more alcohol, have less healthy diets, more hazardous occupations, lower incomes and education, and so forth. Moreover, studies have ascertained that the less healthy habits and risks of smokers eventually extend to non-smoking members of a household and to nonsmoking wives in particular (Gori and Mantel, 1991; Le Marchand, 1991; Margetts and Jackson, 1993; Cress et al., 1994; Lee and Fry, 1994; Emmons, 1995; Thornton et al., 1994). With this in mind, it is no surprise that apparent risks for ETS exposure have been noted only in non-smoking wives of smokers.

Therefore, the slight apparent attributions of risk to ETS could easily disappear after cumulative correction for other risk factors known to cluster in smoking households. In reality, however, the studies listed in Table 3 -- and utilized by EPA for its risk assessment of ETS -- have checked the possible influence of confounders not at all or in the most perfunctory way, as Table 4 taken directly from the EPA report indicates.

Table 4. Control of possible confounders in studies of passive smoking and lung cancer risk in never-smoking US females married to smokers.

AUTHOR	YEAR	ADJUSTED RISK FACTORS
Brownson	1987	Occupation, Socioeconomic status
Buffler	1984	none
Butler	1988	none
Correa	1983	Smoking
Fontham	1991	Urban/rural living, Socioeconomic status
Garfinkel 1	1981	Occupation, Socioeconomic status
Garfinkel 2	1985	Socioeconomic status
Humble	1987	none
Janerich	1990	Urban/rural living
Kabat 1	1984	none
Wu	1985	Urban/rural living

(Data from USEPA, 1992b, Table 5-6)

Despite the very sparse and unsatisfactory attention to potential confounders in the US spousal studies, the EPA report came to the surprising conclusion that no confounding factor "...explains the association between lung cancer and ETS exposure..." (USEPA, 1992b, at 5.4.8). This arbitrary and wholly inadequate conclusion is typical of the one-sided gambits the agency displays over and over in dismissing or trivializing crucial difficulties that are in its way. Another example is how the agency disposed of the obstacles posed by differential biases.

The EPA trivialized the likely influence of differential biases.

One undisputed but difficult to measure bias is the publication bias, whereby studies reporting risk have a better chance of being published in epidemiologic journals (Easterbrook, 1991; Blair, 1995; Saracci, 1995; Lee, 1992; Givens, 1997; Armitage, 1997). As early as 1975, Greenwald found that some 6% of researchers were inclined to submit negative results, against 60% that would do so with positive ones (Greenwald, 1975) The potential effect of this bias were essentially ignored by EPA.

The other major obstacle is presented by what is known as the misclassification bias, and refers to the well known observation that if even a small proportion of study subjects with lung cancer had been smokers but falsely declared to be and to have been nonsmokers, then exposure to ETS could erroneously show as a lung cancer risk. The EPA report freely recognizes that "*[t]here is ample evidence that some percentage of smokers...misrepresent themselves as never-smokers...*" (USEPA, 1992b, at 5.2.2), and Table 5 lists examples of the extent of this misclassification, as measured in a sample of various studies not considered by EPA.

Table 5. Misclassification in self-reported nonsmokers

Author	%	Author	%
Ohlin, 1976	12 - 32	Hatziandreu, 1989	28
Vogt, 1977	> 15	Klesges, 1992	4.2
Sillett, 1978	22 - 40	Wagenknecht, 1992	4.2
Cohen, 1980	7 - 19	Perez-Stable, 1992	6.3
Jarvis, 1987	19	Brownson, 1993	6 - 16
Stookey, 1987	25 - 55	Delfino, 1993	> 5
Coultas, 1988	7 - 10	Murray, 1993	6

The US spousal studies utilized by EPA did not collect information that could estimate the extent of misclassification, an omission that in itself should be fatal in precluding the possibility of any conclusions as to the role of ETS in lung cancer -- especially in view of the substantial reports of misclassification from other studies listed in Table 5. The obstacle was again overcome in typical EPA fashion, under cover of an elaborate procedure that pretended to guesstimate a misclassification index for each of the studies involved, on the basis of arbitrary assumptions -- a procedure that predictably ended up trivializing the probable impact of misclassification by ending up with an overall misclassification index of 1.09 (USEPA, 1992b, at 5.2.2).

EPA "cherry-picked" studies, arbitrarily ranked their importance, and relaxed statistical standards to reach preconceived objectives.

EPA also gave different weight to different studies according to arbitrary tiers of utility, affirming that "*..[s]tudy utility does not mean study quality. Utility is evaluated with respect to the research objectives of this report.*" (USEPA, 1992b, p.5-14). Elsewhere, the objectives of the EPA report are clarified as being "*...based on the a priori hypothesis that a positive association exists between exposure to ETS and lung cancer.*" (USEPA, 1992b, p.5-2). In other words, the objective of the report was to prove the agency right when it affirmed that ETS causes lung cancer, an objective that EPA also secured by assigning better weights to the studies favorable to its intent.

As note before, studies of workplace ETS exposures also were available in 1992 and did not show an elevation of lung cancer risk, and many studies of childhood ETS exposures and lung cancer even indicated a pattern of *reduced* lung cancer risk, but were ignored by EPA. Here again, it may be interesting to dwell on the 2 latest studies available to but not considered by EPA in 1992 (Stockwell et al., 1992; Brownson et al., 1992), and the single study that EPA considers of the highest significance (Fontham et al., 1991). The Brownson study shows no risk elevation for spousal exposures while the abstract states that the study results justify smoking restrictions in work places. Yet, the study itself shows a reduction of risk for workplace exposures, a finding shared with the Stockwell study but opposed by the Fontham study. Brownson and Fontham -- but not Stockwell -- agree that childhood exposures to ETS may *reduce* lung cancer risk, but all studies are discordant on diagnostic histopathology results. The Stockwell study

reports elevated risk if cancer patients were interviewed directly, but a *reduction* of risk if next of kin relatives were interviewed. Indeed, the studies register a long list of internal contradictions that extend to all available studies, signifying that the selection of a single high risk value representative of each study is, without doubt, an arbitrary exercise.

EPA concluded its risk assessment with an improper meta-analysis, and reached a misleading estimate of casualties.

Even allowing for statistical improprieties, 3 of the studies listed in Table 3 imply a protective effect of ETS but are not statistically significant, and 8 studies imply an elevation of risk but are also not statistically significant with one barely marginal exception. From a scientific point of view the only tenable conclusion is that no conclusion is possible, but EPA was determined to have its way and resorted to a final piece of trickery known as meta-analysis, to condense in a single risk value the results of the spousal studies available. The procedure has legitimate origins in the consolidation of data from studies that have been planned and conducted according to common study design, selection of participants, data collection and processing methods, such as might be the case for a group of clinical trials. However, the procedure is not legitimate when applied to diverse studies that lack homogeneity, where it would be equivalent to the familiar and illegitimate comparison of apples and oranges (Shapiro, 1998; Blair et al., 1994). Among other differences, the US spousal studies differ for geographic location, time of execution, provenance and selection of cases and controls, matching of controls, questionnaire format and content, direct and proxy sources of information, diagnostic procedures, methods of adjustment and data handling. Besides, most studies report more than one risk calculation depending on different segmentations of the data, whereby the choice of a single high risk value as representative of a given study is in itself an arbitrary decision, as the EPA itself openly admits (USEPA, 1992b, at 5.2.1).

In a terminal show of abuse, EPA introduced an upward "correction" of ETS risk based on its *a priori* assertion that ETS must be a lung cancer risk. It argued that the non-exposed control groups would also be exposed to some presumably ubiquitous level of ETS, thus requiring an upward correction. It did so on the basis of a convoluted fabrication, and conveniently ignored that the entire argument is voided by the absence of overall risk elevation in workplace and childhood studies, whose subjects are unquestionably exposed to ETS.

In the end, it should be obvious that the accumulation of uncertainties and arbitrary assumptions can only qualify the EPA report on ETS as the ultimate exercise in selective wishful thinking. To top it all, the agency adopted further assumptions and announced with implausible precision that ETS is responsible for 3060 lung cancer cases a year in the US alone -- a figure that has been amplified by advocacy and regulatory interests to justify a worldwide social engineering crusade of intolerance that has few parallels in human history.

The agency proceeded on its course even though internal reviewers from EPA's own Cincinnati laboratories were highly critical of the agency's approach and conclusions (USEPA, 1992c). EPA's Science Advisory Board itself -- the highest ranking advisory committee to the agency -- advised the Agency against producing numerical estimates (Stolwijk, 1993), and Dr. Erich Bretthauer, Associate Administrator for R&D at EPA in 1992, had to admit in official correspondence that the excess risk of lung cancer could be virtually zero (Bretthauer, 1992). Also, two assessments by the Congressional Research Service of the Library of Congress reached equally critical conclusions (Gravelle and Zimmermann, 1994; Redhead and Rowberg, 1995).

Epidemiologic studies published after 1992 do not sustain the claim that ETS poses a lung cancer risk in nonsmokers.

ETS studies published after the 1992 EPA report on ETS further reinforce the conclusion that EPA's and later CEPA's claims about ETS are based on unwarranted assumptions, selective use of data, procedural manipulations, and the contrived illusion of numerical precision.

Studies of spousal ETS exposures and lung cancer published since the 1992 EPA report have yielded consistently equivocal results, while studies of lung cancer and ETS exposure in childhood or in the workplace -- while also equivocal -- continue to suggest the possibility of an overall *reduction* of risk. ETS and lung cancer studies available in mid 1998 are listed in Tables 6, 7, and 8, with normal 95% confidence intervals. It is clear from these tables that the absence of statistical significance continues to be prevalent.

TABLE 6. Epidemiological studies of lung cancer among nonsmokers married to smokers.

Author	Year	Location	Sex	Number of lung cancers	Relative risk & 95% confidence intervals
Garfinkel 1	1981	USA	F	153	1.18 (0.90-1.54)
Chan	1982	Hong Kong	F	84	0.75 (0.43-1.30)
Correa	1983	USA	F M	22 8	2.07 (0.81-5.25) 1.97 (0.38-10.32)
Trichopoulos	1983	Greece	F	77	2.08 (1.20-3.59)
Buffler	1984	USA	F M	41 11	0.80 (0.34-1.90) 0.51 (0.14-1.79)
Hirayama	1984	Japan	F M	200 64	1.45 (1.02-2.08) 2.25 (1.19-4.22)
Kabat 1	1984	USA	F M	24 12	0.79 (0.25-2.45) 1.00 (0.20-5.07)
Garfinkel 2	1985	USA	F	134	1.23 (0.81-1.87)
Lam W	1985	Hong Kong	F	60	2.01 (1.09-3.72)
Wu	1985	USA	F	29	1.20 (0.50-3.30)
Akiba	1986	Japan	F M	94 19	1.50 (0.90-2.80) 1.80 (0.40-7.00)
Lee	1986	UK	F M	32 15	1.00 (0.37-2.71) 1.30 (0.38-4.39)
Brownson 1	1987	USA	F	19	1.68 (0.39-6.90)

Table 6. Continued.

Author	Year	Location	Sex	Number of lung cancers	Relative risk & 95% confidence intervals
Gao	1987	China	F	246	1.19 (0.82-1.73)
Humble	1987	USA	F	20	2.20 (0.80-6.60)
			M	8	4.82 (0.63-36.56)
Koo	1987	Hong Kong	F	86	1.64 (0.87-3.09)
Lam T	1987	Hong Kong	F	199	1.65 (1.16-2.35)
Pershagen	1987	Sweden	F	70	1.20 (0.70-2.10)
Butler	1988	USA	F	8	2.02 (0.48-8.56)
Geng	1988	China	F	54	2.16 (1.08-4.29)
Inoue	1988	Japan	F	22	2.25 (0.80-8.80)
Shimizu	1988	Japan	F	90	1.08 (0.64-1.82)
Choi	1989	Korea	F	75	1.63 (0.92-2.87)
			M	13	2.73 (0.49-15.21)
Hole	1989	Scotland	F	6	1.89 (0.22-16.12)
			M	3	3.52 (0.32-38.65)
Svensson	1989	Sweden	F	34	1.26 (0.57-2.81)
Janerich	1990	USA	F	144	0.75 (0.47-1.20)
			M	44	0.75 (0.31-1.78)
Kalandidi	1990	Greece	F	90	2.11 (1.09-4.08)

Table 6. Continued

Author	Year	Location	Sex	Number of lung cancers	Relative risk & 95% confidence intervals
Sobue	1990	Japan	F	144	1.13 (0.78-1.63)
Wu-Williams	1990	China	F	417	0.70 (0.60-0.90)
Liu Z	1991	China	F	54	0.77 (0.30-1.96)
Brownson 2	1992	USA	F	431	1.00 (0.80-1.20)
Stockwell	1992	USA	F	62	1.60 (0.80-3.00)
Liu Q	1993	China	F	38	1.66 (0.73-3.78)
Du	1993	China	F	75	1.09 (0.64-1.85)
Fontham	1994	USA	F	651	1.29 (1.04-1.60)
Layard	1994	USA	F	39	0.58 (0.30-1.13)
			M	21	1.47 (0.55-3.94)
Zaridze	1994	Russia	F	162	1.66 (1.12-2.46)
Kabat 2	1995	USA	F	67	1.08 (0.60-1.94)
			M	39	1.60 (0.67-3.82)
Schwartz	1996	USA	F	185	1.10 (0.72-1.68)
			M	72	1.10 (0.60-2.03)
Sun	1996	China	F	230	1.16 (0.80-1.69)
Wang SY	1996	China	F	82	2.53 (1.26-5.10)
Wang TJ	1996	China	F	135	1.11 (0.67-1.84)

Table 6. Continued

Author	Year	Location	Sex	Number of lung cancers	Relative risk & 95% confidence intervals
Cardenas	1997	USA	F	150	1.20 (0.80-1.60)
			M	97	1.10 (0.60-1.80)
Jöckel-BIPS	1997	Germany	F	53	1.58 (0.74-3.38)
			M	18	1.58 (0.52-4.81)
Jöckel-GSF	1997	Germany	F	242	0.93 (0.66-1.31)
			M	62	0.93 (0.52-1.67)
Ko	1997	Taiwan	F	105	1.30 (0.70-2.50)
Nyberg	1997a	Sweden	F	89	1.20 (0.74-1.94)
			M	35	1.20 (0.57-2.55)
Boffetta	1998	Europe	M&F	649	1.14 (0.88-1.47)
			F	508	1.15 (0.86-1.55)
		Sweden	M&F	70	2.29 (0.65-8.07)
		Germany1	M&F	76	0.88 (0.40-1.95)
		Germany2	M&F	142	1.22 (0.66-2.29)
		Germany3	M&F	31	2.01 (0.71-5.67)
		England	M&F	26	1.38 (0.43-4.28)
		France	M&F	77	0.72 (0.36-1.25)
		Portugal1	M&F	49	2.04 (0.71-5.80)
		Portugal2	M&F	33	2.03 (0.76-5.38)
		Spain	M&F	71	1.10 (0.48-2.68)
		Italy1	M&F	40	0.73 (0.28-1.65)
		Italy2	M&F	19	1.12 (0.35-3.56)
		Italy3	M&F	16	1.36 (0.30-6.45)

TABLE 7. Epidemiological studies of lung cancer among nonsmokers exposed to ETS in the workplace.

Author	Year	Location	Sex	Relative risk & 95% confidence intervals
Kabat 1	1984	USA	F M	0.68 (0.32-1.47) 3.27 (1.01-10.62)
Garfinkel 2	1985	USA	F	0.93 (0.55-1.55)
Wu	1985	USA	F	1.30 (0.50-3.30)
Lee	1986	UK	F M	0.63 (0.17-2.33) 1.61 (0.39-6.60)
Koo	1987	Hong Kong	F	1.19 (0.48-2.95)
Shimizu	1988	Japan	F	1.18 (0.70-2.01)
Janerich	1990	USA	F&M	0.91 (0.80-1.04)
Kalandidi	1990	Greece	F	1.70 (0.69-4.18)
Wu-Williams	1990	China	F	1.10 (0.90-1.60)
Brownson 2	1992	USA	F	0.79 (0.61-1.03)
Stockwell	1992	USA	F	not statistically significant
Fontham	1994	USA	F	1.39 (1.11-1.74)
Zaridze	1994	Russia	F	1.23 (0.74-2.06)
Kabat 2	1995	USA	F M	1.15 (0.62-2.13) 1.02 (0.50-2.09)

Table 7. Continued

Author	Year	Location	Sex	Relative risk & 95% confidence intervals
Schwartz	1996	USA	F&M	1.50 (1.00-2.20)
Sun	1996	China	F	1.38 (0.94-2.04)
Wang TJ	1996	China	F	0.89 (0.46-1.73)
Jöckel-BIPS	1997	Germany	F&M	2.37 (1.02-5.48)
Jöckel-GSF	1997	Germany	F&M	1.51 (0.95-2.40)
Ko	1997	Taiwan	F	1.10 (0.40-3.00)
Nyberg	1997a	Sweden	F&M	1.60 (0.90-2.90)
Boffetta	1998	Europe	M&F	1.17 (0.94-1.45)
			F	1.19 (0.94-1.51)

TABLE 8. Epidemiological studies of lung cancer among nonsmokers exposed to ETS in childhood.

Author	Year	Location	Sex	Relative risk & 95% confidence intervals
Correa	1983	USA	F	not statistically significant
Garfinkel 2	1985	USA	F	0.91 (0.74-1.12)
Wu	1985	USA	F	0.60 (0.20-1.70)
Akiba	1986	Japan	F&M	not statistically significant
Gao	1987	China	F	1.10 (0.70-1.70)
Koo	1987	Hong Kong	F	0.55 (0.17-1.77)
Pershagen	1987	Sweden	F	1.00 (0.40-2.30)
Svensson	1989	Sweden	F	3.30 (0.50-18.80)
Janerich	1990	USA	F&M	1.30 (0.85-2.00)
Sobue	1990	Japan	F	1.28 (0.71-2.31)
Wu-Williams	1990	China	F	0.85 (0.65-1.12)
Brownson 2	1992	USA	F	0.80 (0.60-1.10)
Stockwell	1992	USA	F	1.70 (1.00-2.90)
Fontham	1994	USA	F	0.89 (0.72-1.10)
Zaridze	1994	Russia	F	0.98 (0.66-1.45)
Kabat 2	1995	USA	F M	1.63 (0.91-2.92) 0.90 (0.43-1.89)

Table 8. Continued

Author	Year	Location	Sex	Relative risk & 95% confidence intervals
Sun	1996	China	F	2.29 (1.56-3.37)
Wang TJ	1996	China	F	0.91 (0.56-1.48)
Jöckel-BIPS	1997	Germany	F&M	1.05 (0.50-2.22)
Jöckel-GSF	1997	Germany	F&M	0.95 (0.64-1.40)
Ko	1997	Taiwan	F	0.80 (0.40-1.60)
Boffetta	1998	Europe	M&F F	0.78 (0.64-0.96) 0.77 (0.61-0.98)

Clearly, the many reports available in 1998 continue to show how much the epidemiologic message remains hopelessly garbled. Even if one were to use EPA's procedures that are improperly biased toward obtaining elevated risk, US spousal studies might still suggest a very slight meta-analysis elevation of risk below 0.1, but the meta-analysis of workplace and childhood exposures continue to suggest protection rather than risk elevation.

In the end, attributions of epidemiologic risk to ETS cannot be rationally sustained unless confounders and biases have been convincingly controlled, and adjustments have been transparently justified. Unfortunately, a satisfactory control of confounders and biases is beyond technical feasibility, and ETS epidemiologic studies in general do not hold sufficient promise as profitable investments of scarce research funds. Simply stated, epidemiologic studies are not sensitive and specific enough to justify ETS investigations. In final analysis and based on elementary scientific criteria, the weight of evidence does not challenge the null hypothesis about ETS and lung cancer.

Nasal sinus cancer

In regard to ETS and nasal sinus cancer, CEPA offers an astonishing interpretation of causality that bypasses not only minimal standards of scientific thinking, but also minimal requirements of rationality (CEPA, 1997). Of the studies considered, the Hirayama report on nonsmoking females partially adjusted only for the age and occupation of the smoking husbands and found an association of ETS exposure for nonsmoking wives of smokers, but reported no association for active smokers (Hirayama, 1983). Fukuda and Shibata (1990) also report a greater risk for household exposure of nonsmokers than for active smoking, and give remarkably little information on ETS exposure estimates and on the relationship of the index subjects to the smokers in the household.

Other studies offer equally intriguing dilemmas. Brinton et al. (1984) report a *protective* effect in cigar smokers (RR=0.72, 0.3-1.6 95% CI), while Zheng et al. (1993) report equally *protective* effects in active smokers of less than 15 cigarettes per day (OR= 0.6, 0.3-1.2 95% CI). Actually, the latter study strongly suggests a no-effect threshold for active smoking probably in the vicinity of 30 daily cigarettes actively smoked for over 25 years (Table 2 of the paper). Incidentally, a similar threshold was repeatedly observed for cancers of the oral cavity, pharynx and larynx by Wynder et al. (1957), Keller (1967), and Martinez (1969).

In regard to passive smoking, Zheng et al. (1993) report an incredible OR=3.0 (1.0-8.9 95%CI) with no dose trend for nonsmokers exposed to spousal smoking, versus an overall OR=1.2 (0.7-1.9 95%CI) for active smoking. Clearly, these extraordinary discrepancies and the observations of no effect thresholds for active smoking of cigars/cigarettes indicate massive confounding or reporting bias. Indeed, by all fair and logical reasoning, available studies about nasal sinus cancers sustain a null hypothesis for the active smoking of less than 15 cigarettes/day. For nonsmokers, therefore, the apparent risk of nasal sinus cancers attributed to ETS is most likely the result of uncontrolled confounders and biases, since nonsmokers are subject to doses that are orders of magnitude below threshold doses for active smokers, as noted in Table 1, and must also experience ETS exposures that are a fraction of ETS exposures for smokers.

ETS studies in animal models

The background document submitted to the RoC Subcommittee mentions several tests of tobacco smoke in animals that have no possible relevance to ETS (TPMC, 1998). The facts are that these assays have not tested ETS but combinations of mainstream (MS) and sidestream (SS) smoke at concentrations much too high to be representative of ETS. Moreover, most of the studies were conducted in A strain mice, whose incredible propensity to develop lung tumors makes them unsuitable for risk assessment. The NTP itself would not use these animals in its bioassay program, and the significance to ETS of these tests has been rejected by the UK Scientific Committee on Tobacco and Health, noting that "*...the recent inhalation study where a carcinogenic response was documented in strain A mice exposed to extremely high levels of SS reinforced with some MS was of very limited value and cannot be used to predict hazards to humans.*" (SCOTH, 1998, p.88).

Conclusion

Vast differences in exposure extent and duration, and evidence that actively smoking a few cigarettes daily seems to result in no adverse effects, both preclude inferences of ETS risks, unless we are prepared to forgo all we have learned since Paracelsus about the absence of harm or even the beneficial effects of low exposures to otherwise toxic agents. Indeed, any and all exposures could be harmful and even lethal at appropriate high doses.

Plausible ETS doses are many thousands of times less than doses that appear to have no adverse effect in active smokers, and experimental reports in man or animals do not contradict this observation, which is reinforced by the equivocations of epidemiologic studies. The latter are impotent in controlling for a multitude of confounders, are plagued by irresolvable biases, and for lung cancer are consistent with slightly increased or decreased risk, as to be expected when the actual risk might be null. The few reports of nasal sinus cancer and ETS are not credible at face value because they suggest lower risks for active smokers, who besides their own smoking are also exposed to ETS doses and durations that far exceed any nonsmoker exposure to ETS. Based on plain common sense or on scientific grounds, the weight of direct and indirect evidence does not sustain EPA's and CEPA's assertion that ETS is a cause of lung cancer in nonsmokers, nor CEPA's assertion that nonsmokers are at greater risk for nasal sinus cancer from ETS exposure.

The only tenable summation is that ETS risks are probably null or imponderable and beyond detection, and that a case against ETS as a human carcinogen cannot be made on defensible scientific grounds. Therefore, and in accord with the NTP mission statement and commitment to reliable science, there is no justification for listing ETS in the 9th Annual Report on Carcinogens.

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