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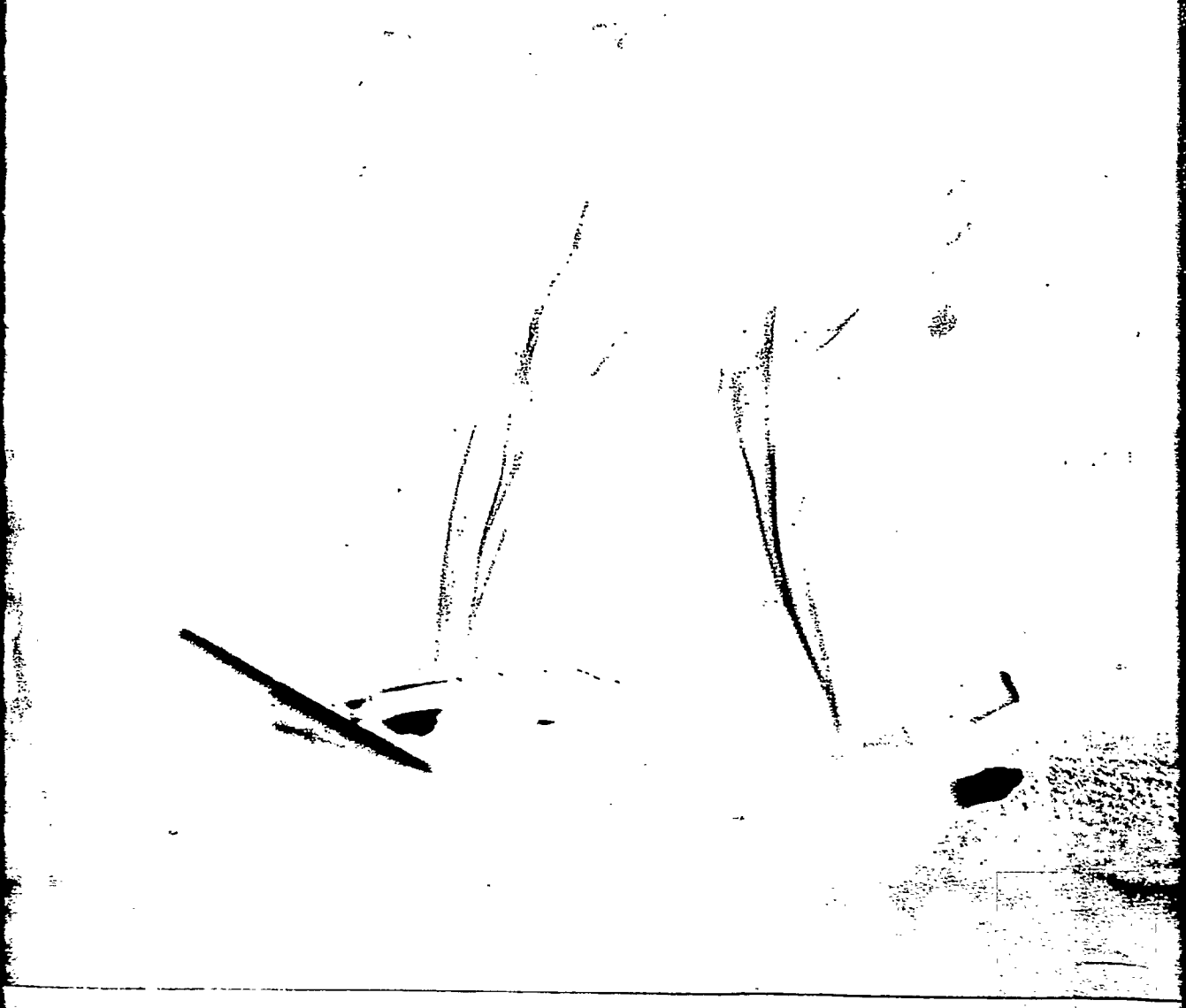

Special Report:

Passive Smoking: How Great A Hazard?

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Reports from medical journals, the popular media, and federal regulatory agencies about the adverse health effects of passive smoking have convinced many jurisdictions to ban smoking in public places. What is often missing from such discussions is the scientific basis for the health-related claims. The following article examines the scientific data concerning the ascertainable risk from inhalation of environmental tobacco smoke. One of its authors, Dr. Gary Huber, spoke at a recent CR *symposium on "Science and Regulation" (see article on page 35).*—Ed.

About 50 million or so Americans are active smokers, consuming well over 500 billion tobacco cigarettes each year. The "secondhand" smoke—usually called "environmental tobacco smoke," or more simply "ETS"—that is generated is released into their surroundings, where it potentially is inhaled passively and retained by nonsmokers. Or is it?

Literally thousands of ETS-related statements now have appeared in the lay press or in the scientific literature. Many of these have been published, and accepted as fact, without adequate critical questioning. Based on the belief that these publications are accurate, numerous public policies, regulations, and laws have been implemented to segregate or restrict active smokers, on the assertion that ETS is a health hazard to those who do not smoke.

What *quantity* of smoke really is released into the environment of the nonsmoker? What is the chemical and physical *quality,* or nature, of ETS remnants in our environment? Is there a health risk to the nonsmoker? In concentrations as low as one part in a billion or even in a trillion parts of clean air, some of the highly-diluted constituents in ETS are irritating to the membranes of the eyes and nose of the nonsmoker. Cigarette smoking is offensive to many nonsmokers and some of these highly-diluted constituents can trigger adverse emotional responses, but do these levels of exposure really represent a legitimate health hazard?

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Clear answers to these questions are difficult to find. The generation, interpretation, and use of scientific and medical information about ETS has been influenced, and probably distorted, by a "social movement" to shift the emphasis on the adverse health effects of smoking in the active smoker to an implied health risk for the nonsmoker. The focus of this movement, initiated by Sir George Godber of the World Health Organization 15 years ago, was and is to emphasize that active cigarette smokers injure those around them, including their families and, especially, any infants that might be exposed involuntarily to ETS.

By fostering the perception that secondhand smoke is unhealthy for nonsmokers, active smoking has become an undesirable and an antisocial behavior. The cigarette smoker has become ever more segregated and isolated. This ETS social movement has been successful in

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reducing tobacco cigarette consumption, perhaps more than other measures, including mandatory health warnings, advertising bans on radio and television, and innumerable other efforts instituted by public health and medical professional organizations. But, has the ETS social movement been based on scientific truth and on reproducible data and sound scientific principles?

At times, not surprisingly, the ETS social movement and scientific objectivity have been in conflict. To start with, much of the research on ETS has been shoddy and poorly conceived. Editorial boards of scientific journals have selectively accepted or excluded contributions not always on the basis of inherent scientific merit but, in part, because of these social pressures and that, in turn, has affected and biased the data that are available for further analyses by professional organizations and governmental agencies. In addition, "negative" studies, even if valid, usually are not published, especially if they involve tobacco smoke, and thus they do not become part of the whole body of literature ultimately available for analysis. Negative results on ETS and health can be found in the scientific literature, but only with great difficulty in that they are mentioned in passing as a secondary variable in a "positive" study reporting some other finding unrelated to ETS.

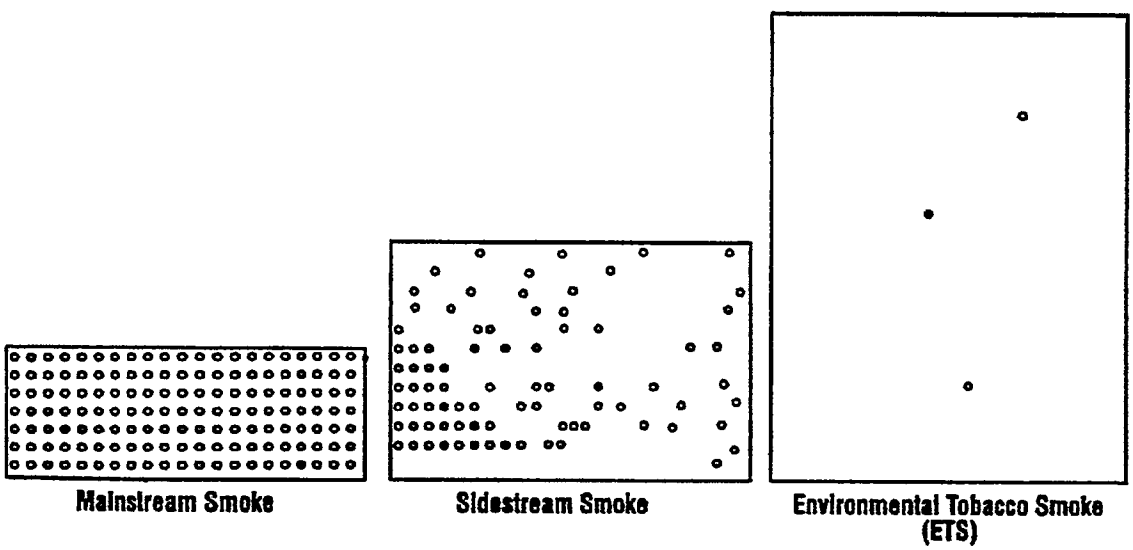
To evaluate critically any potential adverse health effects of ETS, it must first be appreciated that not all tobacco smoke is the same, and thus the risk for exposure to the different kinds of tobacco smoke must be considered independently.[1]

What Is ETS?

The three most important forms of tobacco smoke are depicted in Figure 1. *Mainstream smoke* is the tobacco smoke that is drawn through the butt end of a cigarette during active smoking; this is the tobacco smoke that the active smoker inhales into his or her lungs. The distribution of mainstream smoke is summarized in Table 1 (page 12). *Sidestream smoke* is the tobacco smoke that is released in the surrounding environment of the burning cigarette from its smoldering tip between active puffs. Many publications have treated sidestream smoke and ETS as if they were one and the same, but sidestream smoke and ETS are clearly not the same thing. Sidestream smoke and ETS have different physical properties and they

[1]A burning cigarette has been described as "a miniature chemical factory," producing numerous new components from its raw materials. When a cigarette is smoked, the burning cone has a temperature of about 860 to 900°C during active puffing, and smolders at 500 to 600°C between puffs. When tobacco burns at these temperatures, the products of pyrolyzation are all vapors. As the vapors cool in passage away from the burning cone, they condense into minute liquid droplets, initially about two ten-millionths of a meter in size. Generally, then, all forms of smoke are microaerosols of very small liquid droplets of particulate matter suspended in their surrounding vapors or gases. Thus, all smoke has a "particulate phase" and a "gas phase."

Figure 1: **Particulate Phase and Gas Phase of Tobacco Smoke***



* Schematic representation of the particulate phase and the gas phase of tobacco smoke. Environmental tobacco smoke is not smoke in the conventional sense, but rather a very limited number of highly-diluted remnants or residual constituents of mainstream smoke and sidestream smoke.

Table 1: Distribution of Mainstream Smoke

Total Mainstream Smoke	500*
Wet Total Particulate Matter	22
Nicotine	1.3
Water	3.7
"Tar"	17
Aerosol Gas Phase	
Water	478
Air Components	50
Carbon Monoxide	350
Carbon Dioxide	50
Other Components	8

*All data expressed in milligrams for a 500 mg deliver cigarette, as determined by Federal Trade Commission criteria.
SOURCE: Adapted from Huber, 1989.

have different chemical properties. *Environmental tobacco smoke* is usually defined as a combination of highly diluted sidestream smoke plus a smaller amount of that residual mainstream smoke that is exhaled and not retained by the active smoker. What *really* is ETS? In comparison to mainstream smoke and sidestream smoke, ETS is so highly diluted that it is not even appropriate to call it smoke, in the conventional sense. Indeed, the term "environmental tobacco smoke" is a misnomer.

Why is ETS a misnomer? Several reports on smoking and health from the Surgeon General's Office, a National Research Council review of ETS in 1986, the more recent Environmental Protection Agency's risk assessment of ETS, and several review articles all have provided a long list of chemical constituents derived from analyses of mainstream smoke and sidestream smoke, with the implication that because they are demonstrable in mainstream smoke and sidestream smoke these same constituents must, by inference, also be present in ETS. No one really knows if they are present or not. In fact, most are not so present or, if they are, they are present only in very dilute concentrations that are well below the level of detection by conventional technologies available today.

Only 14 of the 50 biologically active "probable constituents" of ETS listed by the Surgeon General, for instance, *actually* have been measured or demonstrated at any level in ETS. The others are there essentially by inference, not by actual detection or measurement. Thus, there are 36 constituents in these lists that are inferred to be present in ETS, but their presence has not been confirmed by actual detection or measurement. In this sense, then, ETS is really not smoke in the conventional sense of its definition, but rather consists of only a limited number of "remnants" or *residual constituents* present in highly dilute concentrations.

Because the levels of ETS cannot be quantified accurately as such in the environment, some investigators have attempted to measure one or more constituent parts of ETS as a "substitute marker" for ETS as a whole. The most frequently employed such "marker" has been nicotine or its first metabolically stable breakdown product, cotinine. Nicotine was considered an "ideal marker" because it is more or less unique to tobacco, although small amounts can be found in some tomatoes and in other food sources. In the mainstream tobacco smoke that is inhaled by the active smoker, nicotine starts out almost exclusively in the tiny liquid droplets of the particulate phase of the smoke. Because the smoke particles of ETS become so quickly and so highly diluted, however, nicotine very rapidly vaporizes from the liquid suspended particulates and enters the surrounding gas. In technical terms, the process by which nicotine leaves the suspended aerosol particle to enter the surrounding gas phase is called "denudation."

As a vapor or gas, nicotine reacts with or adsorbs onto almost everything in the environment with which it comes into contact. Thus, nicotine is not a representative or even a good surrogate marker for the particulate phase, or even the gas-vapor phase, of ETS. In fact, there are no reliable or established markers for ETS. The remnant or residual constituents of ETS each have their own chemical and physical behavior characteristics in the environment and none is present in a concentration in our environment that reaches an established threshold for toxicity.[2]

Measuring Health Risks

Because the level of exposure to ETS or the dose of ETS retained cannot be quantified under every-day, real-life conditions, the health effects following exposure to residual con-

[2]A *threshold limit value* (usually expressed as milligrams of a substance per cubic meter of air or as parts of a substance present per million parts of respirable clean air) is the recommended concentration of a substance as the maximal level that should not be exceeded to prevent occupational disease through exposure in the workplace. Threshold limit values have not been established for our general, every-day environment outside of industrial exposure. Threshold limit values are determined by toxicologists, epidemiologists, and hygienists through their interpretation of literature, and usually are sanctioned by the American Conference of Governmental Industrial Hygienists. No constituent of ETS has been measured in our every-day environment at levels that exceed the threshold limit values permitted in the workplace.

stituents of ETS have been impossible to evaluate directly. In broad terms, two different approaches have been employed in an attempt to assess indirectly the health risks for exposure of the nonsmoker to the environmental remnants of ETS. The first of these involves a theoretical concept that is called "linear risk extrapolation." Linear risk extrapolation has been employed extensively in attempts to determine the risk for lung cancer in nonsmokers exposed to ETS.[3]

This concept of linear risk assumes that if there is a definable health risk for the active smoker, then there also must be a projected lower health risk for the nonsmoker exposed to ETS. This is represented schematically in Figure 2. The risk has been presumed to be linear from the active smoker to the nonsmoker exposed to ETS, based proportionately on the relative exposure levels and retained doses of smoke; it thus requires some measurement of tobacco smoke exposure for both groups. This is fairly easy to achieve in the active smoker, in part because mainstream smoke has been so well-characterized and it is delivered directly from the butt-end of the cigarette into the smoker. Such is obviously not the case, however for the nonsmoker exposed to ETS.

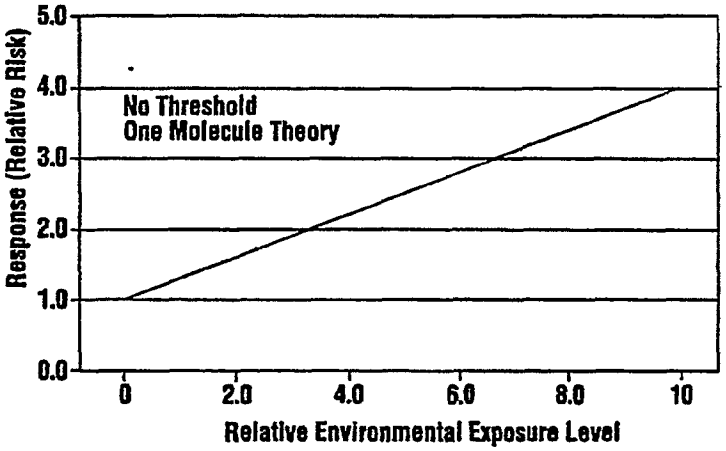
Most projections of linear risk for ETS-exposure have been based on the use of nicotine as a representative marker of exposure. A few projections have been based on carbon monoxide levels or amounts of respirable suspended particulates in the environment, but these approaches are fraught with even greater error. Since nicotine initially is in the particulate phase of the mainstream smoke inhaled by the active smoker and it is present primarily as a highly diluted gas-phase remnant or residual vapor-phase constituent in the nonsmoker's environment, the concept of a linear health risk from the active smoker to the nonsmoker is based on rather shaky scientific-reasoning.

That is to say, it is not valid to estimate a health risk for exposure to the particulate phase in the active smoker and then compare it with the health risk for exposures to the gas phase in the ETS-exposed nonsmoker. Simply stated, "like" is not being compared to "like." Mainstream smoke and the residual constituents of ETS represent very different exposure conditions. Whether present in mainstream smoke or in ETS, particulate phase and gas phase constituents have very different biological properties, as well as different physical and chemical characteristics, and any associated health risks are also very different. The concept of linear risk extrapolation for ETS is based on a theory that when applied to ETS incorporates unsound assumptions that are not valid. There is no way, as yet, to evaluate or compare the levels of exposure in active smokers and nonsmokers exposed to ETS.

The second approach used to evaluate health risks for nonsmokers exposed to ETS has employed epidemiologic studies. Epidemiology is a branch of medical science that studies the distribution of disease in human populations and the factors determining that distribution, chiefly by the use of statistics. The chief func-

[3]The concept is based on a theoretical extrapolation of the risk for lung cancer in the active smoker to the risk for lung cancer in the passive smoker on the basis of a "representative marker" for both smoke exposures. This "linear risk extrapolation" from one to the other is a model that is based on mathematical theory and on several assumptions. The theory assumes that the risk applies to all exposure levels, even if they are very low. Some advocates of the model even assume a "one molecule, one hit" mechanism, where exposures so low that they cannot be detected or measured can still cause disease if only a single molecule reaches a vulnerable body tissue. The linear risk theory also assumes that the risk for accumulative exposure remains constant and, thus, that the exposed individual has no capacity to adapt or develop tolerance mechanisms for the exposure. Since active smokers readily and rapidly develop tolerance through a variety of defense mechanisms, it seems illogical to assume those repeatedly exposed to ETS would not do the same. The linear risk model assumes that the risk for exposure to ETS is independent of any confounding factors. Finally, for this theory to be valid, it must be assumed that the risk is linear for duration of exposure and that it is linear for concentration of exposure. None of these assumptions holds true on scientific testing for comparative projections of mainstream smoke to ETS.

Figure 2: **Linear Risk Extrapolation***



*The concept of linear risk extrapolation. In this theory, the health response (expressed as a relative risk) is directly or linearly related to the relative environmental exposure level. This theory suggests that there is no "safe" threshold below which there is no response, and that exposure to as little as one molecule of the environmental substance can cause an adverse response.

"Of the 30 ETS-lung cancer studies, 6 reported a statistically significant association. . .and 24 of those studies reported no statistically significant effect."

tion of epidemiology is the identification of populations at high risk for a given disease, so that the cause may be identified and preventative measures implemented.

Epidemiologic studies are most effective when they can assess a well-defined risk. Because ETS-exposure levels cannot be measured or in any other way quantified directly, even by representative markers, epidemiologists have had to use indirect estimates, or surrogates, of ETS exposure. For nonsmoking adults, the number of active smokers that are present in the household has been used as a surrogate for ETS exposure. Usually the active smoking household member has been the nonsmoker's spouse. With a few limited exceptions, disease rates in nonsmokers exposed to a spouse who smokes have been the basis for all epidemiologic assessments.

Almost all of these studies have evaluated nonsmoking females married to a husband who smokes. For children, the surrogate for ETS exposure has been the number of parents in the household who smoke. Estimates of ETS exposure based on spousal or parental surrogates have been derived by various questionnaires; no study employs any direct quantification of ETS or of ETS remnant constituents in the actual environment of the nonsmoker. Questionnaires of smoking habits are notoriously limited and often inaccurate, in part because of the "social taboo" that smoking has become and, in part, for other reasons related to the ETS social movement. Nevertheless, data from questionnaires about smoking behavior in spouses or in parents are the only estimates of ETS exposure available. Rates for three diseases in nonsmokers exposed (via surrogates) to ETS have been assessed: lung cancer, coronary heart disease, and respiratory illness in infants and small children. Only lung cancer will be discussed in this article.

ETS and Lung Cancer

What is the state of evidence on ETS and lung cancer? Almost all of the epidemiologic studies that are available to answer that question are based on the concept of some measurement of relative risk. None of the studies actually has measured exposure to ETS or to any of its residual constituents directly. Relative risk is a relationship of the rate of the development of a disease (such as lung cancer) within a group of individuals exposed to some variable in the population studied (such as ETS) divided by the rate of the same disease in those not exposed to this variable.

Relative risk is most frequently expressed as a "risk ratio," which is a calculated comparison of the rate of the disease studied in the exposed population divided by the rate of that disease in some control population not exposed to the variable studied. The terms "risk ratio" and "relative risk" are often used synonymously. Thus, the relative risk in all epidemiologic ETS studies on lung cancer is expressed as the rate of lung cancer in the ETS-exposed group (individuals married to a household smoker) divided by the rate of lung cancer where there was no ETS exposure (no household smokers). If the disease rates were exactly the same in these two groups, the risk ratio would be 1.0.

There have been 30 epidemiologic studies on spousal smoking and lung cancer published in the scientific literature. Twenty-seven of these epidemiological studies were case control studies, where the effect of exposure to spousal smoking was evaluated retrospectively on data that had already been available for review. The "cases" in these case-control studies were nonsmoking individuals with lung cancer married to smokers. The rate of lung cancer in these "cases" was compared, by the derived risk ratio, to the rate of lung cancer in "control" or nonsmoking individuals who were married to nonsmokers.

Three of the studies followed cohort populations of individuals exposed to spousal smoking prospectively over the course of time. A "cohort" is any designated group of people. A "cohort study" identifies a group of people that will be exposed to a risk and a group that will not be exposed to that risk, and then follows these groups over time to compare the rate of disease development as a function of exposure or no exposure.

The first studies were published in 1982 and the last studies were published in 1990. The studies originate broadly from different parts of the world and, for the most part, involve evaluations of lung cancer in nonsmoking females married to a smoking male partner; eight of the studies have limited data on nonsmoking males married to smoking females. Some of the stud-

ies are quite small, listing fewer than 20 subjects; others are based on larger populations, with four studies reporting between 129 and 189 cancer cases. Of the 30 studies, six reported a statistically significant association (identified by a positive relative risk ratio in the spousally-exposed to the non-exposed population) and 24 of the studies reported no statistically significant effect. The average estimated relative risk ratio for each study and each sex is listed in Table 2, as are the confidence intervals reported by the authors or, where not reported, calculated by others in published review articles.[4]

Some of the negative studies—that is, some of the 24 studies that did not show a statistically significant association between the development of lung cancer and exposure to spousal smoking—contained data that suggested to the authors or to other reviewers a "positive trend." In most of science, "trends" do *not* count; data stand as either statistically significant or not statistically significant, with significance determined by specific accepted rules of biostatistics. New rules should not be "made to fit" an otherwise unproved hypotheses, just because the subject is tobacco and the observed results do not support the hypothesis investigated.

ETS Risk Weak

A relative risk is called strong or it is called weak, depending on the degree of association, or the magnitude of the risk ratio. A strong relative risk would be reflected by a risk ratio of 5 to 20 or greater. Weak relative risks, by conventional definition, have risk ratios in the range of 1 to 3 or so. Within the 30 epidemiologic studies on ETS and lung cancer, there are 37 different total reported sets of risk ratios for male or female nonsmokers. None of the studies reports a strong relative risk.

Nine of the studies report risk ratios of *less* than 1.0. Thus, the results from all epidemio-

(See SMOKE, page 33.)

[4]A confidence interval is a range of values that has a specified probability of including the true value (as opposed to the estimated average value) within that range. In the data presented in Table 2, the confidence intervals are set such that there is a 95% probability that the true value will fall within the range of values listed.

Table 2: Studies of ETS and Lung Cancer in Nonsmokers

Study	Sex	Number of Cases	Relative Risk*	95% Confidence Interval
Case Control Studies				
Chan and Fung, 1982	F	34	0.75	(0.43, 1.30)
Trichopoulos et al., 1983	F	38	2.13**	(1.18, 3.83)
Correa et al., 1983	F	14	2.07	(0.81, 5.26)
	M	2	1.97	(0.38, 10.29)
Kabat and Wynder, 1984	F	13	0.79	(0.25, 2.45)
	M	5	1.09	(0.20, 5.07)
Buffler et al., 1984	F	33	0.80	(0.34, 1.81)
	M	5	0.51	(0.15, 1.74)
Garfinkel et al., 1985	F	92	1.12	(0.94, 1.60)
Wu et al., 1985	F	29	1.20	(0.50, 3.30)
Akiba et al., 1986	F	73	1.52	(1.00, 2.5)
	M	3	2.10	(0.5, 5.6)
Lee et al., 1986	F	22	1.03	(0.37, 2.71)
	M	8	1.31	(0.38, 4.59)
Brownson et al., 1987	F	19	1.68	(0.39, 2.97)
Gao et al., 1987	F	189	1.19	(0.6, 1.4)
Humble et al., 1987	F	14	1.78	(0.6, 5.4)
Koo et al., 1987	F	51	1.55	(0.87, 3.09)
Lam et al., 1987	F	115	1.65**	(1.16, 2.35)
Pershagen et al.,1987	F	33	1.20	(0.70, 2.10)
Geng et al., 1988	F	34	2.16 **	(1.03, 4.53)
Inoue and Hirayama, 1988	F	18	2.55	(0.91, 7.10)
Katada et al., 1988	F	17	—	(NS;p=0.23)
Lam and Cheng, 1988	F	37	2.01**	(1.12, 1.83)
Shimizu et al., 1988	F	90	1.10	N/A
He, 1990	F	45	0.74	(0.32, 1.68)
Janerich et al., 1990	F	129	0.93	(0.55, 1.57)
Kabat, 1990	M	13	1.20	(0.54, 2.68)
	F	35	0.90	(0.46, 1.76)
Kalandidi et al., 1990	F	91	2.11	(1.09, 4.08)
Sobue et al., 1990	F	64	0.94	(0.62, 1.40)
Svensson, 1990	F	17	1.20	(0.40, 2.90)
Wu-Williams et al., 1990	F	205	0.7	(0.6, 0.9)
Cohort Studies				
Garfinkel, 1981	F	88	1.17	(0.85, 1.89) (0.77, 1.61)
Gillis et al., 1984	F	6	1.00	(0.59, 17.85)
	M	4	3.25	
Hirayama, 1984b	F	163	1.45	(1.04 2.02)
1984a		7	2.28**	(1.19 4.22)

*Weak relative risks have risk ratios of between 1 and 3, or so. Any risk ratio below 1 represents a negative relationship. Note that none of the studies show a strong relative risk.

** Statistically significant at the 5% level.