Letters

A Second Look at Environmental Tobacco Smoke

The article "Smoke and Mirrors: The EPA's Flawed Study of Environmental Tobacco Smoke and Cancer" by Gary L. Huber, Robert E. Brockie, and Vijay K.Mahajan in our 1993 Number 3 issue generated a good deal of comment and criticism. In this special letters section we print some representative reactions to Huber et al., and their response.

TO THE EDITOR:

We feel compelled to respond to the article by Huber et al. (1993 Number 3) criticizing the Environmental Protection Agency (EPA) risk assessment on environmental tobacco smoke (ETS) and lung cancer. It is regrettable to see the same tired approaches that the tobacco industry has used to attack the scientific evidence linking active cigarette smoking to lung cancer surfacing again. Drs. Huber, Brockie, and Mahajan selectively present information from the report in contexts that misrepresent how information was used in the risk assessment. They attempt to claim the high road of science by demonstrating some of the limitations of our knowledge about tobacco smoke and its risks; however, what they are actually suggesting is scientific nihilism such that no conclusion can be drawn scientifically until our understanding of all of the processes involved is complete to the last detail. Our understanding of the biologic processes of life and death remains incomplete, but that does not prevent us from drawing a conclusion that bullets, or for that matter cigarettes, cause death and disability.

Huber et al. place great weight on the differences between mainstream tobacco smoke and ETS and our incomplete understanding of the chemistry of tobacco smoke. Clearly, there are chemical differences between ETS and mainstream smoke. Even among the different brands of cigarettes, there is substantial difference in the chemical composition of the mainstream smoke produced. For example, the tar yield of various brands of cigarettes marketed in the United States varies from one hundredth of a milligram to almost 20 milligrams of tar per cigarette. The question is not whether chemical differences can be identified in mainstream and sidestream tobacco smoke, but rather whether the similarities between mainstream and environmental tobacco smoke are sufficient to allow meaningful comparison.

Both mainstream and sidestream smoke are combustion products of tobacco. A slightly higher yield of toxic and carcinogenic constituents is produced when tobacco is burned at the lower temperatures producing sidestream smoke than at the higher temperatures of mainstream smoke. Most of the same carcinogens identified in mainstream smoke have been identified in sidestream smoke. Therefore, it is reasonable to expect that ETS would be qualitatively similar to mainstream smoke in its potential to cause cancer and that the major differences in toxicity would be related to the differences in exposure dose. The fact that a gram of tobacco burned to produce sidestream smoke produces slightly more (or less) of an individual carcinogen than when it is burned to produce mainstream smoke is far less relevant than the amount of that carcinogen actually inhaled by the individual exposed.

The authors point out that the National Cancer Institute has failed to identify the constituent of cigarette smoke which is "the prime suspect allegedly responsible for causing cancer" and then suggest that this failure interferes with the ability to draw a conclusion that ETS is carcinogenic. It is true that we have yet to fully characterize the human toxicology of the more than 4,000 constituents of cigarette smoke, and we have yet to address the potential interactions among those agents. It is also true that the sum of the carcinogenic effects of individual

constituents of tobacco smoke does not equal the carcinogenic effect of whole tobacco tar in mouse assay systems of carcinogenicity. However, it is logically incorrect to then assume that tobacco tar is not carcinogenic because we have not been able to attribute the carcinogenic effect to individual agents. When sidestream smoke is examined in carcinogenicity assays, it has been demonstrated to be more carcinogenic, rather than less carcinogenic, than mainstream smoke. It is then scientifically inappropriate to discredit the carcinogenicity of ETS by demonstrating that it is not explained by the levels of four or five of the many individual constituents demonstrated to be present in ETS. The inability to precisely assign the total carcinogenic effect of cigarette smoke among each of the several thousand constituents of tobacco smoke has been used by the tobacco industry to argue that we do not yet have the evidence that active cigarette smoke causes lung cancer. That argument is fallacious with active cigarette smoking, and its logic is equally fallacious as applied to ETS. It is the carcinogenicity of the entire exposure that is in question, not the direct and interactional toxicology of the individual constituents.

The authors emphasize the importance of dose in risk estimation. However, they then go on to completely misrepresent the assessment of dose in the EPA report. They chose to present dosage data for a few individual constituents of tobacco smoke as if those constituents explained the risk associated with ETS. They ignore the substantial volume of data that assesses the magnitude of exposure to ETS and its comparison to the dose response extrapolations from active cigarette smoking. The amount of smoke present as ETS when estimated from air sampling is large enough to expect that a substantial risk would exist based on the dose response extrapolations from active smoking. In addition, the amount of nicotine absorbed by those exposed to ETS, as a percentage of the amount of nicotine absorbed by cigarette smokers, is also large enough to expect that there would be a risk of lung cancer due to ETS exposure. Both of those lines of evidence are presented in the EPA report, but are ignored by the authors in their presentation of dose response data.

The authors would lead the reader to believe that the confidence interval in the meta-analysis done by the EPA was used to conclude that ETS is a carcinogen. In fact, the conclusion that ETS is a group A carcinogen was made by examining all of the evidence available and assessing the individual studies with their strengths and weaknesses. The purpose of the meta-analysis was simply to generate a unitary risk estimate that could be applied to the U.S. population for purposes of assessing the number of lung cancer deaths attributable to ETS exposure.

The magnitude of the relative risk for tobacco smoke as a carcinogen is quite high. The relative risk estimate ranges from 10 to 20 in mortality studies of cigarette smokers. What is in question in the EPA report is whether or not the low dose of exposure experienced by those exposed to ETS is sufficient to generate a risk. In this setting, low relative risks would be expected and the fact that the relative risks are less than three is a disingenuous argument intended to confuse the reader.

In summary, it is disheartening to see the same misrepresentation of the scientific process that has been used for over 30 years to discredit active cigarette smoking's link to lung cancer now being applied to ETS exposure. The facts are indeed very clear. Tobacco smoke is a carcinogen for active smokers. The same carcinogens are present in ETS. The levels of ETS in the air in environments where nonsmokers are present is sufficient to expect that there would be a risk from dose response extrapolation. The amount of nicotine absorbed by individuals exposed to ETS is sufficient to expect that exposure would cause an increased risk of lung cancer. Human epidemiologic lung studies of individuals exposed to ETS compared to those who are less exposed demonstrate a statistically significant increased risk.

Those are the facts that form the basis of the EPA conclusion. If the readers question those facts, they simply can refer to the EPA report and should not be confused by the misrepresentation of that report contained in the article by Huber, Brockie, and Mahajan.

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TO THE EDITOR:

The article "Smoke and Mirrors: The EPA's Flawed Study of Environmental Tobacco Smoke and Lung Cancer" by Gary L. Huber, Robert E. Brockie, and Vijay K. Mahajan suggests there are weaknesses in the EPA review but never addresses the central finding that tobacco smoke exposure, whether by active smoking of cigarettes or by environmental exposure to other people's smoking, produces increased risk of lung cancer. The representatives of the tobacco industry have never accepted the evidence showing smoking causes lung cancer. It is hardly surprising that they would now use the same methods to obfuscate the linkage of ETS with lung cancer. Rather they highlight the differences between experimental toxicology and observational science (epidemiology), selectively report results, and otherwise attempt to obfuscate the data, while avoiding the key finding in thousands of studies that tobacco smoke causes cancers in the lungs. We are not surprised by Dr. Huber's position, as his long association with the tobacco industry is well known.

The basis for defining ETS as a carcinogen is clear. Tobacco smoke is a known cause of lung cancer. The carcinogenicity of tobacco smoke has been demonstrated by all methods used to assess risk—that is, in animal bioassay studies, genotoxicity studies, and epidemiologic studies. Epidemiologic studies have shown that active smokers develop lung cancer at a rate at least 10 times that of people who never smoke. Epidemiologic studies have shown that the risk of lung cancer associated with tobacco smoke increases monotonically with exposure. There is no evidence from those studies of active smokers that even the smallest exposures to smoking are free of risk. It follows that environmental exposures to low concentrations of tobacco smoke should be associated with increased risk of lung cancer. That evidence alone is sufficient to define ETS as a lung-cancer hazard.

There is also substantial evidence that nonsmokers are passively exposed to tobacco smoke at nontrivial levels. That nonsmokers are breathing ETS, and are therefore at risk of developing the same disease as active smokers, is a fact so clear it should require no further discussion. A considerable mass of data has been developed estimating environmental exposures to tobacco smoke, direct measurements of ambient indoor concentrations of tobacco smoke, and direct measures of dose based on biologic tissue samples.

Given that tobacco smoke is associated with increased incidence of lung cancer even to the lowest exposures among active smokers, and that there is widespread environmental exposure to tobacco smoke among nonsmokers, increased incidence of lung cancer should be expected among those who never smoke who are chronically exposed to ETS. Indeed, increased incidence of lung cancer has been consistently observed in epidemiologic studies of those who never smoke exposed to ETS. Evidence that woman who never smoke with smoking spouses have increased risk of lung cancer only confirms what was apparent from the carcinogenicity of tobacco smoke itself.

Huber et al. argue that the composition of ETS differs from mainstream tobacco smoke. This long diatribe has no relevance to the issue however. Mainstream tobacco smoke also varies by cigarette brand, by method of smoking, by cigarette length, etc., but no reasonable person has doubted its danger for years.

Huber et al. question the methods used to assimilate the existing published data in the EPA review. They first suggest the magnitude of the effects is too small to be believed. However given the low exposures to ETS, a stronger association would not be expected. The observed weak associations among those who never smoke only confirm that the extrapolation from the high-exposure, active-smoking case is appropriate.

Huber then suggests that the epidemiologic data are inconsistent. Given the compelling evidence of the association of tobacco smoke with lung cancer cited above, the hypothesis to be tested is not that tobacco smoke has no statistically significant association with lung cancer in epidemiologic studies. Rather, the hypothesis to be tested is that ETS does not increase lung cancer risk. Of the 30 studies reviewed by the EPA, only one study was not consistent with an increased lung-cancer risk associated with spousal smoking (that is, did not include a positive risk within the 95 percent confidence interval). The consistency of those results across so many independent studies showing a positive association between lung cancer and spousal smoking is a very strong statement of the robustness of those findings.

This consistency is clearly seen in Figure 2 of the Huber et al. article, which presents the range of effects estimates (relative risks) of studies from the United States. Results to the right of the no effect levels, that is above a relative risk of 1.0, show an increased risk, while those to the left indicate a protective effect. The weight of the evidence---that is, the most ink in this figure---is clearly to the right of the line, indicating increased risk from exposure to smoking by their spouse. The EPA review has quantified this observation by a meta-analysis, but the results are only a summary of what is apparent to the eye of an unbiased observer. The statistical analysis is only a tool to summarize what is seen in the graphic presentation.

Huber et al. then suggest that the data was manipulated by statistical maneuvers or biased exclusion of studies in the EPA review. The arguments regarding statistical significance are irrelevant. As Bradford Hill stated almost 30 years ago in his classic paper regarding causal inference in environmental studies: "No formal test of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis."

Huber et al. then suggest that the results of the EPA analysis would have been different if two studies published after the EPA review was completed had been included. In testimony presented before the House Subcommittee on Specialty Crops and Natural Resources on July 21, 1993, Dockery presented a review as suggested by Huber et al. based on the original data reported in each study, including the studies published after the completion of the EPA report. The estimated effect of spousal smoke on lung cancer in nonsmoking women was 1.21 with a 95 percent confidence interval of 1.11 to 1.31, which was only slightly different from the estimate based on the studies included in the EPA review of 1.24 with a 95 percent confidence interval of 1.13 to 1.35.

Huber et al. finally suggest that the observed associations may be the result of uncontrolled confounding, that is failure to adequately consider a third variable associated with both ETS and lung cancer which might be an alternative causative explanation. They highlight diet as one such risk factor. It is known that a diet deficient in anticarcinogenic nutrients will increase the risk of lung cancer in smokers. However, there is no evidence that lack of dietary nutrients will produce lung cancers in people who have no exposure to a causative agent. Thus while diet may reduce the risk of lung cancer in smokers, suggesting diet is the causative agent in nonsmokers is only another example of obfuscation in this article.

In our opinion, the toxicologic and epidemiologic evidence for an association between lung cancer and ETS is compelling. The EPA Report is a comprehensive, rigorous, balanced, and scholarly summation of the current state of the science which supports such a finding. While epidemiologic studies alone cannot demonstrate causality, the universal finding of the carcinogenicity of tobacco smoke in animal and genotoxicity studies corroborate the epidemiology. There is no doubt that tobacco smoke is an environmental carcinogen.

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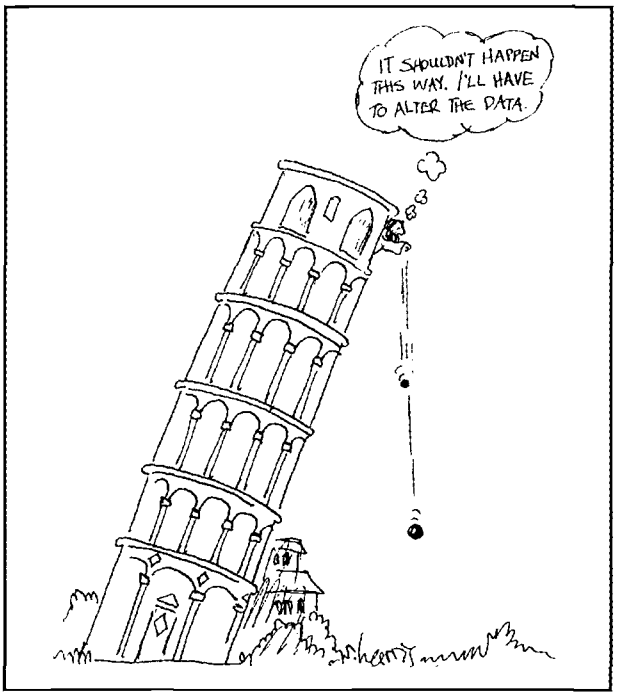

HUBER, BROCKIE, AND MAHAJAN REPLY:

The scientific publications and related debate regarding the potential health risks of ETS may often appear ambiguous and perplexing to the layman, and the associated claims are sometimes less than accurately portrayed in the lay press. In responding to the letters of Burns and of Edelman and Dockery, therefore, we will focus on those key *scientific* issues that are most crucial to understanding.

The critiques by Burns, and by Edelman and Dockery, are highly generalized. By and large, they do not address any specific scientific points or numerical data. The comments by Burns, in particular, are extremely diffuse. Like so many spokespersons for the ETS social movement, the issues Burns emphasizes are based on emotion and opinion, not on scientific data. He makes remarkable assertions and fails to cite a single scientific reference, and uses Orwellian logic to reach a politically correct position. We will confine our response to matters of scientific debate.

The single most important point that we again would like to emphasize is that the residual constituents of ETS that have been detected in the environment of smokers are in aggregate *not* quantitatively or physically the same substance that smokers generate and inhale while consuming tobacco cigarettes. A very large number of scientific publications are unequivocally clear and consistent on this matter. Burns, Edelman, and Dockery cite no peer-reviewed scientific data to the contrary. The smoke that active cigarette smokers inhale contains over 5,000 well-characterized chemical components and a large number of additional poorly characterized trace constituents. ETS, in contrast, consists of only a relatively few—in the neighborhood of 50 to 100—readily measurable or identifiable highly diluted residual constituents that were once present in mainstream or sidestream tobacco smoke.

The potential health concerns regarding exposure to those highly diluted residual ETS constituents should not be deliberately entangled with the health risks for active smoking. This is not a scientific debate about active smoking. Scientifically, the crucial question simply is, "Does exposure of the nonsmoker to the residual ETS constituents cause disease?". Why, then, does the EPA report not list the residual ETS constituents and their concentrations in our environmental air? Why do Burns and Edelman and Dockery beg the question of even their existence? The answer, presumably, is because those ETS residual constituents are so highly diluted that they can be detected in environmental air under real-world circumstances only at extremely low levels of concentration—concentrations so dilute that, if scientifically evaluated on the basis of their own potential toxicity, they would not exceed any accepted standards for exposure. Those matters have been comprehensively reviewed in the scholarly and scientifically documented monograph by Guerin et al. from the Oak Ridge National Laboratories.

Edelman and Dockery state that "nonsmokers are breathing ETS, and are therefore at risk of developing the same disease as active smokers, is a fact so clear it should require no further discussion." There are no sound scientific data to support that claim (if there are, please show us the data). Active smokers and passive smokers simply are not inhaling the same substance.

Such a claim defies one of the most important principles of inhalation toxicology: the dose makes the poison. This holds true for common substances, from aspirin to alcohol, to well-characterized environmental toxins that we consume or that we are exposed to sometimes daily. For example, small doses of alcohol, consumed in moderation, are not harmful and, based on several recent studies, may even be beneficial; consumed chronically or even acutely in large doses, however, alcohol can be lethal. The same is true for aspirin or, to push the analogy to the extreme, even for water. These comparisons are not offered to make light of the seriousness of the potential biologic effects of tobacco smoke chemical constituents. Rather, it is crucial to remember that there are important rules of science and toxicology, as well as key time-tested scientific principles, that uniformly apply to all scientific questions. Those rules of science must be applied objectively to all scientific questions concerning ETS, and they must not be changed or discarded to meet an emotional, political, or social agenda. The rules of science are (or should be) the same for assessing questions about tobacco as they are for questions about other substances and, indeed, the scientific questions concerning ETS do in fact require further scientific discussion.

In the absence of objective scientific data on which to assess a true health risk, Burns, Edelman and Dockery, as well as others, employ a theoretical concept called "linear risk extrapolation." In doing so, they appear to be trying to confuse the issue. Linear risk extrapolation is a "no threshold" view of carcinogenicity that claims the risk of lung cancer associated with active smoking can be extrapolated to indicate,

as Edelman and Dockery state, "that environmental exposure to low concentrations of tobacco smoke should be associated with increased risk of lung cancer" in nonsmokers. The EPA considered using linear risk extrapolation in its report and did not do so, for good reason. If one were to actually apply a linear risk extrapolation based on "smoke" exposure (from active smokers to inhalation of ETS residual constituents), the risk predicted by the model is typically indistinguishable from background lung cancer rates. The EPA's risk assessment, which we do not believe to be valid, projected over 3,000 lung cancer deaths per year from ETS—a massive disparity to the number generated by linear risk extrapolation and a projected number that cannot be supported on the basis of sound scientific principles or any known scientific data.

When one needs to assess the risk of an environmental agent that is not even present at readily detectable environmental levels, investigators often turn to laboratory studies in experimental animals. When toxicological animal studies have been conducted in a scientifically credible manner, involving even massively exaggerated exposures to the residual constituents of ETS, they have been consistently negative. That is, they reveal no significant adverse effect of ETS on the lungs of experimental animals even at unrealistically high levels of exposure.

We are left, then, largely with epidemiologic studies to determine whether or not humans are at risk. Edelman and Dockery claim that an "increased incidence of lung cancer has been consistently observed in epidemiologic studies of those who never smoke exposed to ETS," based in part on their assertion that a study is consistent with increased incidence if it "include[s] a positive risk within the 95 percent confidence interval." Those approaches reject conventional statistical methods. It is a long-standing conventional statistical practice and an established scientific standard that any confidence interval which includes the null value (a no-effect relative risk of 1.0) is *only* consistent with no effect. Further, accepted conventional statistical methodologies dictate that a positive effect can be claimed only when the *lower* confidence limit is *above* 1.0, not when the upper limit is. In like manner, a *negative* effect can be claimed only when the upper confidence interval limit is below 1.0. Furthermore, the EPA asks us to accept broader unconventional 90 percent confidence intervals in order to make otherwise nonsignificant results "significant."

Is it justifiable to discard time-proved and conventionally accepted statistical standards merely because the subject is tobacco? Edelman and Dockery appear to ask us to do so, and in doing so to accept some new statistical invention to support and permit their conclusion—an invention that is not supportable by accepted statistical methodologies. Does changing conventional standards really matter or is this just different scientists quibbling over issues that really are not important? If we accept breaking the time-honored rules of statistics and science simply because the issue is tobacco, what target will be next and where will all of this nonsense end? Let the valid rules of science initially test the question. Whether the outcome does or does not meet predetermined expectations, we cannot permit bending or distortion of science to meet a political or social agenda.

We suggested that if the EPA meta-analysis had included all of the available U.S. ETS epidemiologic data, instead of excluding two important studies (including one excluded study that is by far larger than any other), the outcome might have been different. In response to this, Edelman and Dockery cite Dockery's presentation to the House Subcommittee on Specialty Crops and Natural Resources on July 21, 1993, as indicating that inclusion of those studies would make little difference. That statement is inaccurate and misleading: Dockery's Subcommittee presentation involved an analysis based on incorporation of those studies into all of the worldwide data, not just the U.S. studies. In developing its meta-analysis and risk characterization for ETS, the EPA excluded worldwide data. That was a reasonable decision because of the cultural, social, and racial differences among those widely diverse geographical areas. Dockery's inclusion of the "missing" studies into the worldwide data dwarfs and distorts their impact. When the data from all studies on populations from *this* country are combined in a meta-analysis, the results are not statistically significant.

The risk estimates for ETS exposure as a hazard for the development of lung cancer in the 13 published studies derived from U.S. population data are very weak and, in general, statistically nonsignificant; they are consistent only in their questionable significance. When risk estimates are strong (relative risks of 5 to 20 or more) and consistent, cause and effect relationships are more readily inferred, although statistical or observational associations alone, without other corroborating data, are seldom accepted by themselves as sufficient proof for causality. When statistical associations are weak (relative risks of less than 2.0), the possibility that the finding is an artifact determined by lifestyle or uncontrolled variables or confounders is serious and must be carefully evaluated and assessed.

Edelman and Dockery question our statement that confounding factors may explain the small observed risk associations presented in the EPA report, as well as in the primary literature. Edelman and Dockery go on to state "there is no evidence that lack of dietary nutrients will produce lung cancer in people who have no exposure to a causative agent."

What Edelman and Dockery are saying is remarkable. There is no basis in the scientific literature to support the implied assumption that each of the cancer victims in those dietary studies was exposed to a specific cancer-inducing agent. To suggest that this is the case discredits the entire field of epidemiology, for it amounts to an assertion that those studies were unable to control for certain variables or confounders that consequently render the results invalid. If, indeed, this is the position of Edelman and Dockery, it amounts to a remarkable indictment of the very scientific tool on which their position on ETS entirely depends.

Edelman and Dockery go on to claim that "while diet may reduce the risk of lung cancer in smokers, suggesting diet is the causative agent in nonsmokers is only another example of obfuscation in this article." Here Edelman and Dockery either betray their circular reasoning or they are showing their utter lack of knowledge about the subject. The evidence is quite clear on this matter. For example, Candelora et al.

report that "the results of [our] study suggest a strong protective effect associated with vegetable consumption and carotene intake in the prevention of lung cancer among women who are lifetime nonsmokers." Alavanja et al. report "our study finds a strong, increasing trend in lung cancer risk associated with increased saturated fat consumption among nonsmoking women," independent of exposure to ETS. Mayne et al. report, "This is the largest study to date of dietary factors and lung cancer in nonsmokers; results suggest that dietary beta carotene, raw fruits and vegetables, and vitamin E supplements reduce the risk of lung cancer in nonsmoking men and women." Additionally, Block et al., in a review of earlier epidemiologic evidence about fruit and vegetable intake, state that "for lung cancer, significant protection was found in 24 of 25 studies after control for smoking." Edelman and Dockery's statements appear to be merely wishful thinking designed to obscure reality; diet clearly has a role in lung carcinogenesis.

Finally, it is important to address the comments of Burns and Edelman and Dockery in reference to the tobacco industry. Our contribution to *Regulation* was not funded by the tobacco industry, or by any sources other than the publisher, and none of us are employed by or speak for the tobacco industry. None of us now receive, or ever have received, any income from the tobacco industry. We collectively have published, however, 262 contributions on smoking and health in the medical and scientific literature, all of which have been peer reviewed. Those contributions are a matter of public record. In addition, most of our contributions on smoking and health have been critically reviewed by a committee of senior scientific faculty at Harvard University. That report also is a matter of record, and one of its conclusions was that it found no bias or industry influence in any of our research or in any of our writings.

Attempts (in this case by evoking associations with the tobacco industry) to demonize the messengers discredits the scientific process. Let the value of scientific data be debated on its own merit by scientific processes, regardless of source, not by innuendos or rhetorical flourishes. Those techniques may be well-suited for the political arena, but they damage the scientific process.

Questions concerning the potential health effects of exposure to ETS deserve clear answers. To be valid, those answers must come from objective science, not from rhetoric or from speculative theories derived by the manipulation of time-honored scientific principles, by assumptions that cannot be substantiated by scientific data, or by wishful extrapolations made without scientific validity. Neither Burns nor Edelman and Dockery offer a single scientific fact to contradict our argument, nor do they even address the specific scientific information we provided in our initial contribution. What they do, in fact, is offer a lot of arm waving and say, "Trust us, because we are against tobacco." We would rather trust science.

The EPA is charged with addressing important environmental issues critically, objectively, and honestly, with credible science, not with promoting a political agenda or by predetermined policies. To solve a number of important problems in our environment, we, the people, must be able to depend on sound scientific judgment, based on established scientific principles, and not on political or emotional distortions. As Richard Lindzen of The Massachusetts Institute of Technology has emphasized, when we compromise those scientific principles we leave our society with a resource of some importance diminished. Those who are charged with developing public policies must not distort scientific fact for their own political needs; they must develop public policies only by using accepted scientific methodologies. Such was not the case with the EPA's risk assessment on ETS, nor was it the case with the responses to our article by Burns and Edelman and Dockery.

(Technical references available from the authors or from *Regulation* on request.)

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