Response to Loomis et al.

I would like to address comments of Loomis et al. about inferences drawn from studies using group-level exposure variables, the use of the tobacco analogy, the application of Hill’s criteria for causality, and the use of the Hertz-Picciotto criteria for evaluating studies. Whether the hybrid studies under discussion (3–5) are considered partly ecological (6,7) or individual level with exposure misclassification, bias (ecological or otherwise) is possible and should be checked. I hope that these discussions will lead to more considerations of the interplay between outcomes and confounders assessed at the individual level and exposure measured at the group level.

Loomis et al. suggest that biases stemming from the “ecologic fallacy” do not apply to the PM$_{2.5}$ air pollution studies because they are individual-level studies where exposure is measured with error. That is, by implication there is one PM exposure variable. But as indicated by Morgenstern (8,9), ecologic bias can arise when the mean of a group-level exposure variable has an effect on the individual-level exposure. By this definition there will be ecologic bias whenever the ecologic exposure variable has an effect, and when there is also an individual-level exposure effect in addition to the ecologic exposure effect. Unmeasured individual-level exposure to PM$_{2.5}$ from all sources can be several orders of magnitude higher than ambient PM$_{2.5}$ concentrations (10) because of extensive exposure to unmeasured sources such as tobacco and indoor combustion. These individual-level exposures vary for individuals within the group and contribute to the individual-level risk. The additional effect of ambient exposure provides the group-level component that leads to ecologic bias.

The American Cancer Society (ACS) Study (4) and the Six Cities Study (5) suggest that an increase of about 20 µg/m$^3$ PM$_{2.5}$ results in a 20–30% increase in total mortality. I sought to test the consistency of these findings by comparing risk estimates based on group-level exposure estimates to those based on individual-level exposure to a similar but more thoroughly studied particular (i.e., tobacco smoke). Applying the models developed in these studies to tobacco smoke, one can predict that a 20-µg/m$^3$ difference in ambient PM$_{2.5}$ between cities is too small to result in a measurable difference in overall mortality (6). If this is true, the differences in mortality between cities may be due to causes other than differences in PM. Whether there is ecologic bias or not, exposure misclassification bias operating at the individual level, or uncontrolled bias from other sources, the tobacco analogy suggests that bias away from the null may be operating in these studies.

Loomis et al. suggest that the tobacco analogy presents “strong evidence of a supralinear dose–response relationship between particles and mortality.” In order to fit the data, the degree of supralinearity would have to be enormous. In fact, an increase of 19.6 µg/m$^3$ in ambient PM$_{2.5}$ and an increase of 16,000 µg/m$^3$ from smoking would have to result in a similar 20–30% increased risk (Figure 1) It is not plausible that two increases in exposure, which differ by almost three orders of magnitude, would both produce the same response. A more plausible inference is that either the PM$_{2.5}$ or the smoking risk estimates are in error. However, I would place more credence in the smoking relative risks (RRs) because smoking is measured at the individual rather than the group level, and the smoking RRs are compatible with a large body of literature.

It is not necessarily correct to infer, as Loomis et al. do, that lowering community-wide air pollution below existing levels will reduce community mortality rates. In making this inference, one assumes there is independent evidence for a causal relationship between ambient PM$_{2.5}$ and mortality. These studies (4,6) showed that there were differences in total mortality, but did not show why mortality was higher in cities with higher PM$_{2.5}$ concentrations. If PM$_{2.5}$ is the reason for increased mortality, all important individual risk factors must be taken into account to a reasonable degree. Total mortality has a large number of risk factors. It is speculative therefore to assume, as Loomis et al. do, that lowering PM$_{2.5}$ concentrations beyond existing levels will provide a “logical and efficient means of minimizing the health impact of a widespread exposure,” and that the proposed cure will produce the desired effect. The tobacco analogy provides evidence against such an effect.

Loomis et al. state that the effects of potential confounders are too small to explain the observed associations in the PM studies. In my paper (6) I assessed differences in lung function and sedentary living as two examples of possible confounders because some evidence was available to me. Even in these examples, individual-level data were not available to adequately estimate or adjust for these effects (6). There are undoubtedly many other examples such as personal lifestyle factors or other inadequately controlled variables that are correlated with dirty versus clean cities or with geography. Based on the tobacco analogy, it appears that whatever biases are operating resulted in a large overestimate of the PM$_{2.5}$ risk.

I agree with Loomis et al. that to apply Hill’s (7) criteria appropriately requires a “careful review not of one study design, but rather of the entire body of literature pertaining to the hypothesis of a causal

Figure 1. Association of total mortality with group level ambient PM$_{2.5}$ exposure and individual level tobacco smoke exposure. Data from the Six Cities Study (5).

*Approximately 16,000 µg/m$^3$. 

Environmental Health Perspectives • Volume 107, Number 8, August 1999
association between [chronic PM] air pollution exposure and health [mortality]. In applying these criteria, I have included experimental studies in animals and epidemiologic studies in humans (6). Rodents exposed to high concentrations of diesel exhaust for life did not show early or increased mortality (6). The available epidemiologic studies (3-5) showed only weak associations across a narrow exposure range. The possible role of PM and lung function in the Six Cities Study suggested that there were differences in lung function between cities, but no measurable effect attributable to PM$_{2.5}$. In the Seventh Day Adventist Study (5), there appeared to be a coherent relationship between PM and self-reported symptoms, but not between PM and mortality. However, the analyses required to evaluate fully this PM-symptoms association were not reported. Furthermore, short-term exposures and hospital admissions may have little to no relevance for mortality from chronic exposure (6,11). Finally, individual-level measurements of an analogous surrogate PM$_{2.5}$ exposure from the same populations and same cities provided a test of the internal consistency and biological coherence of the ambient PM$_{2.5}$ associations. I know of no other experimental or clinical human studies that can be used as a more appropriate test.

I did not say or mean to imply that all of Hill's (1) criteria must be obeyed before accepting cause and effect. The only criterion that must be met is that exposure must precede the effect (6,12). I agree with Loomis et al. that Hill's (1) guidelines can be "helpful at the margins of epidemiologic interpretations" (as with PM), but also provide a good framework for assessing causality in general. I do not believe that evidence was excluded, as alleged by Loomis et al., although further tests of the plausibility and coherence of these associations with PM may be possible.

Regarding the use of Hertz-Piccioiino's criteria (2), my point was to assess whether the EPA was justified in developing quantitative concentration-response information useful in developing an annual PM$_{2.5}$ standard from these studies. Table 5 in my paper (6) was an attempt to do this; because both studies were of the same design, the criteria were applied to both the design and the two individual studies. I concluded (6) that

none of the Hertz-Piccioiino criteria for quantification of risk and setting air quality standards using [these] epidemiology studies are met.

I believe these are useful guidelines and that they do "contribute to a firmer scientific foundation for low-dose risk estimates and the ensuing regulatory actions" (2).

I suggest that the tobacco analogy analysis provides evidence "that a given type of bias did ... occur" and that it did "quantify its direction and magnitude," as stated by Loomis et al., within the limits of the data available. It was only possible to suggest possible sources of bias. The magnitude of the confounding could not be calculated as suggested by Loomis et al. for several reasons. The univariate distributions were not provided in the reports of these studies. The bivariate distributions based on individual-level data cannot be determined (6) because the exposure variable is based on aggregate data. Sensitivity analyses are valuable, but I suggest that the tobacco analogy provides a useful and fundamentally sound method for what Loomis et al. describe as "quantitative exploration of potential biases."

I suggest that one cannot be sure, with any degree of certainty, that studies using group-level measures of exposure are free from the potential biases afflicting completely ecological designs. This is an area where research using individual-level data is needed to improve the quality of information used to guide regulatory decisions.

John Gamble
Exxon Biomedical Sciences, Inc.
East Millstone, New Jersey
E-mail: jgambil@fpln.eerenj.com

References and Notes

1. Hill AB. The environment and disease: association or causation? Proc R Soc London Ser B 58:295-300 (1965).
2. Hertz-Piccioiino I. Epidemiology and quantitative risk assessment: a bridge from science to policy. Am J Public Health 85:489-491 (1995).
3. Dockery DW, Pope CA, Yu, S, Spengler JD, Ware JH, Fay ME, Ferris B Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753-1759 (1993).
4. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Health CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:689-674 (1995).
5. Abbey DE, Hwang BL, Burchette RJ, Vancuren T, Mills PK. Estimated long-term ambient concentrations of PM$_{10}$ and development of respiratory symptoms in a nonsmoking population. Arch Environ Health 50:139-152 (1995).
6. Gamble JF. PM$_{2.5}$ and mortality in long-term prospective cohort studies: cause-effect or statistical associations? Env Health Perspect 106:535-540 (1998).
7. Künzli N, Tager IB. Comments on "PM$_{2.5}$ and mortality in long-term prospective cohort studies: cause-effect or statistical associations?" (letter). Environ Health Perspect 107: A224-A225 (1999).
8. Morgenstern H. Ecologic studies in modern epidemiology. In: Modern Epidemiology (Rothenman K, Greenland S, eds). 2nd ed. Lippincott Raven Publishers, 1998:499-480.
9. Morgenstern H. Uses of ecologic analysis in epidemiologic research. Am J Public Health 72:1336-1344 (1982).
10. U.S. EPA. Air Quality Criteria for Particulate Matter, EPA-600-AP-95-001C. Washington, DC: U.S. Environmental Protection Agency, 1996.
11. Gamble JF. Reply to Künzli and Tager regarding causality in PM$_{2.5}$ cohort studies [letter]. Environ Health Perspect 107:A224-A225 (1999).
12. Rothman KJ. Modern Epidemiology. 1st ed. Boston, MA: Little, Brown, and Company, 1986.

"Double Exposure": How Real Is It?

The Focus article "Double Exposure" [EHP 107:A196-A201 (1999)] is, for the most part, nothing more than the continued complaining of those who don't realize that living is a hazard. They would place a risk on everything and then ignore those they don't like. I would like to challenge Manuel to provide a laboratory analysis from any reliable source [the American Cancer Society (ACS), etc.] that can identify even half of the stated 4,500 components he cites. The ACS stated that ≥ 2,000 components were present in smoke, but when asked to list them, they could not. The California Air Resources Board cites < 50 components at current detectable levels. Only the tars and benz[a]pyrene have even been proven harmful to rats, and this has been in massive doses. As a retired chemical engineer with an extensive background in chromatography and mass spectrometry, I can say with certainty that if 4,500 components exist in tobacco smoke, then the clean air we breathe must contain 6,000 or more. At 66 years of age and a smoker of over two packs of cigarettes a day for 47 years, I was recently rejected for a Veterans' Administration lung health study because my lungs were "too healthy." Three guesses what their study results will show.

William C. Briggs
Chemical Engineer, retired
Concord, California
E-mail: mlbill2b@silcon.com

Response to Briggs

The figure of more than 4,500 compounds in tobacco smoke was obtained from an article titled "Assessment of Exposure to Environmental Tobacco Smoke" (1). The U.S. Environmental Protection Agency (2) cites a figure of "more than 4,000 compounds" in its 1992 report. A table of many of the constituents is listed on pages 3-5 through 3-9 of that report.

John Manuel
Durham, North Carolina
E-mail: jmanuel782@aol.com

References and Notes

1. Jaskola MS, Jaskola JJK. Assessment of exposure to environmental tobacco smoke. Eur Respir J 10:2366 (1997).