

## Comments on EPA's Proposed Rule, National Ambient Air Quality Standards for Particulate Matter

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### Introduction and Summary

EPA has proposed lowering the level of the National Ambient Air Quality Standard (NAAQS) for PM<sub>2.5</sub>. Under EPA's proposal, the 24-hour PM<sub>2.5</sub> standard would be lowered from 65 micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) down to 35  $\mu\text{g}/\text{m}^3$ , while keeping the annual standard at its current level of 15  $\mu\text{g}/\text{m}^3$ . If adopted, the proposed standard would double the fraction of PM<sub>2.5</sub> monitors that violate federal PM<sub>2.5</sub> standards, resulting in a substantial increase in both the stringency of federal PM<sub>2.5</sub> standards and the difficulty of achieving regional PM<sub>2.5</sub> attainment.<sup>1</sup>

Based on pressure from EPA's Clean Air Scientific Advisory Committee (CASAC) and from environmental groups and newspaper editorial boards, EPA will presumably also consider adopting a 24-hour and/or annual standard of even greater stringency than the current proposed rule. Instead, EPA should scrap its proposed rule to lower the PM<sub>2.5</sub> NAAQS and should keep the PM<sub>2.5</sub> NAAQS at their current levels.

As demonstrated in this comment letter, and contrary to EPA's and CASAC's claims, the current NAAQS already protect public health "with an adequate margin of safety," as required by the Clean Air Act (CAA). Indeed, standards even less stringent than the current PM<sub>2.5</sub> NAAQS would also protect public health.

Health experts justify the current annual and 24-hour federal PM<sub>2.5</sub> standards on the basis of circumstantial evidence. The evidence comes from observational epidemiology studies that report small residual correlations between particulate matter (PM) and premature mortality after controlling for confounders. The implicit assumption about these studies is that after controls are added for known or expected confounders, any residual correlation between air pollution levels and health outcomes represents a genuine causal linkage.

Thousands of observational air pollution health studies have been published in the literature. Proponents of tougher PM<sub>2.5</sub> regulation consider the large number of published studies as evidence for the certainty and seriousness of harm from PM<sub>2.5</sub>. However, experience has shown that observational studies with non-randomly-selected subjects tend to overstate the effects that the researchers are hoping to find. As demonstrated in

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<sup>1</sup> Based on national PM<sub>2.5</sub> monitoring data for 2002-2004 downloaded from EPA at [www.epa.gov/airdata](http://www.epa.gov/airdata).

this and other areas of observational epidemiology, residual confounding, publication bias, and model-selection bias all contribute to the creation of apparent risks from contemporary, historically low levels of PM<sub>2.5</sub> where no risk is likely to exist in fact. Implementing a technique over and over again doesn't increase the robustness or certainty of the evidence for harm from PM<sub>2.5</sub> when the technique itself is fundamentally unable to perform as advertised.

Randomized, controlled studies of PM and mortality could provide more definitive evidence of PM<sub>2.5</sub> risks. Such studies can not, of course, be performed on humans. However, animal studies have failed to provide evidence that PM causes premature death, even at concentrations much higher than ever occur in ambient air. Studies of less adverse PM<sub>2.5</sub> effects have been performed with human volunteers, but these studies have provided little or no evidence for harm at contemporary PM<sub>2.5</sub> levels.

EPA and CASAC have ignored the evidence against the validity of observational epidemiology as a tool for assessing PM<sub>2.5</sub> risks. And they have marshaled evidence selectively so as to create an appearance of greater and more certain risks from PM<sub>2.5</sub> than is warranted by the weight of the evidence.

Given that current PM<sub>2.5</sub> standards are sufficiently stringent to protect Americans with an adequate margin of safety, EPA should reject its proposed PM<sub>2.5</sub> NAAQS rule and leave the current PM<sub>2.5</sub> standards in place.

### **Unreliability of Observational Studies**

Observational studies—the cohort and time-series epidemiology studies that are the main justification for the current and proposed federal PM<sub>2.5</sub> NAAQS—are based on the assumption that data from non-randomly-selected subjects can be turned into the equivalent of randomly selected data through statistical controls for confounding. The implicit assumption is that once confounding has been removed, any remaining correlation between, say, PM<sub>2.5</sub> and risk of death represents a genuine causal relationship between air pollution and mortality.

However, experience has shown that adequately controlling for confounding is exceedingly difficult, if not impossible. Much of the evidence comes not from air pollution, but from traditional health studies. For example, based on observational studies of hormone-replacement therapy (HRT), medical researchers concluded that not being on HRT increased a woman's risk of developing heart disease by a factor of 2.<sup>2</sup> An influential meta-analysis of these studies, published in 1991, helped make HRT one of the most prescribed therapies in the United States.<sup>3</sup> But more recently, randomized trials, which eliminate the possibility of confounding by unobserved factors that affect health, indicated that HRT doesn't reduce heart disease risk and might even increase risk.<sup>4</sup>

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<sup>2</sup> This discussion of the implications of HRT studies for air pollution epidemiology is summarized from S. H. Moolgavkar, "A Review and Critique of the EPA's Rationale for a Fine Particle Standard," *Regulatory Toxicology and Pharmacology* 42 (2005): 123-44.

<sup>3</sup> M. J. Stampfer and G. A. Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiologic Evidence," *Preventive Medicine* 20 (1991): 47-63.

<sup>4</sup> E. Barrett-Connor, "Clinical Review 162: Cardiovascular Endocrinology 3: An Epidemiologist Looks at Hormones and Heart Disease in Women," *Journal of Clinical Endocrinology and Metabolism* 88 (2003): 4031-42; J. E. Rossouw, G. L. Anderson, R. L. Prentice et al., "Risks and Benefits of Estrogen Plus

Recent randomized trials have belied other conventional medical wisdom that was based only on observational studies. For example, a study of nearly 49,000 women reported that following a low-fat diet for 8 years did not reduce women's risk of heart disease, breast cancer, or colorectal cancer.<sup>5</sup> Another randomized trial recently showed that calcium and vitamin D supplements do not reduce women's risk of osteoporosis.<sup>6</sup> Observational studies suggested that beta-carotene (Vitamin A) supplements reduce people's risk of dying from heart disease by about 30 percent. But randomized trials have reported a 12 percent *increase* in risk of death from beta-carotene supplements.<sup>7</sup>

The putative risks that observational air pollution studies are attempting to characterize are small in comparison to the risks being assessed in the health studies described above. For example, not being on HRT was initially thought to increase heart disease risk by 100 percent (a factor of 2), while beta-carotene went from a 30 percent decrease in mortality risk to a 12 percent increase. In contrast, observational air pollution studies predict mortality risk increases on the order of a few tenths of a percent to several percent across the range of typical air pollution levels. These observational studies claim to be teasing out these tiny risks from among a sea of confounding factors that are much larger than the putative risks of air pollution. The idea that observational studies could provide reliable information on air pollution health risks thus seems farfetched on its face. Indeed, a number of epidemiologists have suggested that observational studies are inherently incapable of reliably assessing the existence of such small risks.<sup>8</sup>

EPA set the current annual PM<sub>2.5</sub> standard based mainly on two observational cohort studies of long-term PM exposure and mortality: the American Cancer Society (ACS) study, and the Harvard Six Cities (HSC) study.<sup>9</sup> The studies compared death-rates over time for people living in different cities with PM levels in those cities. Both studies reported that the chance of dying over the period studied—7 years for the ACS and 14-16 years for the HSC—increased by several percent for each 10 µg/m<sup>3</sup> increase in long-term

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Progesterin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial," *Journal of the American Medical Association* 288 (2002): 321-33.

<sup>5</sup> S. A. Beresford, K. C. Johnson, C. Ritenbaugh et al., "Low-Fat Dietary Pattern and Risk of Colorectal Cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial," *Journal of the American Medical Association* 295 (2006): 643-54; B. V. Howard, L. Van Horn, J. Hsia et al., "Low-Fat Dietary Pattern and Risk of Cardiovascular Disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial," *Journal of the American Medical Association* 295 (2006): 655-66; R. L. Prentice, B. Caan, R. T. Chlebowski et al., "Low-Fat Dietary Pattern and Risk of Invasive Breast Cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial," *Journal of the American Medical Association* 295 (2006): 629-42.

<sup>6</sup> G. Kolata, "Big Study Finds No Clear Benefit of Calcium Pills," *New York Times*, February 16, 2006, [http://www.nexis.com/research/home?key=1142270535&\\_session=ea791eca-b2b5-11da-a3b8-00008a0c593d.1.3319723335.156196.%20.0.0&\\_state=&wchp=dGLbVzz-zSkBz&\\_md5=346a380bb4ecb68d018dc14c2a261e1f](http://www.nexis.com/research/home?key=1142270535&_session=ea791eca-b2b5-11da-a3b8-00008a0c593d.1.3319723335.156196.%20.0.0&_state=&wchp=dGLbVzz-zSkBz&_md5=346a380bb4ecb68d018dc14c2a261e1f).

<sup>7</sup> G. D. Smith, "Reflections on the Limitations to Epidemiology," *Journal of Clinical Epidemiology* 54 (2001): 325-31.

<sup>8</sup> G. Taubes, "Epidemiology Faces Its Limits," *Science* 269 (1995): 164-69.

<sup>9</sup> D. W. Dockery, C. A. Pope, 3rd, X. Xu et al., "An Association between Air Pollution and Mortality in Six U.S. Cities," *New England Journal of Medicine* 329 (1993): 1753-9; C. A. Pope, 3rd, M. J. Thun, M. M. Namboodiri et al., "Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults," *American Journal of Respiratory and Critical Care Medicine* 151 (1995): 669-74.

PM<sub>2.5</sub> levels. The studies were also the subject of a detailed reanalysis by the Health Effects Institute (HEI), which ostensibly confirmed their results, as did a follow-up report on the ACS.<sup>10</sup> However, the actual results of the studies and subsequent sensitivity analyses suggest that PM<sub>2.5</sub> at current and recent levels is not killing people. For example:

The follow-up ACS study and the HEI reanalysis reported that PM<sub>2.5</sub> kills those with no more than a high school degree, but not those with at least some college; men but not women; and the moderately active but not the very-active or sedentary. These odd variations in PM's ostensible effects don't seem biologically plausible and suggest that the apparent effect of PM<sub>2.5</sub> is actually spurious, resulting from failure to adequately control for confounding factors unrelated to air pollution.

Reanalysis of the ACS data has also shown that considering additional factors in the statistical analysis of the data can make the apparent PM<sub>2.5</sub> effect disappear. For example, when HEI investigators added migration rates into and out of cities to the statistical model relating PM<sub>2.5</sub> and premature death, the apparent effect of PM<sub>2.5</sub> declined by two-thirds and became statistically insignificant.<sup>11</sup>

Cities that lost population during the 1980s—Midwest “rust belt” cities that were in economic decline—also had higher average PM<sub>2.5</sub> levels. The hypothesis is that people who work and have the wherewithal to migrate are healthier than the average person. Thus, the apparent effect of PM<sub>2.5</sub> could actually have resulted from healthier people moving away from areas of the country that were in economic decline, rather than from a change in any individuals' health status due to PM exposure. This example demonstrates the limitations of observational studies. Without a randomized assignment to high and low levels of air pollution, there are almost certain to be unobserved differences between groups that confound the association of air pollution and health, creating spurious results. HEI's sensitivity analyses revealed other confounders that also diminished or eliminated the apparent PM<sub>2.5</sub>-mortality association.

The Harvard Six Cities study suffers from similar problems. It too found no association between PM<sub>2.5</sub> and mortality for people with more than a high school education. The HSC study also reported a statistically significant *decrease* in mortality due to respiratory causes in areas with higher PM<sub>2.5</sub> levels.

Three other epidemiology studies ignored or dismissed by EPA have concluded that PM<sub>2.5</sub> is not associated with increased mortality. One study followed 50,000 male veterans with high blood pressure—a group that should have been more susceptible than the average person to any negative effects of air pollution—over a period of 21 years and found that higher PM<sub>2.5</sub> was not associated with increased risk of death.<sup>12</sup> Another study

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<sup>10</sup> D. Krewski, R. T. Burnett, M. S. Goldberg et al., *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality* (Cambridge, MA: Health Effects Institute, July 2000); C. A. Pope, 3rd, R. T. Burnett, M. J. Thun et al., “Lung Cancer, Cardiopulmonary Mortality, and Long-Term Exposure to Fine Particulate Air Pollution,” *Journal of the American Medical Association* 287 (2002): 1132-41.

<sup>11</sup> Krewski, Burnett, Goldberg et al., *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality*.

<sup>12</sup> F. W. Lipfert, H. M. Perry, J. P. Miller et al., “The Washington University-EPRI Veterans' Cohort Mortality Study,” *Inhalation Toxicology* 12 (suppl. 4) (2000): 41-73.

assessed pollution and mortality at the county level and concluded that if PM<sub>2.5</sub> is increasing risk of death, the threshold was at least 23 µg/m<sup>3</sup>, which is higher than current PM<sub>2.5</sub> levels in more than 99 percent of country and 50 percent greater than EPA's annual PM<sub>2.5</sub> standard.<sup>13</sup> More recently, another cohort study followed 50,000 elderly Californians from 1973 to 2002 and reported that PM<sub>2.5</sub> was associated with a small increase in risk of death during the 1970s, but not from the 1980s onward.<sup>14</sup>

Even taken at face value, the ACS results suggest that whatever the harm from PM<sub>2.5</sub>, it has sharply dropped over time and the effect has become statistically insignificant. The original ACS study covered the period 1982-89 and reported a 6.9 percent increase in risk of death for each 10 µg/m<sup>3</sup> increase in long-term PM<sub>2.5</sub> levels. The follow-up report covered the period 1982-1998 and reported a 4 percent increase in the risk of death. If PM<sub>2.5</sub> was really the causal factor, this means the increased risk from PM<sub>2.5</sub> declined to no more than 3.1 percent for the 1990-98 period—a 55 percent decline in the size of the PM-mortality relationship between the 1980s and the 1990s.<sup>15</sup>

The ACS researchers did not point out this decrease in the apparent PM<sub>2.5</sub> effect size over time. They reported only results for the initial follow-up period (1982-1989) and then for the entire follow-up period (1982-1998). However, the results for the second follow-up period—1990 to 1998—can be inferred from the data presented in the two reports on the study. Other studies, including Enstrom (2005) and Lipfert et al. (2000) suggest a similar decline over time in apparent PM<sub>2.5</sub> relative risks.<sup>16</sup>

The fact that the apparent effect of any given level of PM<sub>2.5</sub> declined by more than half between the 1980s and the 1990s would seem to have great relevance for policy, but EPA has not acknowledged these results. If the declining effect of PM<sub>2.5</sub> represents a continuing trend, then even if we assume that the ACS study uncovered a real effect of PM<sub>2.5</sub>, that effect would by now have disappeared.

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<sup>13</sup> F. W. Lipfert and S. C. Morris, "Temporal and Spatial Relations between Age Specific Mortality and Ambient Air Quality in the United States: Regression Results for Counties, 1960-97," *Occupational and Environmental Medicine* 59 (2002): 156-74.

<sup>14</sup> J. E. Enstrom, "Fine Particulate Air Pollution and Total Mortality among Elderly Californians, 1973-2002," *Inhal Toxicol* 17 (2005): 803-16.

<sup>15</sup> To calculate the size of the PM mortality relationship for 1990-98, you need not only the effect sizes for 1982-89 and 1982-98, but also the fact that the number of deaths in the cohort was twice as high for the 1990-98 period as for the 1982-89 period (because the cohort was older), and also that the size of the cohort was expanded by 22 percent by adding in additional cities. Assuming the estimated PM<sub>2.5</sub> risks were the same, on average, for the added cities as for the original cities, the association of PM<sub>2.5</sub> with mortality would have dropped 55 percent between the two periods.

<sup>16</sup> Summarized in Table 10 of Enstrom, "Fine Particulate Air Pollution and Total Mortality among Elderly Californians, 1973-2002."

## Publication Bias, Data Mining, and More on Confounding

Additional challenges to the validity of the research literature on air pollution health effects are the related problems of publication bias and data mining. Publication bias refers to the tendency of researchers to seek publication of and for journals to accept mainly those studies that find a statistically significant effect, while not publishing studies that don't find an effect.<sup>17</sup> The related problem of data mining refers to the risk that observational studies can become statistical fishing expeditions that turn up chance correlations, rather than real causal relationships. As two recent reviews of air pollution epidemiology cautioned:

Publication bias arises because there are more rewards for publishing positive or at least statistically significant findings. It is a common if not universal problem in our research culture. In the case of time-series studies using routine data there are particular reasons why publication bias might occur. One is that the data are relatively cheap to obtain and analyse, so that there may be less determination to publish "uninteresting" findings. The other is that each study can generate a large number of results for various outcomes, pollutants and lags and there is quite possibly bias in the process of choosing amongst them for inclusion in a paper. In the field of air pollution epidemiology, the question of publication bias has only recently begun to be formally addressed.<sup>18</sup>

Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results.<sup>19</sup>

Publication bias and data-mining are important considerations for the cohort studies discussed above, but they are a far greater threat to the validity of the time-series studies. Time-series studies are relatively easy to perform, because they only require daily data on pollution levels, weather, and counts of daily non-accidental deaths in a given city. Probably thousands of studies have assessed the correlation between daily fluctuations in air pollution levels and risk of death. There are many ways to slice the data and the

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<sup>17</sup> Publication bias is a well-documented problem in a range of disciplines. See, for example, V. M. Montori, M. Smieja and G. H. Guyatt, "Publication Bias: A Brief Review for Clinicians," *Mayo Clinic Proceedings* 75 (2000): 1284-8; A. Thornton and P. Lee, "Publication Bias in Meta-Analysis: Its Causes and Consequences," *Journal of Clinical Epidemiology* 53 (2000): 207-16.

<sup>18</sup> H. Anderson, R. Atkinson, J. Peacock et al., *Meta-Analysis of Time-Series Studies and Panel Studies of Particulate Matter (Pm) and Ozone* World Health Organization, 2004), [www.euro.who.int/document/e82792.pdf](http://www.euro.who.int/document/e82792.pdf).

<sup>19</sup> T. Lumley and L. Sheppard, "Time Series Analyses of Air Pollution and Health: Straining at Gnats and Swallowing Camels?" *Epidemiology* 14 (2003): 13-4.

tendency is to selectively choose and publish those statistical models that give the largest apparent air pollution effects.

Naively combining the results from those studies that happen to have been published in the research literature therefore leads to an overestimate of air pollution's health effects. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) has demonstrated how large the effect of publication bias can be. NMMAPS does not suffer from publication bias, because it applied the same analytical methods to pollution and mortality data for 95 different U.S. cities and published all the results. A recent NMMAPS study of the relationship between ozone and mortality reported an ozone effect 70 percent lower than the result derived from meta-analysis of single-city studies, and concluded that publication bias inflates the ozone health effects estimated based on single-city studies.<sup>20</sup>

The NMMAPS researchers have not published an analysis of the effect of publication bias on estimates of PM effects. However, NMMAPS reported a much smaller PM<sub>10</sub> effect size than other studies—only about 0.2 to 0.25 percent per 10 µg/m<sup>3</sup> increase in PM<sub>10</sub>, as compared with effects of about 0.5 to one percent in single-city studies. A World Health Organization (WHO) study also showed that publication bias inflates the apparent effect of PM on mortality.<sup>21</sup>

Both the WHO analysis and NMMAPS reported additional results that add to concerns about the reliability of observational studies. One of the surprises from NMMAPS was that in about one-third of cities in the study, higher levels of particulate matter and ozone were associated with *lower* risks of premature death.<sup>22</sup> The results were also sensitive to a few outlier cities. When three cities were removed from the analysis—two with increased mortality and one with decreased mortality associated with PM—the average effect of PM across the cities in the study became statistically insignificant.<sup>23</sup> It isn't clear that an average pollution effect across cities even has any meaning when air pollution seems to protect people in some cities and harm them in others.

Like publication bias, data mining also inflates the apparent harm from air pollution, because researchers report only a few results out of many different statistical models they may have screened. To address this, some studies have reported on the results of screening large numbers of plausible models relating air pollution and daily mortality. One study showed that of more than 1,200 different models of air pollution and mortality,

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<sup>20</sup> M. Bell, J. Samet and F. Dominici, *Ozone and Mortality: A Meta-Analysis of Time-Series Studies and Comparison to a Multi-City Study (the National Morbidity, Mortality, and Air Pollution Study)* (Baltimore: Johns Hopkins School of Public Health, July 19, 2004), <http://www.bepress.com/cgi/viewcontent.cgi?article=1057&context=jhubiostat>.

<sup>21</sup> Anderson, Atkinson, Peacock et al., *Meta-Analysis of Time-Series Studies and Panel Studies of Particulate Matter (Pm) and Ozone*.

<sup>22</sup> M. L. Bell, A. McDermott, S. L. Zeger et al., "Ozone and Short-Term Mortality in 95 Us Urban Communities, 1987-2000," *Journal of the American Medical Association* 292 (2004): 2372-8. See figure 3, 2376.

<sup>23</sup> Moolgavkar, *Review of Chapter 8 of the Criteria Document for Particulate Matter (Comments Submitted to EPA)*.

more than one-third predicted that higher air pollution was associated with *lower* mortality.<sup>24</sup>

To address the problem of data-mining in a more comprehensive way, a few researchers have used a technique known as Bayesian model averaging (BMA). Though mathematically complicated, the technique is simple in principle: Take all possible statistical models relating air pollution and other factors, such as weather, to health outcomes; weight the models according to how well they fit the actual data; then take a weighted average of the results. This gives an average and an uncertainty range for the correlation between, say, particulate matter and death, after controlling for the effects of other factors that could affect health.

The result is literally hundreds of potential explanatory variables and trillions of potential models. A recent study based on Bayesian model averaging concluded that the effect of air pollution on mortality is statistically indistinguishable from zero.<sup>25</sup> They cautioned “a method that presents results from a single regression [that is, from a single statistical model] may lead researchers to make misleading inferences about pollution–mortality effects, thereby seriously underestimating the true uncertainty in the statistical evidence.”

Between publication bias, data mining, and uncontrolled confounding, observational studies have proven to be unreliable guides to air pollution health risks. Emphasizing the point, a recent study showed that adding a more sophisticated and complete adjustment for the health effects of weather can cause the apparent harm from PM and ozone to disappear.

When two British researchers allowed in their model for cumulative effects of heat stress over several days, as well as the additional effects of increases in direct sunshine and lower winds, both of which add to heat stress at any given temperature, the associations of air pollution and risk of death were reduced by 60 to 90 percent and became statistically insignificant.<sup>26</sup> In other words, weather confounders not addressed in previous air pollution-mortality studies were shown to eliminate the apparent air pollution-mortality correlation, suggesting that the correlation was spurious, rather than causal.

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<sup>24</sup> The various models differed in the way they controlled for weather and long-term trends. K. Ito, “Associations of Particulate Matter Components with Daily Mortality and Morbidity in Detroit,” in *Revised Analyses of Time-Series Studies of Air Pollution and Health* (Boston: Health Effects Institute, 2003).

<sup>25</sup> G. Koop and L. Tole, “Measuring the Health Effects of Air Pollution: To What Extent Can We Really Say That People Are Dying from Bad Air?” *Journal of Environmental Economics and Management* 47 (2004): 30-54.

<sup>26</sup> Even the BMA study described above did not account for this additional weather effect. W. R. Keatinge and G. C. Donaldson, “Heat Acclimatization and Sunshine Cause False Indications of Mortality Due to Ozone,” *Environmental Research* 100 (2006): 387-93.

## Controlled Animal and Human Studies Fail to Support PM Risk Claims

Given the unreliability of observational studies in cases where the magnitude of the potential risk is small, it is also important to note that controlled toxicological studies with animals have not found evidence that air pollution can cause disease or death at concentrations anywhere near as low as the levels found in ambient air in the United States.<sup>27</sup> A recent review of particulate matter toxicology concluded,

It remains the case that no form of ambient PM—other than viruses, bacteria, and biochemical antigens—has been shown, experimentally or clinically, to cause disease or death at concentrations remotely close to US ambient levels. This lack of demonstration is not for lack of trying: hundreds of researchers, in the US and elsewhere, have for years been experimenting with various forms of pollution-derived PM, and none has found clear evidence of significant disease or death at relevant airborne concentrations.<sup>28</sup>

Despite this conclusion, in December 2005 the *Journal of the American Medical Association* (JAMA) published the results of a study that claimed PM<sub>2.5</sub> at current ambient levels is increasing Americans' risk of developing heart disease. The study exposed mice to 85 µg/m<sup>3</sup> of PM<sub>2.5</sub> concentrated from ambient air for 6 months, or about one-fourth of a typical mouse life-span.<sup>29</sup> Mice fed a high-fat diet and exposed to PM<sub>2.5</sub> had more than a 50 percent greater rate of atherosclerosis (as measured by arterial plaque area) and other signs heart disease, when compared with a control fed a high-fat diet, but not exposed to PM<sub>2.5</sub>. PM<sub>2.5</sub> was associated with greater atherosclerosis in mice on a low-fat diet, but the effect wasn't statistically significant.

A National Institutes of Health press release on the study begins: “test results with laboratory mice show a direct cause-and-effect link between exposure to fine particle air pollution and the development of atherosclerosis...[The study] may explain why people who live in highly polluted areas have a higher risk of heart disease.”<sup>30</sup> The study caused a minor media sensation, with both journalists and health experts claiming the study provides strong evidence that particulate pollution is a significant risk factor in human heart disease.<sup>31</sup>

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<sup>27</sup> L. Green, E. Crouch, M. Ames et al., “What's Wrong with the National Ambient Air Quality Standard (Naaqs) for Fine Particulate Matter (Pm2.5)?” *Regulatory Toxicology and Pharmacology* 35 (2002): 327; L. C. Green and S. R. Armstrong, “Particulate Matter in Ambient Air and Mortality: Toxicologic Perspectives,” *Regulatory Toxicology and Pharmacology* 38 (2003): 326-35; Moolgavkar, “A Review and Critique of the EPA's Rationale for a Fine Particle Standard.”

<sup>28</sup> Green and Armstrong, “Particulate Matter in Ambient Air and Mortality: Toxicologic Perspectives.”

<sup>29</sup> Q. Sun, A. Wang, X. Jin et al., “Long-Term Air Pollution Exposure and Acceleration of Atherosclerosis and Vascular Inflammation in an Animal Model,” *Journal of the American Medical Association* 294 (2005): 3003-10.

<sup>30</sup> National Institutes of Health, “Air Pollution, High-Fat Diet Cause Atherosclerosis in Laboratory Mice,” Washington, DC, December 22, 2005, <http://www.nih.gov/news/pr/dec2005/niehs-22.htm>.

<sup>31</sup> Newspapers carrying articles on the study included the Los Angeles Times, Houston Chronicle, Philadelphia Inquirer, and several others.

Despite the enthusiastic reception, there's much less here than meets the eye. The mice in the study were genetically engineered in ways that make them unrepresentative of even real-world mice, much less people. The mice were engineered to remove the gene for apolipoprotein E, a key substance for fat and cholesterol metabolism. As a result, these apo E "knockout" mice have blood cholesterol levels 5 to 6 times greater than normal mice when fed regular rat chow. ApoE knockout mice have 14 times the cholesterol of normal mice when both are fed a high-fat diet.<sup>32</sup>

These are stupendous cholesterol levels. For comparison, medical authorities define "high cholesterol" as a serum cholesterol level greater than 240 milligrams per deciliter. That's only about 20 percent greater than the average cholesterol level in American men. Only one-in-50 American men has a cholesterol level more than 1.5 times the U.S. average, and only about one-in-500 exceeds twice the U.S. average.<sup>33</sup> Indeed, the very reason for using these grossly unrealistic mice to study PM<sub>2.5</sub> is that PM<sub>2.5</sub> does not kill regular mice or other animals at concentrations relevant to real-world human exposures.

If you build a house out of cards, you would expect even a gentle breeze to knock it down. But this doesn't tell you much about the ability of a wood-frame house to withstand a gentle breeze. Likewise, if you design an artificial mouse that can't regulate its fat or cholesterol levels, it isn't any surprise that even a minor environmental insult can cause it some health problems. But this doesn't tell you much about the effects of low-level air pollution levels on regular mice or on people.

The PM<sub>2.5</sub> doses used in the study were also not relevant to real-world PM<sub>2.5</sub> exposures. The NIH press release on the study claims that "the fine particle [PM<sub>2.5</sub>] concentrations used in the study were well within the range of concentrations found in the air around major metropolitan areas." The press release also quotes one of the study's authors saying that "The average exposure over the course of the study was 15 micrograms per cubic meter, which is typical of the particle concentrations that urban area residents would be exposed to, and well below the federal air quality standard of 65 µg/m<sup>3</sup> over a 24-hour period."<sup>34</sup>

These assertions are inaccurate. The mice were exposed to PM<sub>2.5</sub> at 85 µg/m<sup>3</sup> for 6 hours in a row during five days of each week, and filtered air the rest of the time. Over the 6-month study period, this does indeed average out to about 15 µg/m<sup>3</sup>, the level of the federal PM<sub>2.5</sub> annual standard. But in the real world, areas that average 15 µg/m<sup>3</sup> of PM<sub>2.5</sub> spend far less time with PM<sub>2.5</sub> as high as 85 µg/m<sup>3</sup>. In fact, even the highest PM<sub>2.5</sub> cities spend little time with PM<sub>2.5</sub> near 85 µg/m<sup>3</sup>.

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<sup>32</sup> A few of the news stories mentioned that the study used "specially bred mice prone to heart disease." But this is a great understatement, because it creates the impression that the mice were similar to humans who have a high heart disease risk, and therefore that the study is relevant for human beings. In reality, the mice were genetically engineered to have cholesterol far beyond even the highest levels that would ever occur in humans or in "natural" mice.

<sup>33</sup> Based on National Health and Nutrition Examination Survey (NHANES) data on 4,090 adult men collected from 1999-2002. Data were downloaded from <http://www.cdc.gov/nchs/nhanes.htm>.

<sup>34</sup> National Institutes of Health, "Air Pollution, High-Fat Diet Cause Atherosclerosis in Laboratory Mice,"

For example, in the mouse study, the mice spent the equivalent of 1,560 hours per year breathing  $85 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  (30 hours per week x 52 weeks per year). In contrast, Modesto, California averaged  $16 \mu\text{g}/\text{m}^3$  of  $\text{PM}_{2.5}$  over the past year, but spent only 80 hours at  $85 \mu\text{g}/\text{m}^3$  or above.<sup>35</sup> Forty percent of those high-PM hours occurred between 11 PM and 6 AM, when most people are in bed. There were only 420 hours where Modesto exceeded even  $50 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ —still less than one-third the amount of time the mice were exposed to  $85 \mu\text{g}/\text{m}^3$ .

Even areas with the highest  $\text{PM}_{2.5}$  levels in the country have far fewer hours of high  $\text{PM}_{2.5}$  than were used in the mouse study. For example, Riverside, California averaged  $27 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  over the past year, but had only 135 hours at or above  $85 \mu\text{g}/\text{m}^3$ , and 1,055 hours above  $50 \mu\text{g}/\text{m}^3$ —still much less than the 1,560 hours at  $85 \mu\text{g}/\text{m}^3$  in the mouse study.

Health effects depend not only on the average dose, but on the acute dose. For example, you could take 2 aspirins 4 times per day, or you could take 8 all at once each day. Either way, your average dose is 8 aspirins per day. But you're more likely to suffer ill effects if you take the aspirins all at once. The mice received an analogously unrealistic daily  $\text{PM}_{2.5}$  exposure.

I've discussed the JAMA mouse study in detail, because it was released at the same time EPA released its proposed  $\text{PM}_{2.5}$  NAAQS rule. Given the timing, journalists and environmental activists cited the study as supporting tougher  $\text{PM}_{2.5}$  standards. They are mistaken. The JAMA mouse study leads to just the opposite conclusion.  $\text{PM}_{2.5}$  has such minute health effects that to even get  $\text{PM}_{2.5}$  to cause an increase in heart disease you need mice specially engineered to have unrealistically stupendous cholesterol levels, you have to feed them a high-fat diet, and you have to expose them to unrealistically high acute doses of  $\text{PM}_{2.5}$  five days a week, every week, for a quarter of their lives. Based on the JAMA mouse study, the current  $\text{PM}_{2.5}$  NAAQS are health-protective with plenty of room to spare.

Studies with human volunteers have also failed to support claims about the risks of contemporary  $\text{PM}_{2.5}$  levels. For example, much  $\text{PM}_{2.5}$  comes in the form of ammonium sulfate and ammonium nitrate. Laboratory studies with human volunteers, including volunteers with respiratory diseases, have shown that sulfate and nitrate are non-toxic, even at levels many times the maximum levels found in ambient air.<sup>36</sup>

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<sup>35</sup> Hourly  $\text{PM}_{2.5}$  data were downloaded from CARB at <http://www.arb.ca.gov/aqmis2/paqdselect.php>.

<sup>36</sup> Green and Armstrong, "Particulate Matter in Ambient Air and Mortality: Toxicologic Perspectives."; M. T. Kleinman, W. S. Linn, R. M. Bailey et al., "Effect of Ammonium Nitrate Aerosol on Human Respiratory Function and Symptoms," *Environmental Research* 21 (1980): 317-26; M. A. Sackner, D. Ford and R. Fernandez, "Effect of Sulfate Aerosols on Cardiopulmonary Function of Normal Humans," *American Review of Respiratory Diseases* 115

(1977): 240; M. J. Utell, P. E. Morrow, D. M. Speers et al., "Airway Responses to Sulfate and Sulfuric Acid Aerosols in Asthmatics. An Exposure-Response Relationship," *American Review of Respiratory Disease* 128 (1983): 444-50; M. J. Utell, A. J. Swinburne, R. W. Hyde et al., "Airway Reactivity to Nitrates in Normal and Mild Asthmatic Subjects," *Journal of Applied Physiology* 46 (1979): 189-96.

In fact, ammonium sulfate has been used as an inert control—that is, a compound not expected to have any health effects—in studies of the health effects of acidic aerosols.<sup>37</sup> Inhaled magnesium sulfate is used therapeutically to *reduce* airway constriction in asthmatics.<sup>38</sup>

Laboratory studies also provide little evidence of acute effects from motor-vehicle-related PM—at least at levels representative of real-world exposures. For example, a Health Effects Institute (HEI) study exposed healthy and asthmatic volunteers to 200  $\mu\text{g}/\text{m}^3$  of concentrated ambient PM<sub>2.5</sub> collected in the Los Angeles area. The exposures lasted for 2 hours and the subjects exercised intermittently to increase their respiration rate and therefore their acute PM<sub>2.5</sub> exposures.<sup>39</sup> This represents a “worst-case” real-world PM<sub>2.5</sub> exposure. Even areas with the highest PM<sub>2.5</sub> levels in the country average only about 25  $\mu\text{g}/\text{m}^3$  of PM<sub>2.5</sub>, and peak hourly levels rarely exceed even 100  $\mu\text{g}/\text{m}^3$ .<sup>40</sup>

Despite the relatively high PM<sub>2.5</sub> levels in the study, there were no changes in symptoms or lung function in either the healthy or asthmatic subjects, and little evidence of inflammatory responses. Since many inflammatory markers were measured, and only a few changed, the authors pointed out that these changes could be due to chance.

Another HEI study exposed both healthy and asthmatic volunteers to 100  $\mu\text{g}/\text{m}^3$  of diesel soot for 2 hours while they exercised intermittently on a stationary bicycle.<sup>41</sup> The researchers found little evidence an inflammatory response, and the healthy subjects exhibited more evidence of inflammation than the asthmatics. According to the project summary, the study “did not find inflammatory changes in asthmatic participants after controlled exposure to diesel exhaust.”

## Summary and Recommendations

The evidence indicates that observational studies are not providing reliable information about real air pollution health effects, but are instead turning up spurious correlations due to uncontrolled confounding, publication bias, and data mining. EPA and CASAC have ignored the evidence that observational studies can not provide reliable information on PM<sub>2.5</sub> health effects. They have been selective in the use of this evidence as well, highlighting studies and portions of studies claiming a PM<sub>2.5</sub>-mortality association, while ignoring or dismissing studies or portions of studies that fail to find such an association or that even report a “beneficial” effect of PM<sub>2.5</sub>. They have also ignored the lack of

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<sup>37</sup> J. Q. Koenig, K. Dumler, V. Rebolledo et al., “Respiratory Effects of Inhaled Sulfuric Acid on Senior Asthmatics and Nonasthmatics,” *Archives of Environmental Health* 48 (1993): 171-5.

<sup>38</sup> L. J. Nannini, Jr. and D. Hofer, “Effect of Inhaled Magnesium Sulfate on Sodium Metabisulfite-Induced Bronchoconstriction in Asthma,” *Chest* 111 (1997): 858-61.

<sup>39</sup> H. Gong, Jr., C. Sioutas and W. S. Linn, “Controlled Exposures of Healthy and Asthmatic Volunteers to Concentrated Ambient Particles in Metropolitan Los Angeles,” *Research Report / Health Effects Institute* (2003): 1-36; discussion 37-47.

<sup>40</sup> For example, between February 2005 and January 2006, Riverside, California had a total of one hour with PM<sub>2.5</sub> greater than 200  $\mu\text{g}/\text{m}^3$ , and 6 hours with PM<sub>2.5</sub> greater than 150  $\mu\text{g}/\text{m}^3$ . Bakersfield, California had 3 hours with PM<sub>2.5</sub> greater than 150  $\mu\text{g}/\text{m}^3$  and 200  $\mu\text{g}/\text{m}^3$ .

<sup>41</sup> S. T. Holgate, T. Sandstrom, A. J. Frew et al., “Health Effects of Acute Exposure to Air Pollution. Part I: Healthy and Asthmatic Subjects Exposed to Diesel Exhaust,” *Research Report / Health Effects Institute* (2003): 1-30; discussion 51-67.

robustness of these studies. Sensitivity analyses have shown that previously unacknowledged confounders eliminate the PM<sub>2.5</sub>-mortality association when added to statistical models.

Nevertheless, the spurious results of these studies, filtered through an EPA vetting process that favors those results that support agency goals, are the main justification for the federal PM<sub>2.5</sub> NAAQS and for EPA's current proposal to tighten the PM<sub>2.5</sub> NAAQS. Controlled laboratory studies, in contrast, suggest that PM<sub>2.5</sub> is not deadly at current levels, yet these results do not seem to have affected EPA or CASAC's conclusions.

None of the discussion above would matter if we could reduce air pollution for free. If reducing air pollution were free, we would eliminate all air pollution, even if we had grave doubts about the health effects claims, just on the off chance that even low-level air pollution might be causing some harm.

But reducing air pollution is costly. These costs are ultimately paid by people in the form of higher prices, lower wages, and reduced choices.<sup>42</sup> We all have many needs and aspirations and insufficient resources with which to fulfill them. Spending more on air quality means spending less on other things that improve our health, safety, and quality of life. Air quality regulation proceeds from the false assumption that these tradeoffs do not exist.

Higher incomes are associated with improved health, because people spend a portion of each additional dollar of income on things that directly or indirectly improve health and safety, such as better medical care, more crashworthy cars, and more nutritious food.<sup>43</sup> People made poorer by the costs of regulations do fewer of these things and are less healthy and safe as a result. Risk researchers estimate that every \$17 million in regulatory costs induces one additional statistical death.<sup>44</sup> Thus, regulations are not pure risk reduction measures, but instead inevitably impose tradeoffs between the health benefits of the regulation and the harm from the regulation's income-reducing costs.

Even if we could somehow convince ourselves that additional air pollution reductions would confer net benefits, focusing on air pollution would still be a second-best policy, because other measures would provide far greater health benefits per dollar invested. Based on an assessment of more than 500 life-saving measures in four categories—

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<sup>42</sup> A. P. Bartel and L. G. Thomas, "Predation through Regulation: The Wage and Profit Effects of the Occupational Safety and Health Administration and the Environmental Protection Agency," *Journal of Law and Economics* 30 (1987): 239; D. Schoenbrod, "Protecting the Environment in the Spirit of the Common Law," in *The Common Law and the Environment: Rethinking the Statutory Basis for Modern Environmental Law*, ed. R. E. Meiners and A. P. Morriss (Lanham, MD: Rowman & Littlefield, 2000); A. Wildavsky, *Searching for Safety* (New Brunswick, NJ: Transaction Publishers, 1988). The costs of environmental regulations are also regressive, falling more heavily on the poorest. See F. B. Cross, "When Environmental Regulations Kill: The Role of Health/Health Analysis," *Ecology Law Quarterly* 22 (1995): 729; H. D. Robinson, "Who Pays for Industrial Pollution Abatement?" *Review of Economics and Statistics* 67 (1985): 702-06.

<sup>43</sup> R. Lutter, J. Morrall, III and W. Viscusi, "The Cost-Per-Life-Saved Cutoff for Safety-Enhancing Regulations," *Economic Inquiry* 37 (1999): 599-608; W. K. Viscusi, "The Value of Risks to Life and Health," *Journal of Economic Literature* 31 (1993): 1912-46; Wildavsky, *Searching for Safety*.

<sup>44</sup> Lutter, Morrall and Viscusi, "The Cost-Per-Life-Saved Cutoff for Safety-Enhancing Regulations." The value is adjusted from 1997 to 2004 dollars based on the CPI.

environmental pollution reduction, workplace safety, injury prevention, and medical care—researchers at the Harvard School of Public Health concluded that environmental measures saved by far the fewest years of life per dollar invested.<sup>45</sup>

We could glibly say that we should undertake all available risk-reduction measures and save as many lives as possible. But this begs the question. If we lived in a world of infinite resources and omniscience about the full consequences of our actions, then we would of course undertake literally all health and safety measures available. But in such a world there would be no politics or policy debates over environmental regulations or over anything else. Politics and policy debates exist exactly because resources and knowledge are scarce and insufficient to satisfy all our needs and aspirations. Maximizing human welfare requires spending these scarce resources in ways that generate the greatest health and welfare improvements per dollar invested. Spending money on air pollution means choosing to save far fewer lives than if the same amount of money were spent in other ways.

One might argue that talking about other ways to reduce risk is irrelevant, because it is not as if money is sitting around waiting to be spent on risk reductions and air pollution is just one of many choices. We can choose to reduce air pollution or not, but if we choose not to, this does not mean the government will fund some other risk-reduction measure(s). This reasoning implicitly assumes that only publicly determined risk-reduction priorities and expenditures are legitimate. If people aren't forced to spend money to attain EPA's standards, they will have more money to spend as they see fit. People will spend these funds to improve their health, welfare, and quality of life as they define it. And they will be better off than if they had been forced to spend the money on air pollution reductions that deliver tiny benefits compared to the costs imposed.

Despite the inextricable link between regulatory costs and Americans' health and safety, the Clean Air Act nonsensically requires EPA to set air pollution standards without regard to the costs of attaining them. Unfortunately, Congress can't by law will away the real harm imposed by the costs of attaining federal air pollution standards. We bear them just the same.

However, because attempting to attain the NAAQS does cause offsetting harm to Americans' health, EPA should set the NAAQS at the highest possible level consistent with its CAA charge to protect public health "with an adequate margin of safety." In this way, EPA can meet the letter of the law while also giving a tacit nod to the real-world tradeoff between health improvement from lower air pollution and health degradation due to regulatory costs.

The evidence on the health effects of PM<sub>2.5</sub> indicates that the current federal PM<sub>2.5</sub> NAAQS are more than adequate for protecting public health. EPA should acknowledge this evidence, reject its proposed PM<sub>2.5</sub> NAAQS rule, and not consider any further tightening of federal PM<sub>2.5</sub> standards.

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<sup>45</sup> T. O. Tengs, M. E. Adams, J. S. Pliskin et al., "Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness," *Risk Analysis* 15 (1995): 369-90. Tengs et al. estimated the cost at \$42,000 in 1993 dollars. The value in the text is adjusted to 2004 dollars.