Review of *Environmental Science & Technology* Manuscript ID es-2021-03653z

James E. Enstrom, PhD, MPH, FFACE

July 8, 2021

Low-concentration air pollution and mortality in American older adults: A national cohort analysis (2001-2017)

Liuhua Shi*[1], ScD, Andrew Rosenberg*[1], MPH, Pengfei Liu[2], PhD, Mahdieh Danesh Yazdi[3], PhD, Weeberb Réquia[4], PhD, Kyle Steenland[1], PhD, Howard Chang[5], PhD, Jeremy A. Sarnat[1], ScD, Yang Liu[1], PhD, Kuo Zhang[1,6], MPH, Jingxuan Zhao[7], MPH, Joel Schwartz[3,8], PhD

* LS and AR contribute equally.

1 Gangarosa Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA
2 School of Earth and Atmospheric Sciences, Georgia Institute of Technology, Atlanta, Georgia, USA
3 Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
4 School of Public Policy and Government, Fundação Getúlio Vargas, Brasília, Distrito Federal, Brazil
5 Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA
6 Department of Earth System Science, Tsinghua university, Beijing, China
7 Surveillance and Health Services Research Program, American Cancer Society, Atlanta, Georgia, USA
8 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Lack of Epidemiologic Qualifications of Authors

Lead co-author Dr. Liuhua Shi is Emory University Research Assistant Professor of Environmental Health (https://sph.emory.edu/faculty/profile/index.php?FID=liuhua-shi-10928). She has a 2016 ScD in Environmental Health from Harvard TH Chan School of Public Health (HTHCSPH) and a 2009 BS and 2012 MS in Geography from Beijing Normal University in China. Her 2016 ScD Dissertation, "Estimating Health Effects of Temperature and pm2.5 Using Satellite-Retrieved High-Resolution Exposures," was apparently obtained under the direction of Senior Author and HTHCSPH Professor Joel D. Schwartz. She states "My research focuses on employing massive datasets, including satellite-retrieved high resolution exposures and health data of all Medicare beneficiaries, to investigate how climate change and air pollution influence seniors' health." However, she lists no formal training in Epidemiology, the discipline most relevant to the above manuscript.

Lead co-author Mr. Andrew Rosenberg has a 2021 MPH in Environmental Health from Emory University and is a "Master Student" member of Dr. Shi's "The Environment and Seniors' Health Research Group" (https://www.liuhuashi.com/people/). He lists no formal training in Epidemiology. The stated goal of this Group "is to leverage massive nationwide datasets, including satellite-retrieved high-resolution environmental exposure data and individual-level longitudinal health records, to better understand the influence of environmental risk factors on older adults' health and better frame environmental policy." The Group website does not cite any of the severe flaws of ecological epidemiology used in the Group publications (https://www.liuhuashi.com/publications/).

Based on an initial examination of backgrounds of the ten other authors, they have little or no formal training in epidemiology.

Lack of Public Health Basis for Study Because Current Air Pollution Levels in the US are Very Low

There is NO public health basis for this study because the US already has very low levels of air pollution. Indeed, several of these levels are not much higher than natural background levels. In recent years, the US has had far lower PM2.5 than most other countries. At present, PM2.5 levels in the US are about one-sixth the global average, one-seventh of the China average, and one half of the continental Europe average, as per the 2019 State of Global Air Map (https://www.stateofglobalair.org/data/#/air/map), which is shown on page 30 of this review. In 2019, the average annual population-weighted PM2.5 level was **7.7 µg/m3 in the US** and **48 µg/m3 in China**. The lowest PM2.5 level anywhere in the world was about 6 µg/m3, which must be considered as a realistic minimum level.

Specific Criticism of Manuscript

1. The Abstract makes unjustified scientific and policy claims about air pollution.

Abstract Claims (Line 45): "There was strong evidence of linearity in concentration-response relationships for PM2.5 and NO2 at levels below the current NAAQS, suggesting that no safe threshold exists for health-harmful pollution levels. For O3, the concentration-response relationship shows an increasingly positive association at levels above 30-ppb. In conclusion, long-term exposures to PM2.5, NO2, and O3 were significantly associated with an increased risk of all-cause mortality, particularly at levels below the current NAAQS standards, suggesting that implementing more stringent regulations in air quality may yield substantial health benefits."

There is extensive peer-reviewed evidence that does not support the validity of the EPA NAAQS and the authors have not cited any of this evidence. Instead, the authors suggest "implementing more stringent regulations in air quality" based on their selective and biased analysis of Medicare data that was never intended for this type of analysis. The manuscript completely ignores 30+ years of severe criticism of the ecologic epidemiology used to relate air pollution to mortality. The Senior Author Joel Schwartz is WELL AWARE of this criticism and he continues to deliberately ignore it. A sample of the criticism is shown on pages 6-29 of this review: the classic 1988 AJE "The Ecological Fallacy" (doi:10.1093/oxfordjournals.aje.a114892); the 2002 RTP critique of the PM2.5 NAAQS by Green and Lash (doi:10.1006/rtph.2002.1548); the 2017 and 2018 D-R Reanalysis articles by Enstrom, and the June 29, 2020 Enstrom Comment to EPA on the PM2.5 NAAQS (Enstrom 2020) (http://www.scientificintegrityinstitute.org/EPAPM25JEE062920.pdf).

Note that the 2002 RTP critique, co-authored by Dr. Timothy Lash, current Chair of the Emory University Department of Epidemiology, states: "Associations between airborne concentrations of fine particulate matter (PM2.5) and mortality rates have been investigated primarily by ecologic or semiecologic epidemiology studies. Many investigators and regulatory agencies have inferred that the weak, positive association often observed is causal, that it applies to all forms of airborne PM2.5, and that current ambient levels of PM2.5 require reduction. Before implementing stringent regulations of ambient PM2.5, analysts should pause to consider whether the accumulated evidence is sufficient, and sufficiently detailed, to support the PM2.5 National Ambient Air Quality Standard. . . . Taken together, the toxicologic evidence and lessons learned from analogous epidemiologic associations should encourage further investigation of the association between particulate matter and mortality rates before additional regulation is implemented, and certainly before the association is characterized as causal and applicable to all PM2.5." The PM2.5 death associations have been continuously challenged

since the PM2.5 NAAQS was established in 1997, as documented in Enstrom 2020 (pages 10-29 of this review).

2. The Introduction falsifies the research record regarding PM2.5 and mortality in the US

Introduction Claims (Line 62): "Increasing epidemiological evidence has documented the associations between long-term exposure to fine particulate matter (particles with a mass aerodynamic diameter below 2.5 µm (PM2.5) and reduced life expectancy among adults.(3-7)" References 3 to 7 do not objectively describe the existing US evidence on PM2.5 deaths. Reference 3 (Wu 2020, line 373), Reference 4 (Di 2017, line 376), Reference 7 (Wang 2020, line 384) cite other PM2.5 death findings by Senior Author Schwartz based on Medicare records. These various overlapping findings involve tiny relative risks that do not establish a causal connection between PM2.5 and mortality. The claims of PM2.5 deaths in the ACS CPS II cohort in Reference 5 (Krewski 2009, line 379) were shown to be seriously flawed by Enstrom 2017 and Enstrom 2018. Reference 6 (Ostro 2015, line 381) actually found NO relationship between PM2.5 and total mortality in the CTA cohort, as shown in Enstrom 2017. Enstrom 2020 presents strong evidence that there is NO significant relationship between PM2.5 and total mortality in the US. Furthermore, this current review challenges the validity of all claims of a causal relation between PM2.5 and total deaths based on the multiple ecological epidemiologic analyses of Medicare records by these authors.

3. The Materials *Study Population* section involves likely violations of NIH Human Subjects Research Regulations

Line 98: "Health data were obtained from the Centers for Medicare and Medicaid Services (CMS), including all [68.7 million] Medicare beneficiaries, aged 65 years or older, in the contiguous United States from 2001-2017. We extracted data including age and year of Medicare entry, sex, race, Medicaid eligibility (a proxy for SES), the date of death, and ZIP code of residence **for each beneficiary**. Medicaid eligibility and ZIP code were updated annually. We constructed an open, full cohort containing all Medicare beneficiaries who were alive on January 1 of the year following enrollment into Medicare, through each calendar year of follow-up, with all-cause mortality as the outcome of interest."

I contend that the authors of this manuscript have made unethical use of personal and medical data on 68.7 million Medicare beneficiaries. These beneficiaries include me, many of my extended family members, and many of my scientific colleagues. Consent was never given my me or my family members or my scientific colleagues to have our personal Medicare data used for ecologic epidemiology that I am explaining in this review is bad science. The age and year of Medicare entry, sex, race, Zip code of residence, and date of death is sufficient to identify many beneficiaries, even without their name or exact address. I can identify specific beneficiaries if the investigators produce the deidentified Medicare records for beneficiaries who died during 2001-2005 in a Zip Code that I specify. If the investigators refuse to produce the requested Medicare records, I will use their refusal as evidence that they do not support transparent and reproducible research.

I contend that this NIEHS-funded research violates NIH Human Subjects Research Regulations (https://grants.nih.gov/policy/humansubjects.htm). This research does not satisfy NIH Human Subjects

Exemption Categories (https://grants.nih.gov/sites/default/files/exemption_infographic_v8_508c_1-15-2020.pdf) and does not satisfy the NIH Requirements for Waiver of Informed Consent (https://policymanual.nih.gov/3014-301). Exemption Categories are shown on page 31 of this review. Thus, the authors must provide the evidence that substantiates their claim (Line 110) "This study was approved by the Institutional Review Board of Emory University and a waiver of informed consent was granted." Because of the seriousness of these violations, I am currently pursuing the matter with the appropriate officials at Emory University and the Centers for Medicare and Medicaid Services.

4. The Results section misrepresents full analysis of PM2.5 and deaths in Medicare cohort

Line 208: "Our findings indicate that long-term exposure to PM2.5, NO2, and O3 was significantly associated with an increased risk of all-cause mortality, particularly at levels below the current NAAQS standards for each pollutant (Fig. 2). Line 213: "Assessing each pollutant individually in the full cohort analysis, a 10-µg/m3 increase in PM2.5 . . . was associated with an increase in mortality rate (i.e., HR-1) ranging between 5-7% . . . . In contrast, the low exposure analysis yielded larger effect estimates, with corresponding increases in mortality rate ranging between 10-13% . . . ."

The focus in the Results and the Abstract is on the "low exposure" Medicare beneficiaries, where the HR for PM2.5 has a maximum value of 1.13. But for the full cohort, the HR for PM2.5 averages 1.06 for single-pollutant models and 1.02 for the three-pollutant models, as shown in Figure 2 (Line 253). These HRs are etiologically insignificant and the most likely reason that they are slightly positive is because of selective analysis, the ecological fallacy, and lack of proper control of confounders.

In addition, the authors have not mentioned the large geographic variation found in the first major analysis of Medicare data, the 2008 *EHP* article "Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000–2005)" (doi:10.1289/ehp.11449). Table 3 of the *EHP* article shows large unexplained geographic variation in PM2.5 mortality risk in the Eastern, Central, and Western portions of the US. There was NO relationship in the Western US (mainly CA) and CA is the state which has been subjected to the most restrictive PM2.5 regulations.

The geographic variation in HR (RR) from the *EHP* Table 3 is shown below.

	Eastern US	Central US	Western US	Total US
Age-adjusted HR:	1.155 (1.130-1.180)	1.178 (1.133-1.222)	1.003 (0.981-1.025)	1.091 (1.076-1.107)
Age+SES-adjusted HR:	1.105 (1.084-1.125)	1.089 (1.052-1.125)	0.997 (0.978-1.016)	1.056 (1.043-1.069)
Age+SES+COPD-adjusted HR:	1.068 (1.049-1.087)	1.132 (1.095-1.169)	0.989 (0.970-1.008)	1.044 (1.032-1.057)

The authors must acknowledge this large unexplained geographic variation in their current manuscript. Indeed, the authors must acknowledge that the US HR in the total Medicare cohort may be NULL if it could be fully and properly adjusted on the individual level to account for sex, race, cigarette smoking, education level, co-pollutants, and other relevant confounders. Enstrom 2020 documents that the HR is NULL for nine US cohorts, including the 2008 Medicare cohort, as shown on page 14 of this review.

5. Conclusion is not justified because of all criticisms in this review.

Line 346: “Using a large nationwide cohort and robust epidemiological analyses, we provide strong evidence that long-term exposure to PM2.5, NO2, and O3, at levels below the current national standards, is significantly and independently associated with increased mortality. Amending national standards in the future may pose substantial public health benefits.”

This Conclusion is a complete distortion of their own analysis of the Medicare cohort, for the reasons described throughout this entire review. The authors provide NO evidence that “Amending national standards in the future may pose substantial public health benefits.”

Manuscript Decision: Unequivocally, do not publish this manuscript .

Potential Alternative: A point-counterpoint on the air pollution epidemiology, where Enstrom makes the point criticizing air pollution epidemiology and Schwartz makes the counterpoint promoting air pollution epidemiology.

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 127, No. 5
Printed in U.S.A.
Copyright © 1988 by The Johns Hopkins University School of Hygiene and Public Health
All rights reserved

THE ECOLOGICAL FALLACY

STEVEN PIANTADOSI,[1,2] DAVID P. BYAR,[1] AND SYLVAN B. GREEN[1]

The purpose of this paper is to emphasize for epidemiologists the possibility of serious errors resulting from inferences based on ecological analyses. Variables that describe groups of individuals, rather than the individuals themselves, are termed "ecological" and are often used when the analysis of individuals' data is not possible (1). Ecological analyses may be preferred when 1) variables are more conveniently defined or measured on groups because the analysis on individuals would require excessive time or extensive data gathering; 2) ecological analyses permit study of a wider range of values for the independent variable, as in international studies of diet; 3) the precision of aggregate measures like alcohol consumption is likely to be higher for groups than for individuals; and 4) population responses such as smoking quit rates may be of primary interest. Frequently, more than one reason applies. For example, some of the evidence favoring environmental and dietary causes of cancer comes from the comparison of incidence or mortality rates with average levels of risk factors measured on culturally or geographically defined groups of individuals. The first three reasons are relevant to this type of study.

We assume in this paper that measurements on individuals are not available, as in the diet and cancer example, since when this information is known, it might be used in place of, or to correct for biases in, the ecological analysis. Serious errors can result when an investigator makes the seemingly natural assumption that the inferences from an ecological analysis must pertain either to the individuals within the groups or to individuals across groups. A frequently cited early example of an ecological inference was Durkheim's study of the correlation between suicide rates and religious denominations in Prussia (2) in which the suicide rate was observed to be correlated with the number of Protestants. However, it could as well have been the Catholics who were committing suicide in largely Protestant provinces. The potential falsity of ecological inferences, at least in the case of simple correlations, was pointed out by Robinson (3), who gave it the name "ecological fallacy" and provided the mathematical relation, without proof, between the ecological correlation and the individual correlation across all groups. Duncan et al. (4) have extended the equations to include simple linear regression coefficients. The dangers of inferences about individuals from ecological studies have been emphasized by some investigators (5–7), while others (8–11) have sought to minimize the concern over the possible biases in ecological analyses, proposing alternatives or delineating circumstances in which ecological inferences are justified (e.g., certain linear regression models when data on individuals are available). Firebaugh (11) gives a particularly thorough discussion and list of references related to this aspect of the problem.

Although there has been a persistent interest in the problems associated with ecological analyses in the social science literature, the impression seems to remain, even among seasoned epidemiologists, that ecological analyses may not have large biases,

[1] Biometry Branch, Division of Cancer Prevention and Control, NCI, NIH, Bethesda, MD.
[2] Current address: The Johns Hopkins University, Department of Oncology/Biostatistics, 550 N. Broadway, Suite 1103, Baltimore, MD 21205. (Reprint requests to Dr. Steven Piantadosi at this address.)

The authors thank Dr. Sholom Wacholder, Dr. Charles Brown, and Dr. Peter Greenwald for helpful comments and Jennifer Gaegler for manuscript assistance.

Downloaded from aje.oxfordjournals.org at University of California, Los Angeles on August 3, 2011

Regulatory Toxicology and Pharmacology **35,** 327–337 (2002)
doi:10.1006/rtph.2002.1548

What's Wrong with the National Ambient Air Quality Standard (NAAQS) for Fine Particulate Matter ($PM_{2.5}$)?

Laura C. Green,*,[1] Edmund A. C. Crouch,* Michael R. Ames,* and Timothy L. Lash†

*Cambridge Environmental, 58 Charles Street, Cambridge, Massachusetts 02141; and †Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts 02118

Received January 11, 2002

Associations between airborne concentrations of fine particulate matter ($PM_{2.5}$) and mortality rates have been investigated primarily by ecologic or semiecologic epidemiology studies. Many investigators and regulatory agencies have inferred that the weak, positive association often observed is causal, that it applies to all forms of airborne $PM_{2.5}$, and that current ambient levels of $PM_{2.5}$ require reduction. Before implementing stringent regulations of ambient $PM_{2.5}$, analysts should pause to consider whether the accumulated evidence is sufficient, and sufficiently detailed, to support the $PM_{2.5}$ National Ambient Air Quality Standard. We take two tacks. First, we analyze the toxicologic evidence, finding it inconsistent with the notion that current ambient concentrations of all forms of fine particulate matter should affect pulmonary, cardiac, or all-cause mortality rates. More generally, we note that the thousands of forms of $PM_{2.5}$ are remarkably diverse, yet the $PM_{2.5}$ NAAQS presumes them to be identical toxicologically, and presumes that reducing ambient concentrations of any form of $PM_{2.5}$ will improve public health. Second, we examine the epidemiologic evidence in light of two related examples of semiecologic associations, examples that both inform the PM–mortality association and have been called into question by individual-level data. Taken together, the toxicologic evidence and lessons learned from analogous epidemiologic associations should encourage further investigation of the association between particulate matter and mortality rates before additional regulation is implemented, and certainly before the association is characterized as causal and applicable to all $PM_{2.5}$. © 2002 Elsevier Science (USA)

***Key Words*: particulate matter ($PM_{2.5}$); air pollution; National Ambient Air Quality Standard (NAAQS); health effects; ecologic fallacy; epidemiology.**

INTRODUCTION

Many observational studies have reported weak, positive associations between rates of mortality in populations and moderate concentrations of fine particulate matter ($PM_{2.5}$)[2] measured in ambient air near those populations (see Lipfert and Wyzga, 1995; and Krewski *et al.*, 2000, for reviews). These observational studies include cross-sectional studies (Dockery *et al.*, 1993; Pope *et al.*, 1995), in which mortality in various metropolitan areas is associated with ambient concentrations of $PM_{2.5}$ in those areas, and time-series studies (Samet *et al.*, 2000), in which daily mortality[3] within a metropolitan area is associated with concurrent or lagged daily fluctuations in ambient $PM_{2.5}$ concentrations.

The U.S. Environmental Protection Agency (U.S. EPA, 1996, 1997, 2001) and others (Pope, 2000; Ware, 2000) have taken these associations to be causal, and U.S. EPA has proposed that $PM_{2.5}$ in ambient air be stringently regulated (U.S. EPA, 1997). In particular, the fine particulate matter National Ambient Air Quality Standard (NAAQS) mandates that $PM_{2.5}$ in ambient air not exceed 15 $\mu g/m^3$ as an annual average (calculated as the mean of 3 years of quarterly means of 24-h measurements) and 65 $\mu g/m^3$ as a 24-h standard (calculated as the 98th percentile of 24-h measurements). Although sufficient data on ambient $PM_{2.5}$ have yet to be amassed for portions of the country, indications from many metropolitan areas are that this $PM_{2.5}$ NAAQS will commonly be exceeded (Fitz-Simons *et al.*, 2000), so that emission sources of $PM_{2.5}$ and its precursors will require additional control. Cost estimates for such controls nationwide range from $8 to $150 billion annually (*http://www.rppi.org/es226.html*).

We and others (Lipfert and Wyzga, 1995; Phalen and McClellan, 1995; Moolgavkar and Luebeck, 1996;

[1] To whom correspondence should be addressed. Fax: (617) 225-0813. E-mail: Green@CambridgeEnvironmental.com.

[2] $PM_{2.5}$ refers to all airborne solid or liquid particles with a mass mean aerodynamic diameter less than or equal to 2.5 μm.

[3] Some studies have also investigated various rates of morbidity, such as admissions to emergency rooms for respiratory problems, but the relevant mortality studies have been more numerous, are easier to compare, and form the central basis for the $PM_{2.5}$ NAAQS.

0273-2300/02 $35.00
© 2002 Elsevier Science (USA)
All rights reserved.

Dose-Response:
An International Journal
January-March 2017:1-12
© The Author(s) 2017
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1559325817693345
journals.sagepub.com/home/dos
SAGE

Fine Particulate Matter and Total Mortality in Cancer Prevention Study Cohort Reanalysis

James E. Enstrom[1]

Abstract

Background: In 1997 the US Environmental Protection Agency (EPA) established the National Ambient Air Quality Standard (NAAQS) for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to total mortality in the 1982 American Cancer Society Cancer Prevention Study (CPS II) cohort. Subsequently, EPA has used this relationship as the primary justification for many costly regulations, most recently the Clean Power Plan. An independent analysis of the CPS II data was conducted in order to test the validity of this relationship.

Methods: The original CPS II questionnaire data, including 1982 to 1988 mortality follow-up, were analyzed using Cox proportional hazards regression. Results were obtained for 292 277 participants in 85 counties with 1979-1983 EPA Inhalable Particulate Network $PM_{2.5}$ measurements, as well as for 212 370 participants in the 50 counties used in the original 1995 analysis.

Results: The 1982 to 1988 relative risk (RR) of death from all causes and 95% confidence interval adjusted for age, sex, race, education, and smoking status was 1.023 (0.997-1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The fully adjusted RR was null in the western and eastern portions of the United States, including in areas with somewhat higher $PM_{2.5}$ levels, particularly 5 Ohio Valley states and California.

Conclusion: No significant relationship between $PM_{2.5}$ and total mortality in the CPS II cohort was found when the best available $PM_{2.5}$ data were used. The original 1995 analysis found a positive relationship by selective use of CPS II and $PM_{2.5}$ data. This independent analysis of underlying data raises serious doubts about the CPS II epidemiologic evidence supporting the $PM_{2.5}$ NAAQS. These findings provide strong justification for further independent analysis of the CPS II data.

Keywords
epidemiology, $PM_{2.5}$, deaths, CPS II, reanalysis

Introduction

In 1997 the US Environmental Protection Agency (EPA) established the National Ambient Air Quality Standard (NAAQS) for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to total mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort, as published in 1995 by Pope et al.[1] The EPA uses this positive relationship to claim that $PM_{2.5}$ *causes* premature deaths. However, the validity of this finding was immediately challenged with detailed and well-reasoned criticism.[2-4] The relationship still remains contested and much of the original criticism has never been properly addressed, particularly the need for truly independent analysis of the CPS II data.

The EPA claim that $PM_{2.5}$ *causes* premature deaths is implausible because no etiologic mechanism has ever been established and because it involves the lifetime inhalation of only about 5 g of particles that are less than 2.5 μm in diameter.[5] The $PM_{2.5}$ mortality relationship has been further challenged because the small increased risk could be due to well-known epidemiological biases, such as, the ecological fallacy, inaccurate exposure measurements, and confounding variables like copollutants. In addition, there is extensive evidence of spatial and temporal variation in $PM_{2.5}$ mortality risk (MR) that does not support 1 national standard for $PM_{2.5}$.

[1] University of California, Los Angeles and Scientific Integrity Institute, Los Angeles, CA, USA

Corresponding Author:
James E. Enstrom, University of California, Los Angeles and Scientific Integrity Institute, 907 Westwood Boulevard #200, Los Angeles, CA 90024, USA.
Email: jenstrom@ucla.edu

Creative Commons CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Check for updates

Dose-Response:
An International Journal
April-June 2018:1-7
© The Author(s) 2018
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1559325818769728
journals.sagepub.com/home/dos
SAGE

Response to Criticism of "Fine Particulate Matter and Total Mortality in Cancer Prevention Study Cohort Reanalysis"

James E. Enstrom[1]

Keywords
epidemiology, PM2.5, deaths, CPS II, reanalysis

Response to Criticism by CPS II Investigators

Drs C. Arden Pope III (Pope), Daniel Krewski (Krewski), Susan M. Gapstur (Gapstur), Michelle C. Turner (Turner), Michael Jerrett (Jerrett), and Richard T. Burnett (Burnett),[1] as well as Gapstur and Otis W. Brawley (Brawley)[2] strongly criticized my *Dose-Response* article, Enstrom,[3] but they did not identify a single error, particularly regarding my findings of no relationship between fine particulate matter (PM2.5) and total (all-cause) mortality. Thus, my peer-reviewed findings showing no PM2.5-related deaths during 1982 to 1988 in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort stand unchallenged. In particular, my null findings indicate that the positive findings in 3 seminal publications by these investigators: Pope[4] and Health Effects Institute, HEI (2000)[5] and HEI (2009),[6] are not robust and not supportive of the claim that PM2.5 causes premature deaths. Instead of assessing the validity of my findings, these investigators focused on other aspects of their many analyses of CPS II data.

Their "Expanded Analyses of the ACS CPS-II Cohort" section inaccurately questions the validity of my findings: "The assertion regarding selective use of the CPS-II and PM2.5 data is false." I published prima facie evidence that their 1982 to 1989 PM2.5 mortality findings were indeed sensitive to selective use of PM2.5 and CPS II data. My evidence can be easily checked with minor modifications to the SAS programs that they used to calculate the findings in Table 34 of HEI (2009).[6] Instead of confirming or refuting my evidence, these investigators reiterated their various published analyses of PM2.5 deaths in CPS II, as summarized in their Table 1 and their Figure 1. All of their analyses could be just as sensitive to selective use of PM2.5 and CPS II data as the results in Pope,[4] HEI (2000),[5] and HEI (2009).[6]

Their "Deficiencies in Enstrom's Reanalysis" section does not identify a single error in my findings and suggests that they did not examine the data and findings in my article. For instance, they state, "In contrast, Enstrom[8] asserts that he estimates smaller PM2.5-mortality associations because he uses the 'best' PM2.5 data. He provides no evidence in support of this assertion nor does he provide any measures of the relative quality of models using alternative PM2.5 data." Strong evidence supporting my assertion is clearly presented in Tables 2 and 3 of my article and is described in the "Results" section on page 4. Then, they state, "It is not clear how or why his 'IPN' PM2.5 data differ from the 'HEI' PM2.5 data—especially given that these data come from the same monitoring network." The differences between the Inhalable Particulate Network (IPN) PM2.5 and HEI PM2.5 data are clearly shown in my Appendix Table A1 and discussed in the "Conclusion" section on page 6. To make sure that these differences are fully recognized and understood, an expanded version of Appendix Table A1 is shown in Table 1.

Their "Broader Evidence" section is not relevant to the validity of my findings and diverts attention away from my challenge to the PM2.5 death findings in Pope,[4] HEI (2000),[5] and HEI (2009).[6] Their last paragraph contains the following inaccurate statement: "But the study by Enstrom does not contribute to the larger body of evidence on the health effects of PM2.5 . . . " In conclusion, the authors have not assessed the validity of my peer-reviewed evidence of no relationship between PM2.5 and total mortality in the CPS II cohort and have not been willing to engage with me in addressing the substantive points of my findings.

Response to Criticism by ACS Officials

The ACS Vice President of Epidemiology Susan M. Gapstur and ACS Executive Vice President and Chief Medical Officer

[1] UCLA and Scientific Integrity Institute, Los Angeles, CA, USA

Corresponding Author:
James E. Enstrom, UCLA and Scientific Integrity Institute, 907 Westwood Boulevard #200, Los Angeles, CA 90024, USA.
Email: jenstrom@ucla.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

June 29, 2020

To:
Docket ID No. **EPA–HQ–OAR–2015–0072**
FRL–10008–31–OAR
Review of the National Ambient Air Quality Standards for Particulate Matter
https://www.regulations.gov/comment?D=EPA-HQ-OAR-2015-0072-0069
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

From:
James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
907 Westwood Boulevard #200
Los Angeles, CA 90024
http://www.scientificintegrityinstitute.org
jenstrom@ucla.edu
(310) 472-4274

This Comment strongly supports the EPA Administrator's proposed decision to retain the current **National Ambient Air Quality Standards for Particulate Matter**, as described in the April 30, 2020 Federal Register. The summary of this decision is "Based on the Environmental Protection Agency's (EPA's) review of the air quality criteria and the national ambient air quality standards (NAAQS) for particulate matter (PM), the Administrator has reached proposed decisions on the primary and secondary PM NAAQS. With regard to the primary standards meant to protect against fine particle exposures (*i.e.,* annual and 24-hour PM2.5 standards), the primary standard meant to protect against coarse particle exposures (*i.e.,* 24-hour PM10 standard), and the secondary PM2.5 and PM10 standards, the EPA proposes to retain the current standards, without revision." and "the Administrator proposes to conclude that the scientific evidence that has become available since the last review of the PM NAAQS, together with the analyses in the PA based on that evidence, does not call into question the public health protection provided by the current annual and 24-hour PM2.5 standards." Currently, the EPA has primary and secondary standards for PM2.5 (annual average standards with levels of 12.0 micrograms per cubic meter (µg/m³) and 15.0 µg/m³, respectively; 24-hour standards with 98th percentile forms and levels of 35 µg/m³; values are averaged over 3 years).

1. The first justification for retaining the current PM NAAQS is contained in the 257-page December 16, 2019 EPA Clean Air Scientific Advisory Committee (CASAC) PM Policy Assessment (PA) Report. The CASAC Chair LOUIS ANTHONY (TONY) COX, JR., PhD, is a distinguished scientist and a renowned expert in the health risks associated with PM2.5. His impressive background is summarized in his own Bio Sketch shown below.

LOUIS ANTHONY (TONY) COX, JR., PH.D., BIO SKETCH
(http://cox-associates.com/index_htm_files/Coxbio.pdf)
Cox Associates, 503 Franklin Street, Denver, Colorado, 80218
(303)-388-1778 (Phone); (303)-388-0609 (Fax); tcoxdenver@aol.com

Tony Cox is a risk analyst and President of Cox Associates (www.cox-associates.com), a Denver-based applied operations research and analytics company specializing in data science and statistics applied to public and occupational health, safety, and environmental risk analysis; epidemiology; policy analytics; and customer behavior modeling. Since 1986, Cox Associates' analysts and scientists have applied epidemiological, risk analysis, and operations research models and advanced analytics to measurably improve health and environment risk assessment and decision-making for public and private sector clients. In 2006, Cox Associates was inducted into the Edelman Academy of the Institute for Operations Research and Management Science (INFORMS), recognizing outstanding real-world achievements in the practice of operations research and the management sciences. In 2012, Dr. Cox was inducted into the National Academy of Engineering (NAE), "For applications of operations research and risk analysis to significant national problems." He has served as a member of the National Academies' Board on Mathematical Sciences and their Applications (BMSA) (2012-2016) and currently chairs the Clean Air Scientific Advisory Committee (CASAC) for the United States Environmental Protection Agency (EPA).

Dr. Cox holds a Ph.D. in Risk Analysis and an S.M. in Operations Research, both from MIT; an AB from Harvard University; and is a graduate of the Stanford Executive Program. He has served as Honorary Full Professor of Mathematics at the University of Colorado, Denver, lecturing on applied statistics, data science, decision and risk analysis, biomathematics, health risk modeling, and causality; on the Faculties of the Center for Computational Mathematics and the Center for Computational Biology; and as Clinical Professor of Biostatistics and Informatics at the University of Colorado Health Sciences Center. He has served as an expert in risk analysis on many National Academies, World Health Organization, EPA, USDA, and other agency projects, committees, and advisory boards.

Dr. Cox is Editor-in-Chief of *Risk Analysis: An International Journal.* He is Area Editor for Real World Applications for the *Journal of Heuristics,* and is on the Editorial Boards of *Decision Analysis* and the *International Journal of Operations Research and Information Systems*. He is a Fellow and an Edelman Laureate of INFORMS, a member of the American Statistical Association (ASA), and a lifetime Fellow of the Society for Risk Analysis (SRA). In 2015 and 2018, his research applying machine learning to high-throughput screening data for endocrine disruptors and carcinogenicity won Best Published Papers Demonstrating an Application of Risk Assessment awards from the Society of Toxicology Risk Assessment Specialty Section. His previous research has won the Society of Toxicology's Outstanding Published Paper in Risk Assessment Award and the Society for Risk Analysis Outstanding Risk Practitioner Award. In 2008, his solution to a challenge on "Statistical Methods to Predict Clinical Response" won an Inno Centive Award.

Dr. Cox has taught many graduate and professional courses in risk analysis, decision analysis, and advanced analytics. He has authored and co-authored over 200 journal articles and book chapters on these fields. His most recent books are *Causal Analytics for Applied Risk Analysis*(Springer, 2018), *Breakthroughs in Decision Science and Risk Analysis* (Wiley, 2015), *Improving Risk Analysis* (Springer, 2013), *Risk Analysis of Complex and Uncertain Systems* (Springer, 2009) and the *Wiley Encyclopedia of Operations Research and Management Science* (Wiley, 2011), which Dr. Cox co-edited. He has over a dozen U.S. patents on applications of artificial intelligence, signal processing, statistics and operations research. His current research interests include computational statistical methods for causal inference in public and occupational health risk analysis, data-mining, and advanced decision analysis, optimization, and learning in uncertain and changing environments.

Key quotes from the December 16, 2019 CASAC PM PA Report, with key phrases in bold, are as follows:

Page 1: The Draft PM PA depends on a Draft Particulate Matter (PM) Integrated Science Assessment (ISA) that, as noted in the April 11, 2019, CASAC Report on the Draft PM ISA, does not provide a sufficiently comprehensive, systematic assessment of the available science relevant to understanding the health impacts of exposure to PM, due largely to a lack of a comprehensive, systematic review of relevant scientific literature; inadequate evidence and rationale for altered causal determinations; and a need for clearer discussion of causality and causal biological mechanisms and pathways. Given these limitations in the underlying science basis for policy recommendations, and diverse opinions about what quantitative uncertainty analysis and further analysis of all relevant data using the best available scientific methods would show, **some CASAC members conclude that the Draft PM PA does not establish that new scientific evidence and data reasonably call into question the public health protection afforded by the current 2012 PM2.5 annual standard**.

Page 3: Future changes in public health risks that might be caused by reducing PM2.5 exposures are currently highly uncertain. The CASAC recommends that the PM PA better characterize this uncertainty using quantitative uncertainty analysis. Such an analysis should account for model uncertainty, exposure estimation errors, and both inference (internal validity) and generalization (external validity) uncertainties. As described above and in further detail in the consensus responses, the CASAC members did not come to consensus on whether the new scientific evidence and data reasonably call into question the public health protection afforded by the current 2012 PM2.5 annual standard. The CASAC recommends that the final PM PA provide quantitative uncertainty and sensitivity analyses to provide a clearer technical and scientific basis for data interpretation and policy making. **The CASAC agrees with the EPA and finds that the available evidence does not call into question the adequacy of public health protection afforded by the current 24-hour PM2.5 standard and concurs that it be retained.**

Page B-10: To "serve as a source of policy-relevant information that informs the Agency's review of the NAAQS for PM," the PA should use valid and empirically validated scientific methods to address the question of whether and how much changes in policy would affect public health risks. As just mentioned, the current draft PA is based largely on epidemiological evidence of positive associations between exposures and health effects in studies that do not fully test and control for confounding, coincident historical trends, and other non-causal sources of associations. These associations (such as the beta coefficients in Table C-1) are then used as if they were known to be valid causal predictors for simulating how changes in exposure would change health risks. This is not sound science. **The resulting conclusions and predictions are not scientifically valid and should not be used to guide policies that are to be based on sound science.**

Page B-19: The PA provides no valid scientific information about how changing PM air quality standards would change (or, in the recent past, has changed) public health risks. A scientifically sound analysis would require considering relevant real-world evidence that the PM has ignored ; clearly defining and then appropriately calculating beta values (or other formulas for quantifying causal effects on public health of changing PM2.5) while correcting for causally relevant covariates (e.g., month and high and low daily temperatures and other confounders), exposure estimation errors, and modeling errors and biases; and distinguishing between association and causation. **Since the PA does not do these things, it should not be used as if it provided valid scientific information about health risks.**

Page B-21: "The PA states (p. 3-21) that "The draft ISA concludes that, 'collectively, this body of evidence is sufficient to conclude that a causal relationship exists between long-term PM2.5 exposure and total mortality'." However, since "this body of evidence" consists primarily of associations in studies that did not fully control for causally relevant covariates (such as month and daily high and low temperatures) and that were not designed or analyzed to permit valid causal inferences, **the conclusion that "this body of evidence is sufficient to conclude that a causal relationship exists between long-term PM2.5 exposure and total mortality" is unwarranted. It is not implied by, or consistent with, the principles of sound science previously discussed.**

2. The second justification for retaining the current PM NAAQS is my extensive epidemiologic evidence that there is NO relationship between PM2.5 and total mortality in the US. This weak epidemiologic relationship drives the claim that PM2.5 *causes* premature deaths and the cost-benefit justification for many EPA Regulations. The evidence that there is NO relationship negates the primary public health justification for the PM2.5 NAAQS. There are six primary reasons that PM2.5 does not *cause* premature deaths:

a) No Etiologic Mechanism: This is no experimental proof that 1-5 lifetime grams (<µg/day) of PM2.5 causes death $PM_{2.5}\mu g/m^3$

b) Weak Epidemiologic Risk: Tiny positive relative risks (RR<1.10) do not prove that PM2.5 causes death and reductions of in PM2.5 levels have not clearly reduced the supposed mortality risks

c) Ecological Fallacy: PM2.5 monitors of ambient air provide inaccurate measurements of individual human exposure and there are NO PM2.5 measurements of individual exposure

d) Uncontrolled Confounding Variables: Co-pollutants, temperature, geography, and other factors can reduce or eliminate an apparent relationship

e) Access to Underlying Data: Enstrom independent analysis of American Cancer Society data (CA CPS I and CPS I) demonstrates the importance of access to underlying epidemiologic data (see next section)

f) Totality of US Cohort Studies Shows NO Relationship: Objective meta-analysis shows NO statistically significant relationship between long-term PM2.5 exposure and total mortality in nine US and six California prospective epidemiologic cohorts

My detailed October 17, 2019 Comment on the 2019 Draft EPA PM PA contains strong evidence that there is NO causal relationship between PM2.5 and total mortality in the US and it demonstrates the importance of access to underlying data as per the proposed EPA Transparency Rule. To illustrate the severe flaws in 2019 PM PA, I focus on the "All-cause mortality" portion of Figure 3-3 within Section 3.2.3 PM2.5 Concentrations in Key Studies Reporting Health Effects of Chapter 3 REVIEW OF THE PRIMARY STANDARDS FOR PM2.5 of the 2019 PM PA. A key sentence on page 3-52 states "To evaluate the PM2.5 air quality distributions in key studies in this review, we first identify the epidemiologic studies assessed in the draft ISA that have the potential to be most informative in reaching conclusions on the primary PM2.5 standards."

Unfortunately, Figure 3-3 on page 3-54 does not properly describe the results from the nine US prospective cohort studies of PM2.5 and total mortality. Figure 3-3 of 2019 PM PA deliberately misrepresents the US epidemiologic evidence on the relationship of PM2.5 to total (all cause) mortality and obscures the null relationship that exists in a proper meta-analysis of the nine major US cohort studies with published findings. Particularly troubling is the unjustified omission from the 2019 PM PA of my March 28, 2017 "Fine Particulate Matter and Total Mortality in Cancer Prevention Study Reanalysis" in *Dose-Response* (Enstrom 2017) and my May 29, 2018 "Response to Criticism" in *Dose-Response* (Enstrom 2018). My seminal reanalysis of ACS CPS II identified major flaws in Pope 1995, the key study underlying the 1997 PM NAAQS.

Instead of properly examining the detailed findings in my reanalysis, SECTION 11.2: Long-Term PM2.5 Exposure and Total Mortality of the 2018 PM ISA dismissed my reanalysis in two *inaccurate* sentences: "A recent reanalysis of early ACS results observed a null association between county-level averages of PM2.5 measured by the Inhalable Particle Network between 1979 and 1983 and deaths between 1982 and 1988 (HR: 1.01; 95% CI: 1.00, 1.02) (Enstrom, 2017). Inconsistencies in the results could be due to the use of 85 counties in the ACS analysis by Enstrom (2017) and 50 Metropolitan Statistical Areas in the original ACS analysis (Pope et al., 1995)."

A proper meta-analysis of the relationship between PM2.5 and total mortality in nine US cohort studies is given in the September 28, 2018 Intrepid Insight (II) article **"**Statistical Review of Competing Findings in Fine Particulate Matter and Total Mortality Studies".

II Table B3: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis

Nine US Cohorts That Analyzed Ambient Fine Particulate Matter (PM2.5) and Total (All-cause) Mortality

Relative Risk (RR and 95% CI) of Total Mortality Associated with Increase of 10 $\mu g/m^3$ in PM2.5

US Cohort Studies	Author Year	RR Table	F-U Years	RR	95%CI(L)	95%CI(U)
Veterans Study	Lipfert 2000	T6	1986-1996	0.890	0.850	0.950
Medicare (MCAPS) Eastern US	Zeger 2008	T3	2000-2005	1.068	1.049	1.087
Medicare (MCAPS) Central US	Zeger 2008	T3	2000-2005	1.132	1.095	1.169
Medicare (MCAPS) Western US	Zeger 2008	T3	2000-2005	0.989	0.970	1.008
ACS Cancer Prevention Study (CPS II)	HEI RR140 2009	T34	1982-2000	1.028	1.014	1.043
Nurses Health Study	Puett 2009	T3	1992-2002	1.260	1.020	1.540
Health Professionals FU Study	Puett 2011	T2	1989-2002	0.860	0.720	1.020
Harvard Six Cities Study (H6CS)	Lepeule 2012	T2	1974-2009	1.140	1.070	1.220
Agricultural Health Study	Weichenthal 2015	T2	1993-2009	0.950	0.760	1.200
NIH-AAPR Diet and Health Study	Thurston 2016	T2 F3	2000-2009	1.025	1.000	1.049
National Health Interview Survey	Parker 2018	T3corr	1997-2011	1.016	0.979	1.054
Intrepid Insight Random Effects Meta-Analysis	Summary RR			1.031	0.997	1.066

Q Test Statistic = 109.5100704 I^2 90.87%
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)
P-Value = 6.69843E-19 → Since Studies fail Test for Homogeneity, Random Effects Meta-Analysis Yields Summary RR = 1.031 (0.997-1.066), which is statistically consistent with 1.000 (NO relationship)

The original Zeger 2008 analysis of the Medicare cohort (MCAPS) was included in this meta-analysis rather than the Di 2017 analysis, because of the serious concerns about Di 2017 that I stated in my October 12, 2017 *NEJM* letter. Dominici, the key author on both studies, does not explain how the overall RR increased from 1.044 in the Zeger 2008 analysis to 1.073 in the Di 2017 analysis. Di 2017 does not even cite Zeger 2008. If the Medicare (MCAPS) cohort is removed from the meta-analysis because it does not properly control for confounders, II Table B4 shows that the Summary RR = 1.014 (0.973-1.057), which is also NO relationship.

Contrary to the evidence in the detailed II Table B3, the 2019 PM PA Figure 3-3 misrepresents the US evidence and inappropriately includes Canadian evidence. For instance, Figure 3-3 omits the null findings in the original Veterans Study (Lipfert 2000), as shown in II Table B3. In addition, Figure 3-3 includes results from the CPS II cohort twice (Pope 2015 and Turner 2016) and does not mention that my reanalysis found serious flaws in Pope 1995, HEI 2000, and HEI 2009. These flaws raise doubts about the validity of subsequent 'secret science' CPS II analyses by Pope and Turner. Figure 3-3 includes results from the Medicare cohort five times (Di 2017, Shi 2016, Wang 2017, Kiomourtzoglou 2016, Zeger 2008). There is no mention that the original Medicare study (Zeger 2008) is not consistent with the recent study (Di 2017). Figure 3-3 includes results from the Nurses Health Study twice (Puett 2009 and Hart 2015) and there is no mention that Puett 2009 and Puett 2011 omitted California subjects, who most likely had null findings. Inclusion of multiple hazard ratio (RR) results from the same cohort is inappropriate and gives the misleading impression that the RRs in most of the US cohorts are positive. Inclusion in Figure 3-3 of results from Canadian studies is totally inappropriate because these positive Canadian RRs are not relevant to PM2.5 findings and policy assessment in the US. To show how the 2019 PM PA presented these results, Figure 3-3 on page 3-54 of the 2019 PM PA is reproduced below. First, I document that there is NO relationship between PM2.5 and total mortality in California.

II Table B7: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis

Six CA Cohorts That Analyzed Ambient Fine Particulate Matter (PM2.5) and Total (All-cause) Mortality

Relative Risk (RR and 95% CI) of Total Mortality Associated with Increase of 10 $\mu g/m^3$ in PM2.5

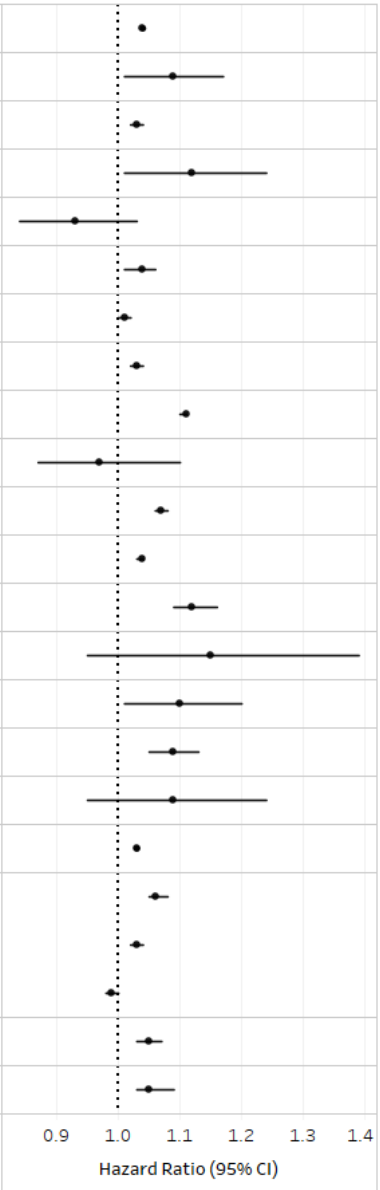
California Cohort Studies	Author Year	RR Table	F-U Years	RR	95%CI(L)	95%CI(U)
Adventist Health Study (AHSMOG)	McDonnell 2000	T3+	1977-1992	1.000	0.950	1.050
CA ACS Cancer Prevention (CA CPS I)	Enstrom 2005	T7	1983-2002	0.997	0.978	1.016
Medicare (MCAPS) Western US	Zeger 2008	T3	2000-2005	0.989	0.970	1.008
CA ACS Cancer Prevention (CA CPS II)	Krewski 2010	T2	1982-2000	0.968	0.916	1.022
California Teachers Study	Ostro 2015	Appx	2001-2007	1.010	0.980	1.050
CA NIH-AAPR Diet and Health Study	Thurston 2016	T2 F3	2000-2009	1.017	0.990	1.040
Intrepid Insight Fixed Effects Meta-Analysis		Summary RR		0.999	0.988	1.009
Intrepid Insight Random Effects Meta-Analysis		Summary RR		0.999	0.988	1.009

Q Test Statistic = 4.7683 I^2 -4.86%
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)
P-Value = 0.4448 → Since Studies satisfy Test for Homogeneity, Fixed and Random Effects Meta-Analysis Yield Summary RR = 0.999 (0.988-1.009), which is statistically consistent with 1.000 (NO relationship)

2019 PM PA Figure 3-3. Epidemiologic studies examining associations between long-term PM2.5 exposures and [all-cause] mortality.

All-cause mortality

Exposure Proxy	Country	Citation	Cohort	Health Data	Air Quality Data	Reported PM Mean (Range)(ug/m3)
Modelled	U.S.	Di et al., 2017b	Medicare	2000-2012	2000-2012	11 (5th and 95th: 6.21- 15.64)
		Hart et al., 2015	Nurses Health	2000-2006	1999-2006	12.0 (NR)
		Pope et al., 2015	ACS CPS-II	1982-2004	1999-2004	12.6 (1.0–28.0)
		Puett et al., 2009	Nurses Health	1992-2002	1988-2002	13.9 (5.8–27.6)
		Puett et al., 2011	Health Professionals	1989-2003	1988-2003	17.8 (NR)
		Shi et al., 2016	Medicare	2003-2008	2003-2008	8.12 (0.8-20.22)
		Thurston et al., 2016	NIH-AARP	2000-2009	2000-2008	12.2 (2.9-28.0)
		Turner et al., 2016	ACS CPS-II	1982-2004	1999-2004	12.6 (1.4-27.9)
		Wang et al., 2017	Medicare	2000-2013	2000-2013	NR (Median: 10.7) (6.0-20.6)
		Weichenthal et al., 2014	Ag Health	1993-2009	2001-2006	Iowa: 8.8; North Carolina: 11.1 (NR)
	Canada	Crouse et al., 2012	CanCHEC	1991-2001	2001-2006	8.7 (1.9- 19.2)
		Crouse et al., 2015	CanCHEC	1991-2006	1984-2006	8.9 (0.9- 17.6)
		Pinault et al., 2016	CCHS	2000-2011	1998-2011	6.3 (1.0-13.0)
Monitor	U.S.	Goss et al., 2004	U.S. Cystic Fibrosis	1999-2000	2000	13.7 (NR)
		Hart et al., 2015	Nurses Health	2000-2006	2000-2006	12.7 (NR)
		Kiomourtzoglou et al., 2016	Medicare	2000-2010	2000-2010	12.0 (Mean Range: 9-13) (NR)
		Lepeule et al., 2012	Harvard Six-City	2001-2009	1979-2009	1974-2009: 15.9; 2000 onwards mean range: <15-<18 (NR)
		Lipfert et al., 2006	Veterans	1997-2001	1999-2001	14.3 (NR)
		Zeger et al., 2008	MCAPS	2000-2005	2000-2005	Central region: NR (Median: 10.7) (NR) Eastern region: NR (Median: 14.0) (NR) Western region: NR (Median: 13.1) (NR)
	Canada	Crouse et al., 2012	CanCHEC	1991-2001	1987-2001	11.2 (NR)
		Weichenthal et al., 2016a	CanCHEC	1991-2009	1998-2009	9.8 (4.74-13.62)



3. The third justification for retaining the current PM NAAQS is the strong evidence that I provided in my March 18, 2020 Comment and my April 17, 2020 Comment in support of the March 18, 2020 Supplemental Proposed EPA Rule supplemental rule "Strengthening Transparency in Regulatory Science." in the Federal Register "This supplemental notice of proposed rulemaking (SNPRM) includes clarifications, modifications and additions to certain provisions in the Strengthening Transparency in Regulatory Science Proposed Rulemaking." On April 30, 2018, the EPA published its proposed rule in the Federal Register "This document proposes a regulation intended to strengthen the transparency of EPA regulatory science. The proposed regulation provides that when EPA develops regulations, including regulations for which the public is likely to bear the cost of compliance, with regard to those scientific studies that are pivotal to the action being taken, EPA should ensure that the data underlying those are publicly available in a manner sufficient for independent validation." My independent access to underlying ACS data (CA CPS I and CPS II) made possible the NULL evidence that I have published shown NO relationship between PM2.5 and total mortality, as shown in II Table B3 and II Table B7 above.

The request for data underlying EPA regulations dates back to the May 16, 1994 CASAC Chair George T. Wolff, MD letter to EPA regarding the then forthcoming Particulate Matter Review: "As scientists affiliated with CASAC, we are concerned that the appropriate analyses be conducted prior to our review. In that spirit, we request that the Agency take steps to assure that crucial data sets linking exposure to particulate matter and health responses are available for analysis by multiple analytical teams, thereby assuring the validity of the results before they are used in making regulatory decisions on the National Ambient Air Quality Standards for Particulate Material." The full 1994 letter is shown below.

The June 13, 1996 CASAC Chair George T. Wolff, MD letter to EPA illustrates the weaknesses of the evidence regarding the establishment of the 1997 PM2.5 NAAQS. Of the eight PM experts in the three most relevant disciplines (epidemiology, toxicology, and statistics), four (Drs. Larntz, Mauderly, Sly, and Stolwijk) recommended an annual PM2.5 standard that varied from 15 to 30 $\mu g/m^3$ and averaged 23.1 $\mu g/m^3$, and four (Drs. McClellan, Menzel, Samet, and Speizer) recommended NO annual PM2.5 standard. The annual 1997 PM2.5 standard as set at 15 $\mu g/m^3$, the low end of all these recommendations. A key quote from the letter states the uncertainties that still exist "The diversity of opinion also reflects the many unanswered questions and uncertainties associated with establishing causality of the association between PM2.5 and mortality. The Panel members who recommended the most stringent PM2.5 NAAQS, similar to the lower part of the ranges recommended by the Staff, did so because they concluded that the consistency and coherence of the epidemiology studies made a compelling case for causality of this association. However, the remaining Panel members were influenced, to varying degrees by the many unanswered questions and uncertainties regarding the issue of causality. The concerns include: exposure misclassification, measurement error, the influence of confounders, the shape of the dose-response function, the use of a national PM2.5 / PM10 ratio to estimate local PM concentrations, the fraction of the daily mortality that is 2.5 advanced by a few days because of pollution, the lack of an understanding of toxicological mechanisms, and the existence of possible alternative explanations." The full 1996 letter is shown below.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 16, 1994

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-CASAC-COM-94-005

The Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, SW (1101)
Washington, DC 20460

Subject: Data Sets for PM_{10}

Dear Ms. Browner:

As you are aware, the Agency is in the early stages of preparing an updated document on "Air Quality Criteria for Particulate Material" which will in turn lead to a related Staff Position paper. The Agency staff has briefed the Clean Air Scientific Advisory Committee (CASAC) on the plans for developing the two documents. CASAC is charged with reviewing the scientific and technical underpinnings of Agency proposals for National Ambient Air Quality Standards. As scientists affiliated with CASAC, we are concerned that the appropriate analyses be conducted prior to our review.

In that spirit, we request that the Agency take steps to assure that crucial data sets linking exposure to particulate matter and health responses are available for analysis by multiple analytical teams, thereby assuring the validity of the results before they are used in making regulatory decisions on the National Ambient Air Quality Standards for Particulate Material.

From the Agency briefings, it is clear that substantial new data are available that will need to be considered in the new Criteria Document and Staff Position Paper. In particular, several recent published reports have indicated effects on both morbidity and mortality at about the level of the current PM_{10} standard. In some cases, the analyses are extremely complex because of the need to correct a wide range of potential confounders, such as temperature, cigarette smoking and other pollutants.

It is already apparent that these analyses and the related published papers will have a central role in the Criteria Document and Staff Position Paper, the related discussions and recommendations of the Clean Air Scientific Advisory Committee, and in your final decision on reaffirmation or revision of the standard for particulate material. In view of their importance, it is crucial that two or more groups analyze the same key data sets linking exposure and morbidity/mortality response to verify the adequacy of the complex analyses and that different analysts using the same data reach similar conclusions. The importance of such validations and

Recycled/Recyclable
Printed with Soy/Canola Ink on paper that contains at least 50% recycled fiber

the difficulty in carrying them out was apparent from presentations on PM_{10} effects at a recent meeting at the National Academy of Sciences Beckman Center in Irvine, CA. At that meeting, divergent results were obtained by two different analytical teams which were reputed to have analyzed the same data. As it turned out, the data sets for the same city and time period analyzed by the two research teams had subtle differences. Hence, we are left with uncertainty as to the validity of either reported analysis.

The answer to this dilemma seems clear: The EPA should take the lead in requesting that investigators make available the primary data sets being analyzed so that others can validate the analyses. Further, the Agency should actively facilitate the conduct of such validating analyses. For example, the Agency could take steps to insure that the data are made available in an electronic media format that will facilitate transfer of the data to other teams for analysis.

Efforts such as we have proposed may to time-consuming and require some expenditures. Nonetheless, modest expenditures to assure the scientific validity of key analyses that impact on regulatory decisions would seem to be appropriate investments where the regulatory decisions will have multibillion dollar impacts on society. Some might also argue that the kind of actions recommended infringe on the rights of individual scientists to control their own data. This is obviously a hollow argument recognizing that in almost all instances federal funds were used at least to some extent to obtain the original data. Moreover, it would appear that the steps outlined are essential steps for the Agency to take if it is to assure the scientific validity of any reaffirmation or revision of the National Ambient Air Quality Standards for Particulate Material.

The Clean Air Scientific Advisory Committee would appreciate being advised of the Agency's plans for addressing the issues we have raised.

Sincerely,

George T. Wolff

George T. Wolff, Ph.D.
Chair, Clean Air Scientific
Advisory Committee

Roger O. McClellan

Roger O. McClellan, D.V.M.
Past Chair, Clean Air Scientific
Advisory Committee

June 13, 1996

EPA-SAB-CASAC-LTR-96-008

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M. Street SW
Washington, DC 20460

Subject: Closure by the Clean Air Scientific Advisory Committee (CASAC) on the Staff Paper for Particulate Matter

Dear Ms. Browner:

The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board (SAB) has held a series of public meetings during its peer review of the Agency's draft documents which will form part of the basis for your decision regarding the National Ambient Air Quality Standards (NAAQS) for Particulate Matter (PM). The Committee has held public meetings on December 12-13, 1994 (planning and introductory issues); August 3-4, 1995 (review of the initial draft Criteria Document); December 14-15, 1995 (review of the revised draft Criteria Document and the first draft of the Staff Paper); February 29, 1996 (review of the revised draft Criteria Document - specified chapters only, and the Office of Air Quality Planning and Standards (OAQPS) Risk Assessment Plan); and May 16-17, 1996 (review of the revised draft Staff Paper). The primary Agency draft documents that we have reviewed are the: a) *Air Quality Criteria for Particulate Matter* (the "Criteria Document" prepared by the National Center for Environmental Assessment - Research Triangle Park, NC - ORD), b) *Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information* (the "Staff Paper" prepared by the Office of Air Quality Planning and Standards - Research Triangle Park, NC - OAR), and c) *A Particulate Matter Risk Analysis for Philadelphia and Los Angeles* (draft), 1996, Prepared by Abt Associates for US EPA.

As part of our review process, we have kept you informed of our findings through three letter reports: a) *Clean Air Scientific Advisory Committee (CASAC) Comments on the April 1995 draft Air Quality Criteria for Particulate Matter* (EPA-SAB-CASAC-LTR-95-005; August 30, 1995); b) *Clean Air Scientific Advisory Committee (CASAC) Comments on the November, 1995 Drafts of the Air Quality Criteria for Particulate*

Matter and the Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information (OAQPS Staff Paper), (EPA-SAB-CASAC-LTR-96-003, January 5, 1996), and c) *Closure by the Clean Air Scientific Advisory Committee (CASAC) on the draft Air Quality Criteria for Particulate Matter* (EPA-SAB-CASAC-LTR-96-005, March 15, 1996).

The Clean Air Scientific Advisory Committee, supplemented by a number of expert Consultants (hereinafter referred to as the "Panel"), reviewed a first draft of the Staff Paper for Particulate Matter at the December 14 and 15, 1995 meeting in Chapel Hill, NC. At that meeting and in subsequent written comments by individual members which were provided to EPA Staff, the Panel made numerous recommendations for improving the draft document. The Panel met again on May 16, 1996 in Chapel Hill, NC and on May 17, 1996 in Research Triangle Park, NC to review a revised draft of the Staff Paper and the recommendations contained within the Staff Paper for the level and form of the proposed PM NAAQS. This letter is a summary of our findings and conclusions from that meeting.

It was the consensus of the Panel that although our understanding of the health effects of PM is far from complete, the Staff Paper, when revised, will provide an adequate summary of our present understanding of the scientific basis for making regulatory decisions concerning PM standards. Seventeen of the twenty-one Panel members voted for closure. There were two no votes, one abstention, and one absence. However, most of the members who voted for closure did so under the assumption that the Agency would make significant changes to the next version of the Staff Paper which is due by July 15, 1996 (a court ordered mandate). The desired changes have been articulated to your staff at the meeting and subsequently in writing.

The Panel endorses the EPA Staff's recommendation not to establish a separate secondary PM NAAQS for regulating regional haze and agrees that there is an inadequate basis for establishing a secondary NAAQS to reduce soiling and material damage effects.

The attached table (Table I) summarizes the Panel members' recommendations concerning the form and levels of the primary standards. Although some Panel members prefer to have a direct measurement of coarse mode PM ($PM_{10-2.5}$) rather than using PM_{10} as a surrogate for it, there is a consensus that retaining an annual PM_{10} NAAQS at the current level is reasonable at this time. A majority of the members recommend keeping the present 24-hour PM_{10} NAAQS, at least as an option for the Administrator to consider, although those commenting on the form of the standard strongly recommended that the form be changed to one that is more robust than the current standard. There was also a consensus that a new $PM_{2.5}$ NAAQS be established, with nineteen Panel members endorsing the concept of a 24-hour and/or an annual $PM_{2.5}$ NAAQS. The remaining two Panel members did not think any $PM_{2.5}$

NAAQS was justified. However, as indicated in Table I, there was no consensus on the level, averaging time, or form of a $PM_{2.5}$ NAAQS. At first examination of Table I, the diversity of opinion is obvious and appears to defy further characterization. However, the opinions expressed by those endorsing new $PM_{2.5}$ NAAQS can be classified into three broad categories. Four Panel members supported specific ranges or levels within or toward the lower end of the staff's recommended ranges. Seven Panel members supported specific ranges or levels near, at, or above the upper end of staff's recommended ranges. Eight other Panel members declined to select a specific range or level, but most had comments which appear as footnotes in Table I.

A number of Panel members based their support for a $PM_{2.5}$ NAAQS on the following reasoning: there is strong consistency and coherence of information indicating that high concentrations of urban air pollution adversely affect human health, there are already NAAQS that deal with all the major components of that pollution except $PM_{2.5}$, and there are strong reasons to believe that $PM_{2.5}$ is at least as important as $PM_{10-2.5}$ in producing adverse health effects.

Part of this diversity of opinion can be attributed to the accelerated review schedule. While your staff is to be highly commended for producing such quality documents in such a short period of time, the deadlines did not allow adequate time to analyze, integrate, interpret, and debate the available data on this very complex issue. Nor does a court-ordered schedule recognize that achieving the goal of a scientifically defensible NAAQS for PM may require iterative steps to be taken in which new data are acquired to fill obvious and critical voids in our knowledge. The previous PM NAAQS review took eight years to complete.

The diversity of opinion also reflects the many unanswered questions and uncertainties associated with establishing causality of the association between $PM_{2.5}$ and mortality. The Panel members who recommended the most stringent $PM_{2.5}$ NAAQS, similar to the lower part of the ranges recommended by the Staff, did so because they concluded that the consistency and coherence of the epidemiology studies made a compelling case for causality of this association. However, the remaining Panel members were influenced, to varying degrees by the many unanswered questions and uncertainties regarding the issue of causality. The concerns include: exposure misclassification, measurement error, the influence of confounders, the shape of the dose-response function, the use of a national $PM_{2.5}/PM_{10}$ ratio to estimate local $PM_{2.5}$ concentrations, the fraction of the daily mortality that is advanced by a few days because of pollution, the lack of an understanding of toxicological mechanisms, and the existence of possible alternative explanations.

In recommending that the staff carry out a risk assessment, it was the expectation of CASAC that the risk assessments would narrow the diversity of opinion by evaluating how all of the uncertainties propagate throughout the entire model.

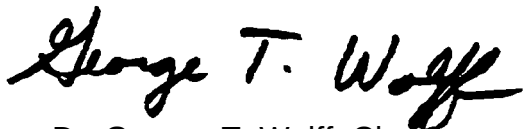
However, not all of the uncertainties could be included and the combined effect of all of them could not be examined. The Panel recommended that additional analyses be conducted to present combined uncertainties. However, currently the risk assessments are of limited value in narrowing the diversity of opinion within the Panel.

The Panel is unanimous, however, in its desire to avoid being in a similar situation when the next PM NAAQS review cycle is under way by a future CASAC Panel. The Agency must immediately implement a targeted research program to address these unanswered questions and uncertainties. It is also essential that we obtain long-term $PM_{2.5}$ measurements. CASAC is ready to assist the Agency in the development of a comprehensive research plan that will address the questions which need answers before the next PM review cycle is completed. We understand that your staff is preparing a PM research plan for our review later this summer. We look forward to providing our comments on this important matter.

CASAC recognizes that your statutory responsibility to set standards requires public health policy judgments in addition to determinations of a strictly scientific nature. While the Panel is willing to advise you further on the PM standard, we see no need, in view of the already extensive comments provided, to review any proposed PM standards prior to their publication in the Federal Register. In this instance, the public comment period will provide sufficient opportunity for the Panel to provide any additional comment or review that may be necessary.

Thank you for the opportunity to present the Panel's views on this important public health issue. We look forward to your response to the advice contained in this letter.

Sincerely,



Dr. George T. Wolff, Chair
Clean Air Scientific Advisory Committee

TABLE I
Summary of CASAC Panel Members Recommendations
(all units μg/m^3)

		$PM_{2.5}$ 24-hr	$PM_{2.5}$ Annual	PM_{10} 24-hr	PM_{10} Annual
Current NAAQS		N/A	N/A	150	50
EPA Staff Recommendation		18 - 65	12.5 - 20	150[13]	40 - 50
Name	**Discipline**				
Ayres	M.D.	yes[2]	yes[2]	150	50
Hopke	Atmos. Sci.	20 - 50[3]	20 - 30	no	40 -50[4]
Jacobson	Plant Biologist	yes[2]	yes[2]	150	50
Koutrakis	Atmos. Sci.	yes[2,5,6]	yes[2,5,6]	no	yes[4]
Larntz	Statistician	no	25-30[7]	no	yes[2]
Legge	Plant Biologist	≥ 75	no	150	40 - 50
Lippmann	Health Expert	20 - 50[3]	15 - 20	no	40 - 50
Mauderly	Toxicologist	50	20	150	50
McClellan	Toxicologist	no[8]	no[8]	150	50
Menzel	Toxicologist	no	no	150	50
Middleton	Atmos. Sci.	yes[2,3,12]	yes[2,5]	150[3,13]	50
Pierson	Atmos. Sci.	yes[2,9]	yes[2,9]	yes[4]	yes[4]
Price	Atmos. Sci./ State Official	yes[3,10]	yes[10]	no[3,4]	yes[4]
Shy	Epidemiologist	20 - 30	15 - 20	no	50
Samet[1]	Epidemiologist	yes[2,11]	no	150	yes[2]
Seigneur	Atmos. Sci.	yes[3,5]	no	150[13]	50
Speizer[1]	Epidemiologist	20 - 50	no	no	40 - 50
Stolwijk	Epidemiologist	75[7]	25-30[7]	150	50
Utell	M.D.	≥65	no	150	50
White	Atmos. Sci.	no	20	150	50
Wolff	Atmos. Sci.	≥75[3,7]	no	150[3]	50

[1] not present at meeting; recommendations based on written comments
[2] declined to select a value or range
[3] recommends a more robust 24-hr. form
[4] perfers a $PM_{10-2.5}$ standard rather than a PM_{10} standard
[5] concerned upper range is too low based on national $PM_{2.5}/PM_{10}$ ratio
[6] leans towards high end of Staff recommended range

[7] desires equivalent stringency as present PM_{10} standards

[8] if EPA decides a $PM_{2.5}$ NAAQS is required, the 24-hr. and annual standards should be 75 and 25 $\mu g/m^3$, respectively with a robust form

[9] yes, but decision not based on epidemiological studies

[10] low end of EPA's proposed range is inappropriate; desires levels selected to include areas for which there is broad public and technical agreement that they have $PM_{2.5}$ pollution problems

[11] only if EPA has confidence that reducing $PM_{2.5}$ will indeed reduce the components of particles responsible for their adverse effects

[12] concerned lower end of range is oo close to background

[13] the annual standard may be sufficient; 24-hr level recommended if 24-hour standard retained

U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee
Particulate Matter Review Panel

Chairman
Dr. George T. Wolff
General Motors
Environmental & Energy Staff
Detroit, MI

Members
Dr. Stephen M. Ayres
Office of International Programs
Virginia Commonwealth University
/Medical College of Virginia
Richmond, VA

Dr. Phil Hopke
Department of Chemistry
Clarkson University
Pottsdam, NY

Dr. Jay S. Jacobson
Boyce Thompson Institute
Cornell University
Ithaca, NY

Dr. Joe L. Mauderly
Inhalation Toxicology Research
Institute
Lovelace Biomedical & Environmental
Research Institute
Albuquerque, NM

Dr. James H. Price, Jr.
Texas Natural Resource Conservation
Commission
Austin, TX

Consultants
Dr. Petros Koutrakis
Harvard School of Public Health
Boston, MA

Dr. Morton Lippmann
Institute of Environmental Medicine
New York University
Tuxedo, NY

Dr. Kinley Larntz
Department of Applied Statistics
University of Minnesota
St. Paul, MN

Dr. Allan Legge
Biosphere Solutions
Calgary, Alberta, Canada

Dr. Roger O. McClellan
Chemical Industry Institute of
Toxicology
Research Triangle Park, NC

Dr. Daniel Menzel
Department of Community
and Environmental Medicine
University of California, Irvine
Irvine, CA

Dr. Paulette Middleton
Science and Policy Associates
Boulder, CO

Dr. William R. Pierson
Energy & Environmental Engineering
Center
Desert Research Institute
Reno, NV

Dr. Carl M. Shy
Department of Epidemiology
School of Public Health
University of North Carolina
Chapel Hill, NC

Dr. John Samet
School of Hygiene & Public Health
Johns Hopkins University
Baltimore, MD

Dr. Christian Siegneur
AER, Inc
San Ramon, CA

Dr. Frank Speizer
Harvard Medical School
Channing Lab
Boston, MA

Dr. Jan Stolwijk
Yale University
New Haven, CT

Dr. Mark Utell
Pulmonary Disease Unit
University of Rochester Medical Center
Rochester, NY

Dr. Warren White
Washington University
St. Louis, MO

Science Advisory Board Staff
Mr. A. Robert Flaak
Designated Federal Official
U.S. EPA
Science Advisory Board
Washington, DC

Ms. Dorothy Clark
Staff Secretary
U.S. EPA
Science Advisory Board
Washington, DC

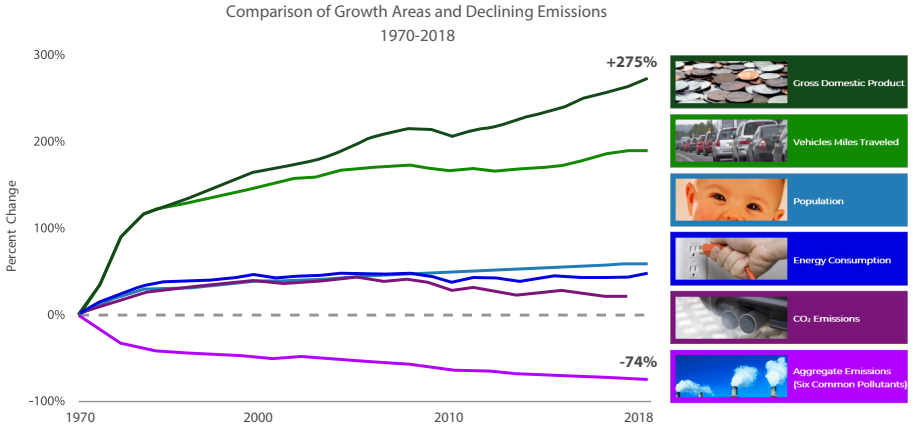
Our Nation's Air

Air Quality Improves as America Grows

https://gispub.epa.gov/air/trendsreport/2019

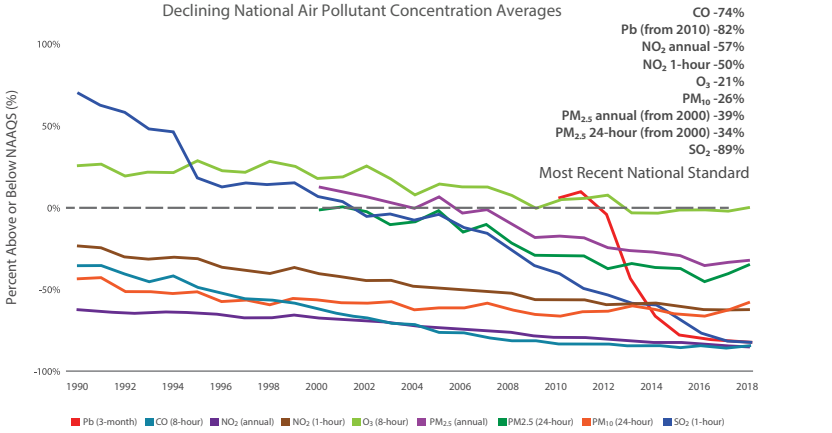
Economic Growth with Cleaner Air

Between 1970 and 2018, the combined emissions of the six common pollutants ($PM_{2.5}$ and PM_{10}, SO_2, NO_X, VOCs, CO and Pb) dropped by 74 percent. This progress occurred while the U.S. economy continued to grow, Americans drove more miles and population and energy use increased.



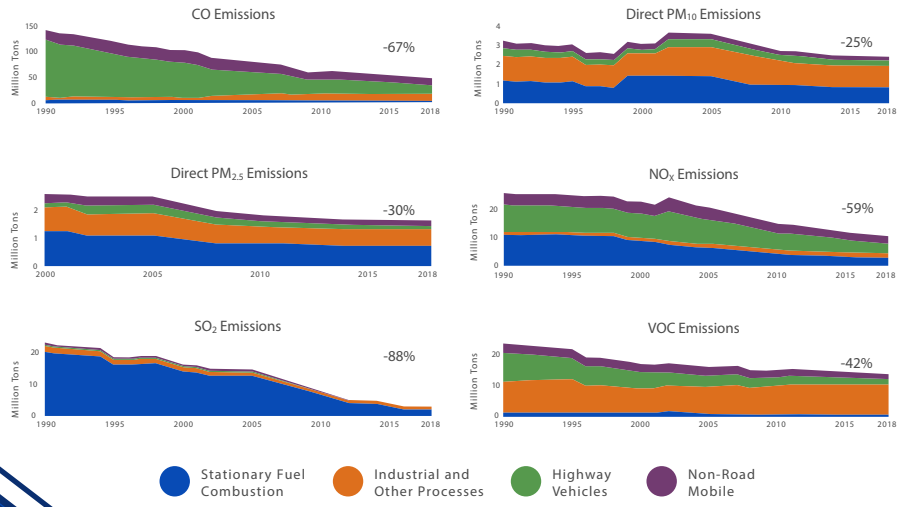
Air Quality Trends Show Clean Air Progress

While some pollutants continue to pose serious air quality problems in areas of the U.S., nationally, criteria air pollutant concentrations have dropped significantly since 1990 improving quality of life for many Americans. Air quality improves as America grows.



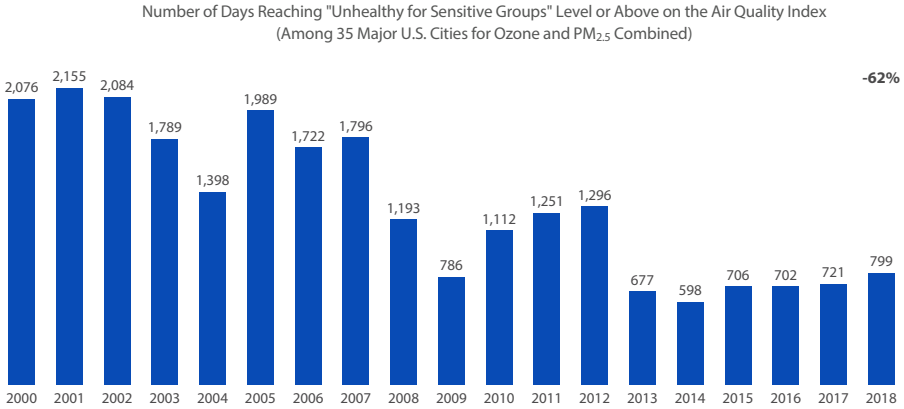
Air Pollutant Emissions Decreasing

Emissions of key air pollutants continue to decline from 1990 levels. These reductions are driven by federal and state implementation of stationary and mobile source regulations.



Unhealthy Air Days Show Long-Term Improvement

The Air Quality Index (AQI) is a color-coded index EPA uses to communicate daily air pollution for ozone, particle pollution, NO_2, CO, and SO_2. A value in the unhealthy range, above national air quality standard for any pollutant, is of concern first for sensitive groups, then for everyone as the AQI value increases. Fewer unhealthy air quality days means better health, longevity, and quality of life for all of us.



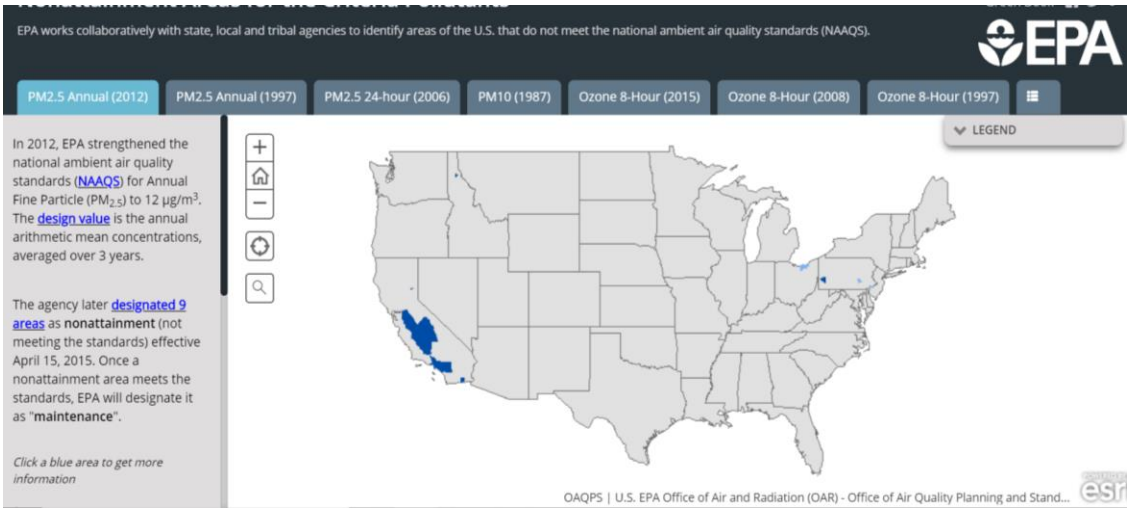
Unhealthy air quality days vary year to year, influenced not only by pollution emissions but also by natural events, such as dust storms and wildfires, and variations in weather.

Status and Trends Through 2018

4. The fourth justification for retaining the current PM NAAQS is contained in Our Nation's Air Summary Chart of "Air Quality Improves as America Grows" shown above and in the points below

a. Recent trends in air quality, including innovation-driven progress across emissions, concentrations, and U.S. competitiveness, demonstrate that a more stringent particulate matter NAAQS is not necessary.

b. In the entire U.S., only 9 full counties and 7 partial counties (out of more than 3,000) fail to meet the most recent national standards for fine particulate matter, which were set by the Obama Administration at a level designed to protect public health with an adequate margin of safety for susceptible populations. 14 of these counties are located in California:

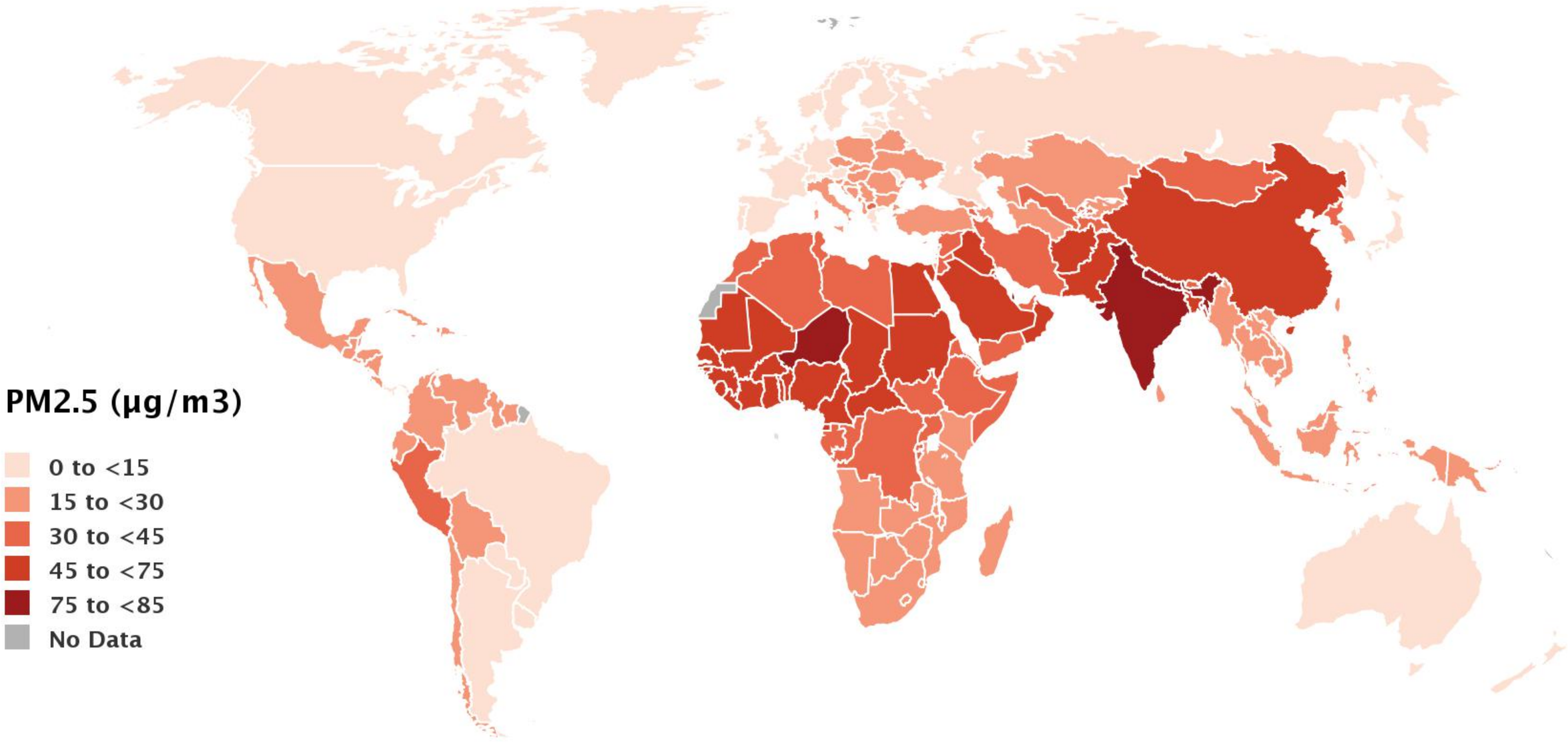


c. In recent years, the U.S. has had far lower fine particulate matter levels than nearly any country on earth. At present, U.S. concentrations are less than one-sixth the global average, seven times below China, and roughly half of particulate matter levels in continental Europe.

d. EPA's June 2020 Our Nation's Air report demonstrates dramatic recent progress for particulate matter. Across the U.S., fine particulate matter concentrations have dropped by roughly 43 percent between 2000 and 2019. Over that same period, direct emissions of fine particulate matter also fell by 43 percent, and anthropogenic emissions of pollutants that can be a precursor to PM2.5 followed a similar trend, including sulfur dioxide (down 88 percent), oxides of nitrogen (down 61 percent), and volatile organic compounds (down 28 percent).

e. Between 1970 and 2019, the combined emissions of the six common pollutants (PM2.5 and PM10, SO2, NOx, VOCs, CO and Pb) dropped by 77 percent. This progress occurred while the U.S. economy continued to grow, Americans drove more miles, and population and energy use increased.

Average Annual Population-Weighted PM2.5 Concentrations in 2019



State of Global Air 2020

Exempt Human Subjects Research

8 Exemptions

Consider

1 Meets the definition of human subjects research.

Exempt studies involve human subjects research: research involving a living individual about whom data or biospecimens are obtained/used/studied/analyzed through interaction/intervention, or identifiable, private information is used/studied/analyzed/generated

2 Meets the criteria of one of the following exemptions:

Exemption 1: conducted in an educational setting using normal educational practices*

*Cannot include any other procedures, such as collection of clinical data or biospecimens

Exemption 2: uses educational tests, surveys, interviews, or observations of public behavior*

*Limited IRB review may be required.

Exemption 3: benign behavioral interventions in adults*

*Limited IRB review may be required.

Exemption 4: involves the collection/study of data or specimens if publicly available, or recorded such that subjects cannot be identified*

*May be identifiable in limited cases. See §46.104(d)(4)(iii) and (iv)

Exemption 5: public service program research or demonstration projects

Exemption 6: taste and food quality evaluations

Exemption 7: storage of identifiable information or biospecimens for secondary research use. *Broad consent* and *limited IRB review* are required.

Exemption 8: secondary research use of identifiable information or biospecimens. *Broad consent* and *limited IRB review* are required.

For more information see the NIH OER Human Subjects Research website.
Send questions/comments to OER-HS@nih.gov.

NIH Requirements:

- HS education
- Inclusion tracking for all except 4.

45 CFR 46 Requirements:

- Limited IRB review for 7 & 8, and some study designs under 2 & 3.
- Broad consent for 7 & 8.

Cannot involve **prisoners**, unless includes a broader population that happens to include prisoners.

Cannot involve **children** in:

- Exemption 2 if investigators participate in the activity being observed or includes identifiable info, OR
- Exemption 3.