Responses to CASAC Questions on the PM PA from Consultant Dr. Frederick W. Lipfert

I organized my responses as follows. First, a background discussion based on observations that may differ from the PA and ISAs that are requisite to "policy relevant" discussions. Then I address specific questions and summarize my responses. Appendix A presents background issues in more detail. Appendix B contrasts short- and long-term studies. Appendix C lists my relevant publications that have not been included in an ISA or the PA

Background on Air Pollution, $PM_{2.5}$, and Human Mortality

The Clean Air Act is not specific; pollutants of concern were defined in the 1970s and remain today although the definition of particulate matter has changed. Concentrations of CO and SO_2 have dropped to trivial levels but are still monitored. The most hazardous pollutants such as benzene, formaldehyde, or benzo(alpha)pyrene are not monitored in the atmosphere. $PM_{2.5}$ might be considered a "target of choice". "Ambient" was intended to represent outdoor air quality alone, perhaps because it was much worse than indoors at that time. This is no longer the case.

$PM_{2.5}$ is not really a pollutant in the sense of defined chemicals (CO, O_3, SO_2). It is a regulatory construct defined solely by particle size and based on the total mass of a mixture of many kinds of particles, some toxic, most not. Those of most concern (metals, ultrafines, carbon compounds) comprise a small fraction of the total mass. No sources emit $PM_{2.5}$ as measured in the ambient; source abatement strategies for specific constituents can thus be arbitrary without evidence of attained health benefits. We are exposed to $PM_{2.5}$ from both indoor and outdoor sources, regulated or not.

Excess mortality has been a focus of air pollution health effects since the advent of regulation; it is an accurate end point for which nationwide individual data have readily been available for decades. Monetary values may be assigned in various ways for cost-benefit analysis. Relative risk can be converted to longevity loss, which may be a more cogent endpoint than numbers of victims.

Epidemiology is concerned with establishing cause and effect, often beginning with statistical associations. However, some cautions are in order. Beyond statistical significance, we need to understand the entire system beginning with emissions. Replication of observational studies based on the same model does not confer validity to any of them. The mere presence of a pollutant in the atmosphere does not constitute a "cause", for which personal exposures and translation to a target organ are required. An "effect" should relate to a target organ and imply specific mechanisms; excess mortality or admissions to hospital may be *consequences* of such clinical effects.

In order to do its job, CASAC must evaluate the extant concentration-response (C-R) functions and the exposure data used to drive them, which should represent actual exposures if the responses are to represent actual health effects. This evaluation should consider three types of C-Rs:

> Short-term (days) fluctuations in air quality that may trigger sudden death in vulnerable individuals. Causality in this mode has been demonstrated by heat wave mortality.
>
> Long-term (decades) individual differences that affect incidence of new cases of chronic disease, for which the extended effects of cigarette smoking are a causal example.

Long-term differences among populations that may involve both of the above as well as attributes of their locations *per se*, such as climate, green spaces, traffic density, or characteristics of housing stock that affect indoor air quality.

It is possible for all three of these relationships to be involved in a given situation. These responses to the CASAC questions reflect these distinctions, specifically the timing of responses relative to exposures and the detailed nature of $PM_{2.5}$ exposures.

Responses to Questions from Dr. Boylan

Chapter 2 - PM Air Quality

Chapter 2 – PM Air Quality

- *Is the discussion on sources of emissions accurate and complete? If not, what additional information needs to be included?*

  No, indoor sources were not discussed.

- *Is the discussion on ambient monitoring accurate and complete? If not, what additional information needs to be included?*

  No, ultrafine PM (UFP) needs more attention. Given the importance of short-term effects, the need for more daily monitoring should be recognized. The need to understand indoor air quality should be recognized.

- *To what extent are biases associated with PM_{10}, $PM_{2.5}$, and ultrafine measurements discussed?*

  Insufficiently.

- *Is the discussion on background concentrations accurate and complete? If not, what additional information needs to be included?*
-
- I have no response here.

Chapter 3 – Review of the Primary $PM_{2.5}$ Standards

- *Is the evidence-based analysis presented in Chapter 3 scientifically sound?*

  No. Accountability was not established. Relationships between short- and long-term effects were not discussed.

- *Are the areas for additional research adequate and complete? If not, what additional areas need to be included?*

  The needs to consider latency and cumulative exposure were not discussed. The need to consider the sum of short-term effects over the lag period was not recognized. Difficulties in defining thresholds were not discussed**.**

Appendix C – Supplemental Information Related to the Human Health Risk Assessment

- *Is the air quality modeling approach to projecting $PM_{2.5}$ concentrations to correspond to just meeting the NAAQS (AQS, CMAQ, Downscaler, SMAT-CE, project monitors to just meet NAAQS, project spatial fields to correspond to just meeting the NAAQS) scientifically sound? If not, what are your concerns and how should they be addressed?*

Historical data are required to estimate cumulative exposures needed for valid long-term C-Rs.

- *Is the health risk modeling approach using BenMAP-CE appropriate for this application? If not, what are your concerns?*

I find the bulk of the PA dedicated to regulatory issues, ignoring the scientific issues that are central to supporting them. The Appendices are intended to discuss an illustrate those issues. I searched the PA to determine inclusion of specific terms central to my discussions and issues. The following were not mentioned in the PA text: indoor, frailty, latent, cumulative exposure, acute. The time-series studies by Murray and Lipfert (2012, 2013) were not cited. The only citation of the Veterans Cohort Study, for which 8 papers have been published (Lipfert et al., 2000, 2003, 2006a, 2006b, 2008a, 2008b, 2009, 2018, 2019 [accepted]) was for the only significant positive $PM_{2.5}$ risk among many negatives and was thus "cherry-picked".

Responses to Questions from Dr. Cox

1. *Are the beta coefficients in Table C-1 of the PA conceptually well defined? That is, are their intended conceptual meanings and causal interpretations clear and unambiguous?*

My answer is "no". Beta coefficients are outputs of models intended to describe the real world so that their increments may be interpreted as specifying effects of changes in inputs. Above I proposed 3 different C-R models that pertain to specific situations and differ from the PA. Their validity depends on the validity of inputs (exposures) and their timing. The PA does not consider indoor exposures and thus strictly applies only to the 10-15% of the time, if that. It does not consider timing of exposures, notably cumulative exposures. A more general discussion of causality and accountability is presented below. Suffice it to note that no victim of long-term exposure to ambient air pollution has ever been identified by autopsy, by contrast with 1952 London fog disaster (Bradley, 1957). The present C-Rs must be regarded as primarily a regulatory device.

2. *On the same topic of clear definitions, does the discussion of the BenMAP-CE beta coefficients in the PA and underlying documentation (described as typically representing "the percent change in a given adverse health impact per unit of pollution") unambiguously specify which of the following concepts the coefficients represent?*

My answer is "no". Those concepts are not physiologically defined, only operationally.

3. *Is the definition of "concentration-response (C-R) relationships" in the PA and its Appendices (cf p. C-38) adequately clear and unambiguous to support simulation of well-defined causal effects of interventions that change pollution levels?*

My answer is "no". Those interventions are not well defined. Ambient $PM_{2.5}$ is a mixture of various types of particles from specific types of sources, some from combustion, some from various types of processes, some from natural sources. $PM_{2.5}$ as measured in the ambient is not emitted from any source. The notion that a given percent reduction of emissions from any of those distinct types of sources would have the same benefit on the various health endpoints that have been considered is patently absurd.

4. *Do the beta coefficients in the PA overcome these methodological objections to using relative risks, regression coefficients, and related measures of association to predict (or simulate) effects of interventions? If so, how were they overcome? If not, does this imply that the simulations in the PA are not necessarily reliable or valid predictors of the real-world effects on public health of reducing PM2.5? Why or why not?*

5. My answer is "no". I get the impression that none of these basic flaws have been considered in conjunction with the establishment or modification of NAAQS.

6. *On the same methodological issue, which, if any, of these measures (relative risks, odds ratios, attributable risks, and regression coefficients) are currently generally accepted in contemporary causal analysis and epidemiology as valid measures of how changing one variable (e.g., exposure) will cause another (e.g., population health responses) to change?*

My problems are with the underlying conceptual model, not the expressions of outputs. I would note however that no lives have ever been "saved" by air pollution control, but some may have been extended. Those longevity extensions under current conditions have ranged from a few days to a few months. The underlying health status of those putative victims has not been considered.

7. *More generally, do the $\Delta y/\Delta x$ values calculated by BenMAP-CE have valid interpretations as causal impacts on y of interventions that change x?*

As discussed elsewhere, my answer is "no". Such predictions have never been verified; they are statistical but not operational. As I understand it, BenMap would have us believe that moving from say, Steubenville, OH, to Madison, WI, would instantly clear our lungs, unclog our arteries, and stop our metastasizing lung cancer, which is clearly nonsense and statistical confidence intervals tell us nothing about this unreality. One might argue that only a few percent of those movers might actually benefit in this way, which would then raise the question of selection: random or according to pre-existing conditions? The more cogent questions, for which we have no answers, might be what role did Steubenville's dirty air play in creating those conditions and how long did it take? Common sense must prevail here.

8. *Have the beta coefficients in the PA been empirically validated?*

As discussed elsewhere, my answer is "no". Long-term effects have never been verified by intervention; short-term effects were validated in London 1952 (Bradley, 1957).

9. *Does the discussion of beta values in the PA, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately describe and discuss the extent (if any) to which their values reflect potential omitted confounders of the association between mortality risks and PM2.5 levels (e.g., lagged daily high and low temperatures and humidity in the weeks preceding mortality, if these contribute both to (possibly delayed) mortality and increased energy usage and PM2.5 pollution?)*

My answer is "no". Statistical confidence intervals portray the precision of a model and depend on sample size. Uncertainties about the validity of the model can be far more important and confounders can depend on model structure and the data available. The sample size of a cohort can only be increased by extending follow-up time, which entails temporal gradients and depletion of its most vulnerable members. I would argue that the more a cohort study is extended the less we know about its members. Only the Veterans Cohort (described below) has considered nonlinear relationships with subjects' physiology (blood pressure) climate, poverty, neighborhood racial mix, exposure timing over 26 y, and age-specific risk estimates. It produced statistically significant *negative* risks of $PM_{2.5}$ and strong positive risks associated with vehicular traffic density. These findings have never been included in an ISA or PA.

10. *Does the discussion of beta values in the PA, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately address the extent (if any) to which their values reflect residual confounding of the association between mortality risks and PM2.5 levels (e.g., by daily high and low temperatures and humidity in the weeks preceding mortality in models that only address seasonal, annual, or averaged temperatures)?*

My answer is "no". The models used to set $PM_{2.5}$ NAAQS did not control for climate.

11. *Does the discussion of beta values in the PA, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately address model uncertainty (e.g., the possibility that the linear no-threshold model specification is incorrect, e.g., because sufficiently low exposure concentrations do not cause pulmonary inflammation and adverse health effects that occur at higher concentrations)?*

My answer is "no".

12. *Does the PA's discussion of beta values, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately address effects on the estimated values of the beta values of exposure uncertainties and estimation errors?*

My answer is "no".

13. *Does the PA adequately assess the suitability of the designs of the studies used to estimate beta values for purposes of valid causal inference and simulation?)*

My answer is "no".

14. *Does the PA's discussion of beta values adequately address attribution of risk in the presence of joint causes? Conversely, how well does the discussion in the PA make clear how much of the estimated beta value for PM2.5 is actually contributed by other variables (such as temperature extremes and poverty) that would not necessarily be changed by an intervention that reduces PM.5 levels?*

My answer is "no".

15. *How confident can policy analysts and decision makers be in the predictive validity of the simulated results?*

There can be no confidence absent accountability through intervention analysis or autopsy; see Henneman et al. (2019). Below I summarized the current state of knowledge and what remains to be determined.

16. *Are there other statistical or methodological issues that you would like to comment on that you believe might help the CASAC to assess the validity and soundness of the PA and its simulations for effects on health risks of changing PM2.5 levels, or that might help to improve the technical and scientific quality of the final PA?*

I discuss these issues in detail below.

17. *How can techniques of formal causal modeling and analysis best be applied to improve the clarity of definitions and communication and scientific soundness of simulations, inferences, causal interpretations, generalizations, and policy-relevant conclusions in the PA?*

I conclude that this PA is essentially beyond redemption, as discussed below. More research on exposure timing and physiological modeling are required.

Responses to Questions from Dr. Frampton

1. *Is there evidence that would support a reconsideration of the current and long-held views of this causal relationship as expressed in the PA and ISA?*
3. *Also please comment on the implications, of any changes in the causality framework that you would recommend, for the analyses and conclusions in this current PA.*

It is my position that causality must be established through observations, in conjunction with statistical analyses. Causality was established in the short term when exposures and responses cycle in concert as in daily mortality or hospitalization. It was proven through autopsies in the 1952 London fog episode (Bradley, 1957). In long-term epidemiology, causality must meet five requirements, none of which has been established for $PM_{2.5}$:

Exposure. Indoor exposures and the contributions of daily peaks have not been considered in long-term studies. Initiation of chronic disease can only occur after a latency period and then depends on cumulative exposures. This has been established for smoking but not for air pollution epidemiology.

Toxicity. $PM_{2.5}$ is not really a pollutant in the sense of defined chemicals (CO, O_3, SO_2). It is a regulatory construct based on mixtures of many kinds of particles, some toxic, others not. Given the multiplicity of health endpoints that have been considered, a statistically significant combination with a PM constituent is likely.

Translocation. Inhalation of a pollutant is not sufficient to imply contact with an organ and initiation of chronic disease. $PM_{2.5}$ translocation from the lung to the bloodstream has not been demonstrated, by contrast with ultrafine particles, for example.

Susceptibility. Given the diversity of the population, the notion that a healthy person could be randomly selected to die coincidently with normal levels of ambient air quality is patently absurd. Time-series studies have shown that acute mortality is associated with both underlying frailty and daily air pollution peaks (Murray and Lipfert, 2012, 2013). Differential susceptibility is also likely the case for incidence of chronic disease, but making this case would require tracking individual cohort members during the latency period.

Accountability. The ultimate test of causality is whether public health has actually improved in response to reduced $PM_{2.5}$ (by a factor of 3 since ca. 1980), after accounting for coincident trends in spatial patterns of reduced smoking and improved medical care. The extant literature does not support this test; Henneman et al. (2019) showed no effect on total mortality (-0.011 [-0.92 – 0.71]) after reducing $PM_{2.5}$ from 10.0 $\mu g/m^3$ in 2005 $\mu g/m^3$ to 7.2 in 2012. However their analysis did not account for latency or cumulative exposures.

By contrast, the epidemiology of smoking has all of these elements. Exposure is self-reported on an individual basis, and the importance of cumulative exposure is shown by the use of pack-years as a predictor of disease after accounting for latency. Toxicity of smoke constituents has been determined by laboratory and animal tests, especially for benzo(alpha)pyrene (B[a)P) which is also an (unmonitored) ambient air pollutant. Translocation is not an issue for the gaseous pollutants and the most serious health effects (cancer, COPD) occur in the lung. Susceptibility comes into play when frail smokers are urged to quit. Accountability is shown by the improved health of quitters.

2. Please opine on the level of uncertainty that is represented by this heterogeneity, and the impact if any, on the conclusions in the PA.

Heterogeneity between cities must be controlled through the use of contextual variables in the regression models, in addition to personal information. This was first shown in the Veterans Cohort Study (Lipfert et al., 2000) in which the inclusion of variables dealing with climate, neighborhood poverty, and neighborhood racial distribution changed the mortality risks for $PM_{2.5}$ and SO_4^{2-} from positive to negative. However, those contextual variables have not been used in other cohort studies. Heterogeneity within cities includes house-to-house variability in indoor air quality and local features like green spaces and high-traffic areas. Figure 1 shows lack of correlation between indoor and outdoor across American cities (Lipfert, 2015) which has also been shown in EPA studies (Baxter et al.1994, 2007, 2010, 2013, 2014, 2017). While indoor $PM_{2.5}$ is about half of outdoor because of infiltration as shown in the Figure, personal exposure can be much higher because of indoor sources like environmental tobacco smoke. EPA has confirmed these observations but they have not been used in EPA-sponsored epidemiology.

4. The CASAC letter to the Administrator (April 11, 2019) states, "There is inadequate evidence for the 'likely to be causal' conclusion for long-term $PM_{2.5}$ exposure and cancer." exposure time frames for most of these studies are insufficient to draw conclusions about incident cancer. Do you agree with the CASAC's findings in this matter?

While response must always follow exposure, the delay depends on the latency period of the endpoint. Sudden death may occur within a week, as shown in time-series analysis; initiation of chronic disease may require decades. Figure 2 shows temporal trends for lung cancer, smoking, and $PM_{2.5}$. based on population-average data. Cancer lags smoking by about 18 years, consistent with cohort and individual data. We would expect a similar relationship for atmospheric particles, for which sufficient historical data are lacking. However, if latency were neglected, a (spurious) longitudinal relationship between lung cancer and $PM_{2.5}$ would be seen in Figure 2, as has been the case in long-term cross-sectional cohort studies. We would expect this concept to pertain to initiation of other diseases as well.

5. Please comment on the appropriateness and completeness of the approaches used in this PA to assess the risks of exposure, and the assessments of risk reduction of alternate standards, for $PM_{2.5}$ and PM_{10} (sections 3 and 4, respectively).

The concepts of causality and appropriate exposures are universal and thus would affect any differences resulting from alternative NAAQS levels. However, estimating any resulting monetary benefits must be revisited. The current practice is to assign a value of several million $ to each life "saved" regardless of the resulting change in life expectancy. Recent analyses have estimated longevity extensions from several days to several months that would have substantially lower value. The current monetization algorithm must be changed.

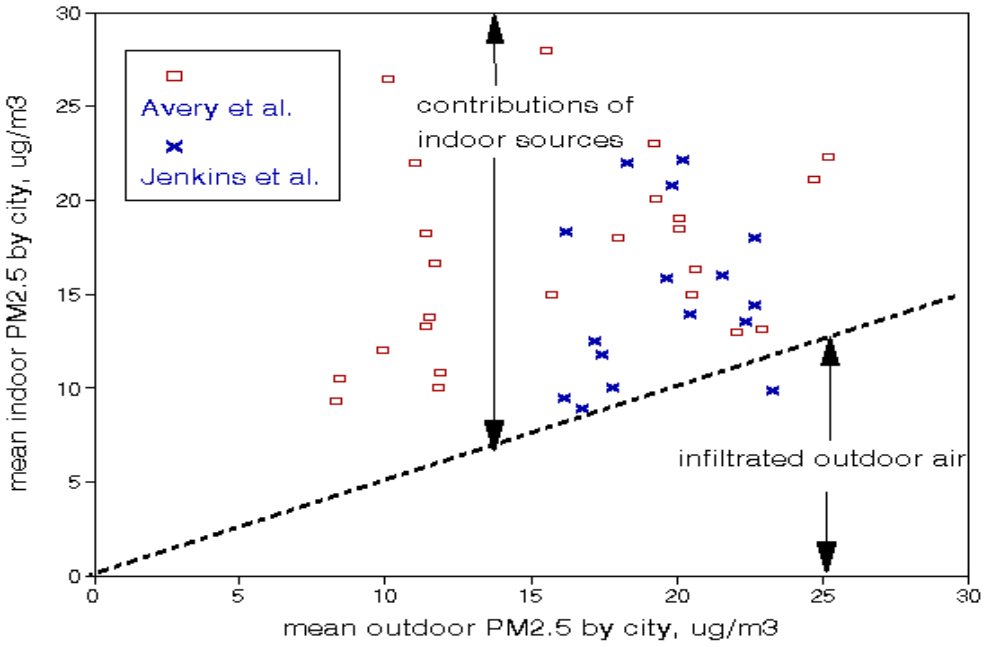

Figure 1. Relationships between indoor and outdoor $PM_{2.5}$ for selected U.S. cities.

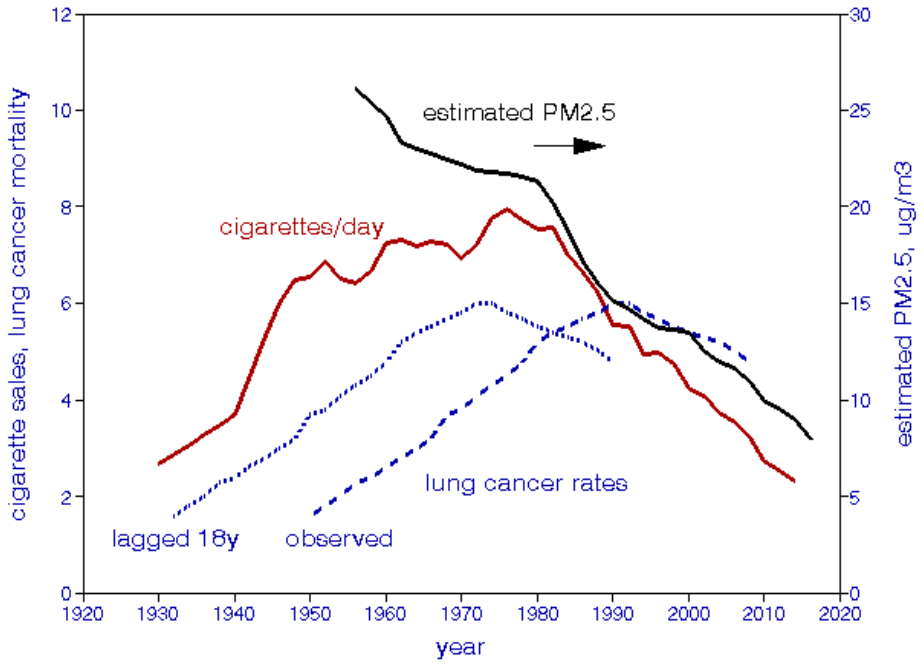

Figure 2. Comparison of trends in annual cigarette sales, estimated $PM_{2.5}$, and lung cancer mortality 18-y later (deaths/10,000 population)

6. Are there additional key studies that should be considered in sections 3 and 4 of the PA?

Here are citations and summaries of some of my relevant publications that have not appeared in the PA or an ISA.

Measurement error and uncertainties

These papers examine the effects of bias and noise in independent variables used in linear regression, especially from correlated air pollutants. They show that the pollutant with the least error will prevail in co-pollutant models. Random measurement error biases the slope of an exposure response function toward the null, which also biases the x-intercept toward the origin and obscures any threshold that may have existed in the absence of measurement error. "Measurement error" may be random (instrumental) or the result of mis-specification or mis-location of monitors.

F.W. Lipfert and R.E. Wyzga (1995), Uncertainties in Identifying "Responsible" Pollutants in Observational Epidemiology Studies, Inhalation Toxicology 7:671-89.

F.W. Lipfert and R.E. Wyzga, Air Pollution and Mortality: Issues and Uncertainties, J.AWMA 45:949-66 (1995).

F.W. Lipfert and R.E. Wyzga (1997), Air Pollution and Mortality: The Implications of Uncertainties in Regression Modeling and Exposure Measurement, J.AWMA 47 517-523.

F.W. Lipfert and R.E. Wyzga (1998), Effects of Exposure Error on Environmental Epidemiology, proc. International Symposium on the Health Effects of Particulate Matter, Prague. AWMA Publ. VIP-80, pp. 155-166.

F. W. Lipfert and R.E. Wyzga, Statistical Considerations in Determining the Health Significance of Constituents of Airborne Particulate Matter, J.AWMA. 49:PM-182-191 (1999).

Lipfert, F.W., The Use and Misuse of Surrogate Variables in Environmental Epidemiology, J. Environmental Medicine 1:267-278 (1999).

Time-series studies

Time-series studies of daily mortality predict acute responses on the first few days of exposure, usually persisting less than a week. Responses are limited to the elderly and are stronger among the most susceptible subjects. Similar risks have been associated with various air pollutants and are strongest for cardiac and respiratory deaths. Murray and Lipfert (2010) considered a new model that predicts the magnitude of an elderly subpopulation most at risk of imminent death on a daily basis, rather than the general population. In this model two conditions are required for an acute air pollution-related death: increased frailty (inability to maintain homeostasis) and increased pollution exposure. Extreme values of either parameter can result in death, thus precluding air pollution thresholds. Acute frailty is represented by membership in a small fluctuating sub-population (P_t) at high risk that is depleted by daily deaths (D_t) and replenished by new entries (N_t). D_t and N_t may be affected by current or previous environmental conditions. The ratio of P_t to D_t is a measure of survival time (i.e., daily life expectancy) in the frail state. The Kalman filter is used to solve these equations. P_t fluctuates with season and averages ~0.08% of the elderly. Life expectancies of subjects in the at-risk pool are about 5-7 days and robust to alternative models and environmental fluctuations. Daily mortality risk estimates are similar to

those from conventional time-series analyses, but information on the accompanying life expectancies provided by this model is novel.

Murray CJ, Lipfert FW. Revisiting a Population-Dynamic Model of Air Pollution and Daily Mortality of the Elderly Population in Philadelphia. J Air Waste Manag Assoc. 2010 60:611-629.

Murray CJ, Lipfert FW. A new time-series methodology for estimating relationships between elderly frailty, remaining life expectancy, and ambient air quality. Inhalation Toxicology 2012 24:89-98.

Lipfert FW, Murray CJ. Air pollution and daily mortality: A new approach to an old problem. Atmos Environ 55; 467-74 (2012).

Murray CJ, Lipfert FW. Inferring frail life expectancies in Chicago from daily fluctuations in elderly mortality. Inhal Toxicol. 2013 Jul;25(8):461-79.

Other time-series papers.

These papers provided short-term risk estimates for numerous pollutants that have not been considered by others: a wide range of particulate measures in which TSP was the most important, and a complete set of PM chemical components from which carbon compounds were the most important.

Lipfert, F.W., Morris, S.C., and Wyzga, R.E. (2000), Daily Mortality in the Philadelphia Metropolitan Area and Size-Classified Particulate Matter, J.AWMA 50:1501-13.

Klemm, R.J., Lipfert, F.W., Wyzga, R.E., Gust, C. Daily mortality and air pollution in Atlanta: Two years of data from ARIES. Inhal Toxicology 16 (Suppl 1):131-41 (2004).

The Veterans Cohort Study

The Veterans Cohort Mortality Study began as a cooperative venture with Washington University at St. Louis (WUSTL), who developed the cohort and originated the study. It is based on a cohort of about 70,000 male veterans who were recruited in 1976 and followed for 26 y This is an important period of study because of the substantial improvements in ambient air quality that were achieved following passage of the 1970 Clean Air Act. The cohort was 37.7% black and 81% had smoked at one time; they were recruited at VA 32 clinics nationwide. it is the first cohort study to examine long-term all-cause mortality risks associated with air pollution for a variety of pollutants by race. The study considered the overall follow-up period (1976-2001) and four sequential mortality periods (1976-81, 1982-88,1989-96, and 1997-2001). The WUSTL proportional hazards model included non-linear terms for age, smoking, body-mass index (BMI), blood pressure, and interaction terms. The first paper showed that the relative importance of $PM_{2.5}$ and SO_4 is contingent on the inclusion of contextual predictor variables in the model including climate, poverty and neighborhood characteristics in the proportional hazards model. Those variables were retained in subsequent analyses. Later papers examined $PM_{2.5}$ constituents, hazardous pollutants, and county-level traffic density, which was the most important predictor along with NO_x and elemental carbon. The 2018 paper examined the effects of cohort aging with respect to temporal trends and found the former to be more important with stronger risks in middle age. $PM_{2.5}$ had consistently negative (beneficial) effects; no effects of accumulated exposures were evident. The most recent (2019) paper found that black veterans were more heavily exposed to traffic, with significantly

negative effects of $PM_{2.5}$ but significantly positive risks for whites similar to those found in other cohorts. This explains the apparently anomalous (negative) $PM_{2.5}$ effects for the entire cohort. It also supports the hypothesis that cross-sectional studies essentially consider differences among *places* per se (counties, zip-codes, etc.) rather than the personal exposures of residents. Traffic effects were found to be stable over the 26-y period; however, those actual risk agents remain unknown, comprising engine exhaust, noise, tire/road dust, undesirable residential locations, but not indoor air pollution.

Lipfert, F.W., Perry, H.M. Jr., Miller, J.P., Baty, J.D., Wyzga, R.E., Carmody, S.E. (2000) The Washington University-EPRI Veterans' Cohort Mortality Study: Preliminary Results, Inhalation Toxicology 12 (Suppl 4):41-73.

Lipfert, F.W., Perry, H.M. Jr., Miller, J.P., et al., 2003. Air Pollution, Blood Pressure, and Their Long-Term Associations with Mortality. Inhalation Toxicology 15, 493-512.

Lipfert, F.W., Wyzga, R.E., Baty, J.D., Miller, J.P., 2006a.Traffic Density as a Surrogate Measure of Environmental Exposures in Studies of Air Pollution Health Effects: Long-term Mortality in a Cohort of U.S. Veterans, Atmospheric Environment 40, 154-169.

Lipfert, F.W., Wyzga, R.E., Baty, J.D., Miller, J.P., 2006b. $PM_{2.5}$ Constituents and Related Air Quality Variables as Predictors of Survival in a Cohort of U.S. Military Veterans, Inhalation Toxicology 18:645-57.

F.W. Lipfert, R.E. Wyzga, Jack D. Baty, J. Philip Miller. Vehicular Traffic Effects on Survival within the Washington University - EPRI Veterans Cohort: New Estimates and Sensitivity Studies, Inhalation Toxicology 20:949-960 (2008).
F.W. Lipfert, R.E. Wyzga On Exposure and Response Relationships for Health Effects Associated with Exposure to Vehicular Traffic. J Expos Sci Environ Epidem 18: 588-599 (2008).

Lipfert FW, Wyzga RE, Baty JD, Miller JP. Air pollution and survival within the Washington University-EPRI Veterans Cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. J Air Waste Manag Assoc. 2009 59:473-89.

Lipfert FW, Wyzga RE. Revisiting the Veterans Cohort Mortality Study: New results and synthesis. J Air Waste Manag Assoc. 2018 Nov;68(11):1248-1268.

Lipfert FW, Wyzga RE. Environmental Predictors of Survival in a Cohort of U.S. Military Veterans: A Multi-level Spatio-temporal Analysis Stratified by Race. Envir Res (accepted 2019)**.**

Trend analysis

Lipfert FW (1998), Trends in Airborne Particulate Matter in the United States. Applied Occupational and Environmental Hygiene 13:370-384

Lipfert FW, Morris SC, Temporal and spatial relationships between age-specific mortality and ambient air quality in the United States: Regression results for counties, 1960-97, Occup Env Med 59:156-74 (2002).

This paper used population data to show how mortality risks associated with air pollution decline with age and are stronger when mortality and exposure are measured coincidentally during a given follow-up period.

Review papers.

Lipfert, F.W., Commentary on the HEI Reanalyses of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality, J. Toxicology and Environmental Health 66:1705-14 (2003).

Lipfert FW. An assessment of air pollution exposure information for health studies. *Atmosphere* 2015, *6*, 1736-1752.

Detailed analyses of indoor air quality data showing indoor infiltration rates and short- but not long-term relationships between indoor and outdoor concentration.

Lipfert FW. Long-Term Associations of morbidity with air pollution: A catalogue and synthesis. JAWMA 2018 68:12-26.

This catalog lists 417 long-term studies of cardiovascular, respiratory, cancer, diabetes, hospitalization, neurological, and pregnancy-birth endpoints with respect to $PM_{2.5}$, PM_{10}, TSP, carbon, ozone, sulfur, vehicular traffic, radon, and indoor air quality. Durations of exposure range from 60 d to 35 y. Most studies were cross-sectional over limited time spans with no consideration of lag or disease latency. 220 studies indicated significant adverse effects. Associations with cardiovascular indicators, lung function, respiratory symptoms, and low birth-weight were more likely to be significant than with disease incidence, heart attacks, diabetes, or neurological endpoints. Elemental carbon (EC), and NO_x were most likely to be significant for cardiovascular outcomes. For all diagnoses, the highest fractions of significant findings were for "other" pollutants including TSP, EC, and metals. $PM_{2.5}$ and PM_{10} had lower risk ratios. Overall, these studies support non-lethal physiological effects of various pollutants, more so for non-life-threatening endpoints and for non-criteria pollutants (TSP, EC, $PM_{2.5}$ metals).

Editorial comments

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Responses to Questions from Dr. Lange

1) *Is it appropriate to compare daily PM2.5 concentrations to the annual average?*

This distinction is an artifice of the extant regulatory framework; these are simply two measures of the same typically log-normal frequency distribution of ambient air quality measures. To my knowledge, all C-R functions are essentially linear, including those for health, vegetation damage, and tombstone erosion, but they all require durations of exposure. Short- vs. long-term health effects are discussed below; cumulative exposures should be used for the latter (but seldom have been), just as the number of pack-years is used in smoking epidemiology or working years in occupational epidemiology.

2) *Is it informative to derive annual average pseudo-design values for study areas in short-term studies (that look at effects of day-to-day PM2.5 concentration changes), in order to determine whether these study areas attained the current annual standard? Although the EPA can technically determine if daily changes in PM2.5 concentration increased health effects in an area meeting the annual standard, does this really inform the health protectiveness of the annual standard? It seems that whether an area showed a positive effect or not could be completely independent of the annual standard and instead dependent on how much the PM2.5 concentrations changed from day-to-day.*

As I understand them, design values are only used for regulatory but not scientific purposes and I have no direct comments about them. "Informing health protectiveness" can only be accomplished by comparing health effects measured before and after pollution abatement. This is shown directly in time-series analysis when death counts track pollution peaks, first up and then back down to normal. Such tests have not been successful for long-term pollution abatement, in part because of the time required for cumulative exposures to decrease. This is analogous with the time required to realize health benefits after smoking cessation.

3) *In contrast to short-term studies that investigate the effects of day-to-day changes in PM2.5 concentrations within a certain geographic area, long-term cohort studies often look at the association between annual average PM2.5 concentrations and time-to-event data (such as the time from cohort entry to death) over long periods of time. For these studies, it is not uncommon for all study subjects in a single geographic area to have the same (or very similar) exposure assignments (e.g. Jerrett et al., 2017; Thurston et al., 2016), in which case the study is assessing the effects of PM2.5 between geographic areas, instead of within geographic areas. In this case, is the pseudo-design value in a single geographic area particularly informative, when the association between PM2.5 and the health effect is driven by the differences between study areas?*

If we define the "area" as based on the surroundings of an ambient monitoring station, uniformity is assumed in cross-sectional epidemiology and the lack thereof constitutes "measurement error" and biases the slope of the C-R function downward. However, this common scenario is at odds with the real world because each affected individual within that area will have had his/her own personal exposure that tend to be controlled by indoor rather than the outdoor conditions where we typically spend only 10-15% of our time. Indoor air quality is in synch with the outdoors because of infiltration from the outdoors, but each residence has its own long-term offsets from smoking, gas cooking, pets, cleaning

agents, fireplaces, etc. I found no long-term spatial correlation between indoor and outdoor PM levels as shown in Figure 1 above (Lipfert, 2015). These indoor-outdoor relationships are consistent with reports from EPA (Baxter et al. 1994, 2007, 2010, 2013, 2014, 2017).

(4) Results of Risk Analysis

Table 1. An incomplete list of possible uncertainties in deriving risk estimates from reductions in PM2.5 concentrations.

Source of Uncertainty	*Example Magnitude*	*Example Reference*
Generating the Concentration-Response (C-R) Function in Epidemiology Studies		
Exposure Measurement Error	*31-85%*	*Spatial error + population error (Dionisio et al., 2016)*
Model Misspecification Error	*50%*	*Generalized linear vs generalized additive models for PM10 (Sheppard, 2003)*
Alternative C-R Functions within One Study	*200%*	*Range of HRs generated using different exposure models (Jerrett et al., 2017)*
Causal Relationship	*0.35-1*	*US EPA Expert Elicitation of PM2.5 causality – provided is the range of probabilities that PM2.5 is causing mortality (Mansfield et al., 2009)*
Air Quality Monitoring/Modeling		
Air Monitoring	*± 10%*	*Allowable variation in 24-hour PM2.5 monitored concentrations*
Air Modeling	*± 30%*	*10-90% range for prediction of change in PM2.5 concentrations (Mansfield et al., 2009)*
Applying the Concentration-Response Function		
Choice of C-R Function	*400%*	*Variability in PM2.5 long-term all-cause mortality estimates presented in Table 3-7 using C-R functions from different studies (PM PA 2019)*
Baseline Incidence Rates	*± 5%*	*Influence Analysis 10-90% range for prediction of base mortality rates (Mansfield et al., 2009)*
Population Forecasts	*± 10%*	*Influence Analysis 10-90% range for census 2020 population forecasts (Mansfield et al., 2009)*
Use of National Estimates	*± 1000%*	*Range of C-R estimates across 77 study cities, compared to the national estimate (Baxter et al., 2017)*

Threshold in C-R	*6-90%*	*Change in premature mortality from CPP repeal cutpoint analysis (LML cutpoint on low end of scale; NAAQS on high end of scale) (USEPA, 2017)*

Re: Table 1. "Causal Relationships" vary by PM composition, disease, age, race, season, and exposure time. Most of these factors have not been explored or discussed in the PA. "Air Monitoring" is inadequate because indoor exposures have not been considered and the databases for daily values and PM constituents are too sparse. There is virtually no ambient data on the ultrafine particles that can enter the bloodstream. I did not respond to questions on the present "C-R functions" because I do not find them credible, as discussed above.

(5) *Is there a quantitative uncertainty analysis method that the EPA could use for this risk assessment that captures more of the uncertainty and variability of the risk estimates (such as those described in Table 1), in order to better inform CASAC and the EPA Administrator about the impact of these uncertainties?*

Statistical methods are available for within-model random uncertainties, but the questions raised above about appropriateness of specific models have not been addressed and are far more important. There are also uncertainties as to responsible pollutants. $PM_{2.5}$ is featured in part because of is extensive ambient monitoring network and the use of mathematical models to estimate more detailed locations. However, considering the time periods (decades) and spatial scale (the entire U.S.) it is likely that other pollutants may be involved, especially $PM_{2.5}$ constituents.

(6) *Could different magnitudes of error amongst different variables in regression analyses be masking the effect of a speciated constituent of PM2.5.*

In general, the database for PM constituents is much more sparse than for $PM_{2.5}$ *per se*; there are fewer locations, shorter periods of record and limited daily data. I searched for relevant mortality studies from the US, UK, or Canada and found the following papers, none of which were cited in the PA:

Olstrup H, Johansson C, Forsberg B. The Use of Carbonaceous Particle Exposure Metrics in Health Impact Calculations. Int J Environ Res Public Health. 2016 Feb 24;13(3). pii: E249.

Kim SY, Dutton SJ, Sheppard L et al. The short-term association of selected components of fine particulate matter and mortality in the Denver Aerosol Sources and Health (DASH) study. Environ Health. 2015 Jun 6;14:49.

Atkinson RW, Analitis A, Samoli E et al. Short-term exposure to traffic-related air pollution and daily mortality in London, UK. J Expo Sci Environ Epidemiol. 2016 Mar-Apr;26(2):125-32.

Ozkaynak H, Baxter LK, Dionisio KL, Burke J. Air pollution exposure prediction approaches used in air pollution epidemiology studies. J Expo Sci Environ Epidemiol. 2013 Nov-Dec;23(6):566-72.

Cakmak S, Dales RE, Rubio MA, Vidal CB. The risk of dying on days of higher air pollution among the socially disadvantaged elderly. Environ Res. 2011 Apr;111(3):388-93.

Mar TF, Norris GA, Koenig JQ, Larson TV. Associations between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect. 2000 Apr;108(4):347-53.

Zhou J, Ito K, Lall R, Lippmann M, Thurston G. Time-series analysis of mortality effects of fine particulate matter components in Detroit and Seattle. Environ Health Perspect. 2011 Apr;119(4):461-6.

Ostro B, Roth L, Malig B, Marty M. The effects of fine particle components on respiratory hospital admissions in children. Environ Health Perspect. 2009 Mar;117(3):475-80.

Ostro BD, Feng WY, Broadwin R et al. The impact of components of fine particulate matter on cardiovascular mortality in susceptible subpopulations. Occup Environ Med. 2008 Nov;65(11):750-6.

Ostro B, Feng WY, Broadwin R, Green S, Lipsett M. The effects of components of fine particulate air pollution on mortality in California: results from CALFINE. Environ Health Perspect. 2007 Jan;115(1):13-9.

Sarnat SE, Suh HH, Coull BA et al. Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. Occup Environ Med. 2006 Oct;63(10):700-6.

Burnett RT, Brook J, Dann T et al. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol. 2000;12 Suppl 4:15-39.

Klemm, R.J., Lipfert, F.W., Wyzga, R.E., Gust, C. Daily mortality and air pollution in Atlanta: Two years of data from ARIES. Inhal Toxicology 16 (Suppl 1):131-41 (2004).

Lipfert, F.W., Wyzga, R.E., Baty, J.D., Miller, J.P., 2006b. $PM_{2.5}$ Constituents and Related Air Quality Variables as Predictors of Survival in a Cohort of U.S. Military Veterans, Inhalation Toxicology 18:645-57.

Lipfert FW, Wyzga RE, Baty JD, Miller JP. Air pollution and survival within the Washington University-EPRI Veterans Cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. J Air Waste Manag Assoc. 2009 59:473-89.

Most of these studies were from localized areas. None of them used long-term data from the Harvard Six Cities, American Cancer Society, or Medicare cohorts; the Veterans Cohort Study used nationwide data (Lipfert et al., 2006b). Measurement errors relative to $PM_{2.5}$ are likely since it tends to be regionally distributed while most of its constituents are more local. There may also be uncertainties in the chemical analyses, notably for carbon compounds that appear to be the most important constituents.

(7) *What happens when multiple potential explanatory factors are included in a single variable in an already-complex multiple regression system? Presumably each PM2.5 component has a different C-R relationship with the health effect (even if that relationship is zero), and each is a somewhat better or worse surrogate for the relationship between actual exposure vs measured exposure.*

What kind of an impact would this inclusion of multiple potential explanatory factors into one variable have on the final C-R function, and how accurate would that C-R function be?

A common problem is that of multicollinearity, since many PM constituents are interrelated. A better procedure might be to develop hypotheses from toxicity data and test them against specific causes of death, relying more on physiology than statistics *per se*.

Responses to Questions from Dr. Packham

(1) *Are there areas (e.g., specific aspects of biological causation, pulmonary toxicology, or causality in epidemiology) in which additional knowledge is required to appraise the adequacy and basis of existing, new, or revised PM NAAQS to protect public health with an adequate margin of safety?*

Biological causation has not been addressed by health endpoint. A critical issue is translocation of PM from lung to bloodstream according to particle size and whether $PM_{2.5}$ as measured in the ambient is capable of doing so. Health effects centered in the respiratory system must be evaluated in terms of deposition, clearance, and importance of cumulative deposition. All of this must be characterized by PM constituent; if only EC could be shown to be harmful, then control strategies and accountability must focus on EC. This is especially important for ultrafines (UFP), for which exposures are essentially unknown.

The findings of strong effects of traffic density (the 3rd type of C-R mentioned in the Introduction) should be replicated in other cohorts. Such data are readily available.

(2) *Can you suggest additional specific scientific disciplines and areas of biomedical informatics and research (e.g., systems biology methods for clarifying biological causal pathways, mechanisms, modes of action, quantitative causal dose-response relationships) that should be included in future reviews of other criteria pollutants.*

Causality, speciation, and accountability go together. Short-term causality was shown in London 1952 by autopsy (Bradley, 1957) that indicated black carbon deposits. Accountability in short term effects is shown by synchronicity of exposure and response after controlling for weather, the only rational confounder. No such demonstrations have been reported for long-term effects. Animal tests in the 1970s were inconclusive and there have been no sufficiently long morbidity experiments that might demonstrate associations between $PM_{2.5}$ as measured in the ambient and development of atherosclerosis, for example. Human (or animal) experiments on concentrated particles (CAPS) in previous decades should be reviewed and possibly extended to PM components or UFPs.

(3) *Can you describe the research efforts necessary to provide the required information?*

Long-term morbidity experiments or evaluation of associations with long-term hospitalizations, nursing home stays, etc. Occupational studies on PM components, especially EC, OC, SO_4, NO_3. Existing cohort studies should be reevaluated using lags and cumulative exposures. Within- and between-city data on indoor air quality are needed (See Figure 1, above).

(4) *To what extent has the needed research already been done, or started? For example, are there crucial experiments or research initiatives that could clarify the shape of the PM2.5-chronic inflammation causal dose-response relationships at relevant exposure concentrations?*

Not that I'm aware of.

(5) *Are there specific data analyses (e.g., testing for confounding by weather variables over more days prior to mortality) that could clarify the causal interpretation of epidemiological associations relied on in the draft PA to simulate effects of interventions?*

Yes. See sensitivity studies of temperature and air pollution lags in Murray and Lipfert (2012, 2013). Those studies should be replicated for other times and places. Short-term studies essentially comprise "interventions" (caused by atmospheric changes, week-days vs. weekends).

(6) *Can you suggest additional areas of scientific literature review on species and individual human organism's capacities of adaptation to inhaled environmental stressors that might help establish margins of safety when exposed to ambient levels of air pollution?*

Respiratory effects of cumulative exposures are well known for smoking and occupational exposures. Parallel information is needed for CVD, stroke, etc.

(7) Could you provide additional information on the relative contributions to air pollution concentrations and resulting health effects of natural and anthropogenic activity? For example, is either one alone, or are both natural and anthropogenic activities together, sufficient to cause the magnitudes of adverse health effects attributed to PM2.5 in the Draft PA?

This requires PM speciation and is important for indoor sources and wood smoke, including wildfires.

(8) *Could you provide additional information on any adverse public health, welfare, social, economic, or energy effects which may result from various strategies for attainment and maintenance of such national ambient air quality standards?* No.

Discussion of Issues

A. Causality

A causal relationship between exposure and response is required to justify regulation intended to benefit public health. Causality in air pollution epidemiology must rest on five requirements, none of which has been established for $PM_{2.5}$. The purpose of this exposition is not to demolish the existing regulatory structure but to advocate for reframing it by addressing each of the 5 points.

1. Exposure. Indoor exposures and daily peaks have not been considered in long-term studies. Initiation of chronic disease only occurs after a latency period and responds to cumulative exposures. This has been established for smoking but not for air pollution epidemiology.
2. Toxicity. $PM_{2.5}$ is not really a pollutant in the sense of defined chemicals (CO, O_3, SO_2). It is a regulatory construct based on mixture of many kinds of particles, some toxic, others not. These mixtures will have varied or time and among locations. Given the multiplicity of health endpoints that have been considered, some statistically significant combinations with a PM constituent are likely.
3. Translocation. Inhalation of a pollutant is not sufficient to imply contact with an organ and initiation of chronic disease. $PM_{2.5}$ translocation from the lung to the bloodstream has not been demonstrated, by contrast with ultrafine particles, for example.
4. Susceptibility. Given the diversity of the population, the notion that a healthy person could be randomly selected to die coincidently with normal levels of ambient air quality is patently absurd. Time-series studies have shown that acute mortality is associated with both underlying frailty and daily air pollution peaks. Such differential susceptibility is also likely the case for incidence of chronic disease, but cohort members would have to be tracked during the disease latency period to make this case.
5. Accountability. The ultimate test of causality is whether public health has actually improved in response to reduced $PM_{2.5}$ (by a factor of 3 since ca. 1980), after accounting for coincident trends in spatial patterns of reduced smoking and improved medical care. The extant literature does not support this test; Henneman et al. (2019) showed no effect on total mortality (-0.011 [-0.92 – 0.71]) after reducing $PM_{2.5}$ from 10.0 $\mu g/m^3$ in 2005 $\mu g/m^3$ to 7.2 in 2012. Note that their analysis did not account for latency or cumulative exposures.

By contrast, the epidemiology of smoking has all of these elements (Lipfert, 2019). Exposure is self-reported on an individual basis, and the importance of cumulative exposure is shown by the use of pack-years as a predictor of disease after accounting for latency. Toxicity of smoke constituents has been determined by laboratory and animal tests, especially for benzo(alpha)pyrene (B[a)P) which is also an (unmonitored) ambient air pollutant. Translocation is not an issue for the gaseous pollutants and the most serious health effects (cancer, COPD) occur in the lung. Susceptibility comes into play when frail smokers are urged to quit. Accountability is shown by the improved health of quitters.

B. Interactions between short- and long-term air pollution effects

Consider time-lines for daily deaths, frailty (morbidity), and air pollution (AP) exposure, for a population with no secular or seasonal trends over a period of decades. Each parameter progresses through daily peaks and valleys over time. When death and air quality peaks preceded by sufficient frailty coincide, a sudden AP death occurs. That person is replaced by a healthy person and the process continues along the time-lines. Frailty may also be affected by AP. The remaining deaths and air quality exposures accumulate, also with replacement. However, deaths would not be replaced in cohort analyses, leading to depletion of the most susceptible subjects. A non-peak AP death occurs when exposure accumulates to a level sufficient to initiate a specific disease. The total AP death count for the overall period includes peak and non-peak AP deaths.

This process is carried out in other locations and their total death counts are compared with their accumulated exposures to derive the ratio of total AP deaths to exposure for the group using cross-sectional analysis. Each AP death would have been preceded by an exposure of duration depending on

frailty level and cause of death. The short-term peak deaths are of separate interest because they are limited to the most-frail subjects and do not constitute incidence of a new disease. Incidence of cancer or COPD may require 20-30 y exposures, cardiovascular diseases somewhat less. There may be other causes of death associated with intermediate exposure periods about which we have no information. These exposure differences suggest cause-specific analyses, each with its own exposure timing.

This scenario is straightforward, absent secular trends. However, air quality and medical care have been improving since about 1970, and relevant exposures for deaths in say, 2000, may reach back to the 1970s when air quality was much worse. The upshot is that we can't estimate appropriate long-term AP exposures for all-cause deaths, but they are surely higher than exposures at the time of death. Corresponding risk coefficients would thus be reduced. Table 1 compares the attributes and shortcomings of short- and long-term studies.

Table 1. Characteristics of time-series and cross-sectional mortality studies

	time-series	long-term populations	long-term cohorts
dependent variable	death count	mortality rate	dead (yes, no)
subjects	subpopulations	populations	individuals
likely causes	sudden death	---------- ischemic heart disease ----------	
confounders	weather climate	city characteristics contextual variables	personal characteristics holidays
exposures	daily	cumulative annual av'g	cumulative annual av'g
timing	lag days	after latent period	after latent period
indoor exposure effects	attenuation	confounding, bias	confounding, bias
secular trend	accounted for	exposure bias	cohort depletion by age
threshold	frailty dependent ----------obscured by measurement error----------		

Issues of exposure timing

Above I defined three types of C-R relationships that may be involved in a given situation:

(a) Short-term (days) fluctuations in air quality that may trigger sudden death in vulnerable individuals. Causality in this mode has been demonstrated by heat wave mortality.

(b) Long-term (decades) individual differences that affect incidence of new cases of chronic disease, for which the extended effects of cigarette smoking are a causal example.

(c) Long-term differences among populations that may involve both of the above as well as attributes of their locations *per se*, such as climate, green spaces, traffic density, or characteristics of housing stock that affect indoor air quality.

The sum of pollution-related deaths from (a) and (b) comprises the total long-term mortality effect, as derived from cross-sectional cohort analysis and reported by most of the $PM_{2.5}$ analyses used in the PA. However, there are no short-term effects involved with the contextual variables in type (c) and those effects are likely to have been stable over time so that cumulative exposures introduce no bias. The Veterans Cohort Study (Lipfert, et al., 2006 a,b) introduced the traffic density variable, the logarithm of which was a highly significant predictor of all-cause mortality over the 26-y follow-up period, better than either population or housing densities. In a 2-pollutant model, both traffic density and ozone were significant, comprising a combination of all three C-R modalities. However, ozone effects were sensitive to exposure timing (Lipfert et al., 2000).

Including additional lags in a short-term study may attribute more deaths to the previous exposures, thus *in*creasing the risk coefficient. By contrast, considering prior cumulative exposures in a long-term study increases the *exposure* associated with the observed mortality, thus decreasing the risk coefficient. The effects of stable contextual variables are not sensitive to timing issues for long-term residents of a given location (e.g., county).

C. Summary

The current EPA paradigm linking mortality from chronic diseases with long-term air pollution exposure does not comport with observations. Here's what's been observed:

1. Exposure to high levels of black smoke and SO_2 for a few days has been linked with excess mortality by autopsies that show lung deposits of carbonaceous material. Those identified victims had suffered from preexisting cardiopulmonary diseases. Causality was supported by mortality levels returning to normal after air quality returned to normal.
2. Responses to daily fluctuations are included in annual variations.
3. Chronic effects should be characterized by cumulative exposures, similar to observations of smoking effects based on pack-years.
4. The timing of response following exposure depends on latency that varies by disease.
5. Adults typically spend 85-90% of their time indoors.
6. Long-term levels of outdoor air quality can be worse than indoors because of unregulated indoor sources that vary substantially within cities.
7. Short-term (daily) fluctuations in indoor air quality follow the outdoors with concentrations reduced by about 50%.
8. Some pollutants (O_3, SO_2) are adsorbed onto indoor surfaces and are thus not at issue.
9. Not all potentially important pollutants have been monitored adequately.
10. Frailty plays an important role in short-term health effects.
11. Ischemic heart disease (IHD) has been associated with long-term exposure to air pollution. Sudden death comprises about half of IHD and thus could be an outcome of short-term exposures consistent with relationships between the long- and short-term effects.

This is what has *not* been observed:

12. Deaths attributed to long-term exposure verified by autopsy.
13. Sufficient data on personal exposures to airborne pollutants adequate for epidemiology.
14. Translocation of inhaled particles from lung to blood stream.

15. Long-term morbidity effects that could support pollution-related incidence of chronic disease or onset of frailty.

The following may be inferred from statistical modeling:

16. Time-series analyses show similar short-term relationships with various pollutants including black smoke and other PM constituents, worldwide.
17. Short-term effects may persist for several days; total responses are given by the sum over the lag period.
18. A new time-series mortality model that includes frailty in conjunction with air quality shows that healthy individuals are not affected by air quality fluctuations. Since there is no upper limit on the severity of frailty (life expectancies can be as short as one day), there can be no short-term air quality threshold.
19. Remaining life expectancy is a better outcome metric than numbers of lives "saved" and has been estimated to range from days to months (but not years).
20. The validity of long-term dose-response modeling depends on controlling a wide variety of potential confounders including contextual variables that describe places of residence.
21. Long-term air pollution studies have inadequately controlled confounding including climate and personal income for cohort studies and smoking, obesity, and poverty for population-based studies.
22. Those confounders are not important for short-term effects.
23. Mortality differentials have been associated with places *per se* such as green spaces or traffic hot spots rather any accompanying air pollution exposure differentials. Such long-term associations may be affected by age but not by timing, confounded by indoor air pollution, nor limited by the available ambient air quality monitoring.

Here's what can be concluded from the above:

24. Short-term effects have been substantially underestimated since most have been based on 1-2 day average exposures rather than sums over lags. Short-term indoor exposures are attenuated, thus increasing their risk coefficients.
25. Long-term effects have been overestimated since cumulative exposures are much higher and latency pushes the applicable air quality levels back in time when they were much worse.
26. Any true long-term effects must be based on differences between estimates derived from annual vs. daily averages and would thus be problematic after adjusting for the above.
27. Long-term personal exposures are unknown because of variable contributions from indoor sources.
28. Responsible pollutants cannot be confirmed because of inadequate ambient monitoring.
29. Increased research on short-term effects will require substantial expansion of daily monitoring.
30. More attention should be given to ultrafine particles that can enter the blood stream.
31. "Safe" air quality levels cannot be defined because of the controlling effects of physical frailty. Society must judge how much (non-zero) risk can be tolerated.
32. Accountability for long-term air pollution abatement is problematic due to lingering effects of prior cumulative exposures.
33. Long-term health effects associated with places of residence rather air pollution exposures *per se* are not subject to these limitations and are thus more rational.

34. Future research should try to account for these limitations and focus on pollution-related morbidity that may lead to frailty and short-term effects.

References are listed after Appendix C

Appendix A. Background Issues

1.1 The potential lethality of ambient air pollution was established by the 1952 London fog disaster though autopsies that found black carbon deposits in the lungs of victims. Subsequent time-series analyses at various locations during normal atmospheric conditions found associations between mortality and daily air pollution peaks over several days, some of which also involved black carbon. Summing those deaths over lag periods provides larger estimates of excess deaths than previously reported. Time-series analyses using econometric methods found that these excess deaths were limited to previously frail subpopulations rather than the population at large. These procedures are consistent with analyses of heat wave mortality, when victims were also limited to the frail. Short-term effects are thus controlled by frailty as well as environmental conditions and are not mutually exclusive. A sufficiently frail subject may succumb to minor pollutant exposures and vice-versa, precluding observation of thresholds in either. Short-term effects have been well established; proof of existence through statistical testing is no longer required.

1.2 Particulate pollutants have been measured in various ways over time, beginning with filter staining, referred to as British smoke, black smoke, smokeshade, or coefficient of haze (COH) and equivalent to elemental carbon mass (EC). Early U.S. data were measured in terms of the total mass collected on filters: total suspended particulate matter. Atmospheric visibility has also been used. Sulfate content was also reported then but those early readings are suspect because gaseous SO_2 reacted passing through the alkaline filters, creating artifact sulfates. Beginning ca. 1980 better sampling methods were devised, with segregation by particle size, originally $PM_{3.5}$ and PM_{15} and later changed to $PM_{2.5}$ and PM_{10}. Daily TSP ranked highest in a comprehensive comparison of PM metrics in Philadelphia (Lipfert et al., 2000).

1.3 $PM_{2.5}$ infiltrates indoors but not uniformly (Sarnat et al., 2012). Penetration varies by season (and presumably climate), time of day, composition, and particle size. Submicron particles have the largest indoor/outdoor ratio, peaking at about 0.3 μm; EC penetrates indoors better than $PM_{2.5}$. Part of the focus on $PM_{2.5}$ came from the Acid Precipitaion Program that posited that acidity (H^+) of filter deposits was a human health hazard. Subsequent epidemiology ruled this out but concern about $PM_{2.5}$ remained, originally about respiratory effects that had been demonstrated in the Harvard Six Cities program. Based on subsequent epidemiology, emphasis shifter to heart disease for which mechanistic support remains incomplete.

1.4 Estimates of long-term effects of air pollution on specific cohorts or populations at large have been limited to cross-sectional comparisons across locations for which outdoor ambient air quality levels were estimated. These associations have been interpreted as evidence for causing new cases of chronic disease; however, neither latency periods nor cumulative exposures have been considered nor have pollutants toxic to specific organs been identified. These cross-sectional analyses are thus inconsistent with well-established protocols for analyzing smoking effects (Lipfert, 2019). By contrast with effect of smoking, death by long-term air pollution exposure has never been confirmed by autopsy. In addition, there have been no sufficiently long-term morbidity or animal studies to provide support for the chronic effect hypothesis.

1.5 The timing of exposures relative to responses is important. Exposure must precede response, as has been shown in time-series studies. Long-term studies have been based on annual averages, but those averages *include* the daily peaks for which short-term responses were estimated separately. Any true long-term effects must thus be defined as *differences* between those based on annual averages and those based on daily peaks. Short-term effects should be summed over lags and long-term effects should account for latency and cumulative exposures. These fundamental requirements have not been recognized in the extant literature.

1.6 Only outdoor air pollution has been assumed to be relevant even though we spend ~85% of our time indoors, more for the severely frail. Indoor air pollution was not addressed in the Clean Air Act, is not regulated, and is thus not routinely monitored. In much of the United States, outdoor air may be dirtier than indoors for some pollutants, in which case further improvements in outdoor air quality would be moot. EPA has a separate entity for indoor air quality but those concerns have not been recognized in epidemiology and differ between short- and long-term exposures. About half of outdoor air pollution infiltrates indoors with the same frequency distributions; short-term effects may thus be experienced indoors but with larger risk coefficients. Long-term effects are dominated by unregulated indoor sources including environmental tobacco smoke, gas stoves, pets, candles, hobbies, etc., for which few data are available. Cross-sectionally, there are no long-term relationships between indoor and outdoor air quality, especially for particulate matter that has many types of indoor sources. The victims of air pollution occupy only a tiny fraction of a community's residences, practically precluding estimating their indoor exposures.

1.7 The implications of future climate change and of the likely efforts to ameliorate it should also be considered. There may be less vehicle exhaust but not tire and road dust. Rising temperatures will bring increased demand for residential air conditioning. The accompanying reduced infiltration of outside air will exacerbate effects of indoor air pollution sources.

1.8 The selection of criteria pollutants has involved circularity: The agency suspects health effects for a given pollutant based on prior information. It then deploys a monitoring network designed solely for that pollutant. The resulting data are used in epidemiology studies that find significant effects for that pollutant (alone), thus justifying the original decision. However, that decision would have been made in the absence of parallel counterfactual information for comparison, which would have required monitoring other candidate pollutants in parallel. Epidemiology can only consider the pollutants that have been measured that are typically designed to support the *a priori* decision to regulate.

A good example involves constituents of $PM_{2.5}$, such as metals, carbon compounds (black smoke), or ultrafines (UFPs). The limited information available, including from foreign sources, suggests that each of these alternatives may be more toxic than $PM_{2.5}$ per se. But lacking parallel monitoring data, especially on a daily, these hypotheses cannot be tested. This lack of more specific information is critical in designing abatement strategies. There are no sources that directly emit the $PM_{2.5}$ used in epidemiology studies; they only emit specific constituents, making it difficult to design an efficient abatement strategy. This may help explain the lack of successful $PM_{2.5}$ accountability studies.

1.9 How can these concepts be reconciled with the extensive archive of existing studies that found significant risks? The subdivision of the total mortality effect into short-term and differential (true) long-term components does not invalidate the estimated total risks from existing epidemiology studies but drastically changes their interpretation. The total risk remains the same (those existing studies are not

"wrong") but a portion of the risk must be ascribed to short-term daily effects, discussed below under "causality". Finding a threshold in the short-term portion is extremely unlikely since in a sufficiently large population during a sufficiently long lag period there will always be at least one person sufficiently frail so as to succumb to a minor excursion in ambient air quality. The difference between total cross-sectional risk and the acute portion of the risk cannot be assumed to have resulted in chronic disease incidence without considering cumulative exposures prior to the latency period. These determinations have not been made. Lacking defined thresholds, society must decide how much risk it will tolerate.

2.0 All epidemiology is concerned with both time and place. Results from time-series analyses are more credible when those from different cities agree. However, most long-term (i.e., spatial) studies have been limited to fixed time periods; longitudinal studies are rare but are required to establish accountability for the predicted benefits of improved air quality. Only one study has evaluated the effects of cohort aging separately from temporal trends (Lipfert and Wyzga, 2018). Cohort studies often give the impression that they are about people, but exposure to ambient air quality inevitably involves geography. In the absence of personal exposure data, the extant long-term cohort studies are about *places* rather than their residents. They cannot identify individual risks but may indicate that living in City A may be riskier than in City B for any of several possible reasons other than ambient air quality:

- climate, which can affect time spent outdoors and exposure to extreme weather conditions
- physical characteristics such as green space or traffic density
- differences in housing stock such as high-rises or dilapidated construction.

Literal interpretation of a cross-sectional study implies that moving from City A to City B would instantly confer health benefits. However, as shown by the delay involved in benefiting from smoking cessation, this could only be the case with acute effects.

2.1 The Clean Air Act requires that thresholds be identified with an "adequate margin of safety". Such thresholds have not been identified for particulate matter, for any or all of the following reasons:

- Underestimated exposures (indoor sources)
- PM constituents that change with $PM_{2.5}$ concentration level
- Mixtures involving different copollutants
- Daily effects on frail subjects that are embedded with long-term effects
- Measurement errors that bias the slope of the dose-response function downward.

This situation was inconceivable to the framers of the 1970 Clean Act or even its subsequent amendments, but it suggests that society may now have to decide how much risk may be tolerated; zero risk can never be achieved or maintained.

Appendix B. Air pollution epidemiology

Acute exposures.

Following the disastrous London fog of 1952 that increased daily and air pollution mortality rates by an order of magnitude, accountability was obtained by autopsy. Under these conditions, the probability of having randomly selected a victim of the episode was around 90%, by contrast with current conditions (fortunately). The working hypothesis was that this extreme excess mortality had been caused by

a. black smoke.
b. SO_2.
c. dense fog.
d. adverse ambient temperature levels.
e. Combinations of the above.

Air quality including indoors was so bad that it was reported that cinemas had to close because the projected images could not reach the screen. This episode lasted for a few days and the excess death count was the sum over that period.

At that time, emissions from traffic (NO_x, CO, VOCs) would not have been involved because travel was curtailed by the dense fog. Ozone would not have formed due to the absence of sunlight. Particulate matter would have comprised elemental carbon (EC), organic compounds from incomplete coal combustion, and sulfates, and would have been ascertained by filter staining rather than by mass. Heavy metals such as Pb would not have been an issue. Autopsies found lungs that contained black carbon particles which then became the prime suspect although sulfates could not be ruled out. These sulfate compounds tended to be acidic and soluble and may have been overwhelmed the natural ammonia defenses. Individual victims could be identified with relative certainty and they were found to largely comprise persons with preexisting cardiorespiratory conditions.

The working hypothesis was then supported by analysis of subsequent but milder episodes in London, New York City and elsewhere. As air quality improved such episodes became rare and continuous time-series analyses were performed by OLS regression over periods long enough to attain statistical significance. They were limited to SO_2 and black smoke, the only pollutants monitored daily at that time. The most comprehensive such analysis was published by Schimmel (1980) and showed that black smoke was the likely culprit over 14 y in New York City. Heavy residual oil containing metals was the main fuel. Excess mortality was only of the order of a few percent, precluding the identification of specific victims.

Hundreds of similar daily mortality and hospitalization studies followed, limited mainly by the availability of daily air quality data. In the United States, particulate matter was then ascertained by the mass collected on filters without regard to particle size; sulfur was the only PM constituent identified. The only classification of victims was by age group, usually aged 65 and over. Allowance for coincident weather effects such as heat waves is also important, including lagged effects. The most recent nationwide analysis of daily mortality and $PM_{2.5}$ (Di et al., 2018) considered only the average of lags 0,1, thus underestimating the effects by about a factor of 3 that would have yielded a risk of 3.3% per 10 $\mu g/m^3$. Blomberg et al. (2019) investigated interactions between radon and $PM_{2.5}$ and estimated the $PM_{2.5}$ effect at about 2.8% per 10 $\mu g/m^3$ at the mean radon level but lag assumptions were not specified.

Around 2000, a new time-series methodology appeared that identified the subpopulations most at risk using Kalman filter methods as developed by econometricians. It postulates the existence of a fluctuating group of extremely frail elderly that is depleted by daily deaths and augmented by newly frail individuals. The life expectancies of such groups were of the order of weeks; the fractions of deaths associated with air pollution were similar to those from conventional time-series. Kundi et al. (2019) noted that prediction of post-hospital cardiovascular outcomes was significantly improved by considering a "frailty score" index. The important feature of the new model is that excess deaths are driven by the product of the population at risk and the air pollution level. An excess death can result from either extreme frailty or bad air quality or both. As a result, *there is no threshold for air pollution exposure alone*. Wen (2017) reported mortality hazard ratios around 5.0 for severe frailty while air pollution ratios are typically around 1.05.

This model has been applied to Philadelphia, Chicago, and Atlanta, with similar findings for several pollutants (Murray and Lipfert, 2012, 2013). For example, we typically found that these frail subpopulations had remaining life expectancies of a few weeks, a small fraction of which was associated with air pollution with about 2% excess mortality. For comparison, assuming that life expectancies for those aged 65 ranged from 1 day to 30 y with a log-normal distribution the bottom 2% of which would have a life expectancy of 24 days, in rough agreement with the new model. Another element of this methodology is the extent to which air pollution may been involved in worsening the onset of the severe frailty required for an acute. This possibility has been explored but not resolved. No other investigators have since adopted this new modeling protocol.

Another important aspect of time-series analysis is that of delayed responses. Some studies have considered lag periods up to 7 days, but most of them were aimed at identifying the lag days of greatest statistical significance, as if to establish the *existence* of such relationships. However, the validity of these findings was established by the 1952 London event; the magnitudes of subsequent events are now of primary interest based on excess deaths accumulated over the lag period as was the case in London. It thus appears that most of the extant literature may have underestimated the severity of short-term effects on mortality, perhaps by a factor of 2-3.

Long-term exposures.

Long-term studies are based on annual average concentrations over various aggregation or follow-up periods. Such studies began in the 1970s based on differences in annual mortality rates among the populations of various cities or counties, for which personal data such as smoking habits or socioeconomic status were not available. Beginning with the Harvard Six Cities Study (Dockery et al., 1993), mortality rates were studied in defined cohorts having such personal data. However, no published long-term study has recognized that the deaths accumulated over a year in a given location include those precipitated by daily peak exposures, as discussed above. The true long-term effect is thus the difference between long-term and short-term analyses. The largest long-term mortality risks have been ascribed to ischemic heart disease (IHD), which includes "sudden" death and heart attacks, thus showing overlap between acute and chronic causes of death.

For example, daily mortality across those 6 cities increased by 1.5 (1.1-1.9) percent per 10 $\mu g/m^3$ for a 2-day average of $PM_{2.5}$ (Schwartz et al., 1996). The cumulative effect for the 2 days was thus 3.0 (2.2-3.8)% which might increase to 4.5 (3.3-5.7)% when additional days are considered (Staniswallis et al. 2009). For comparison, the long-term effect of $PM_{2.5}$ for these cities was reported as 12 (4-21)% per 10

$\mu g/m^3$. Dockery et al. (1993) commented that cumulative exposures over prior years should have been considered (especially for lung cancer) and that not all confounding variables had been controlled (notably climate and personal income). Both of these considerations would reduce the long-term effect estimates and render the difference between long- and short-term effects nonsignificant.

In general, short-term mortality effects have been underestimated by not summing over sufficient lag periods, and long-term effects have been overestimated by not considering prior cumulative effects and a complete suite of potential confounders. Most daily analyses have focused on statistical significance for the most lethal day instead of the total "yield". In a long-term study, the risk coefficient is reduced when the true exposure is increased. When the early studies based on annual averages found risk estimates that exceeded those from daily studies, they assumed that the effect pertained to the incidence of chronic disease. However, this hypothesis has not been tested or confirmed.

Latency is a further issue in long-term studies. Lung cancer incidence lags smoking by 15-30 y, perhaps less for heart disease. Thus, mortality from 1982-8 studied by Pope et al. (2002) should have been linked to pollution data as far back as 1952 when urban air was far more polluted (Lipfert, 1994). The total mortality risk coefficient should have been around 2% per 10 $\mu g/m^3$, again not significantly different than typical short-term values when summed over lag periods. Latency may also explain why it has been difficult to establish accountability for air quality improvement. Just as the benefits of smoking cessation appear only after a 5-10 y abstinence, similar lags may delay the effects of cleaner air.

Long-term studies are generally conducted over decades to increase the number of deaths and for stability. Doing so invokes temporal trends in air quality and medical care, during which a cohort may be depleted of its most susceptible subjects. Lipfert and Wyzga (2018) found that cohort aging was more important than secular trends and that risks decreased with age. Lipfert et al. (2002) used population data to also show this aged effect and found stronger risks when mortality and exposure were measured coincidentally rather than lagged.

Classification of air pollution exposures is an important issue seldom considered in the extant literature, especially for cohorts; exposures have been based on measurements or estimates of outdoor air quality at fixed times and locations. They represent characterizations of those locations (places) but not the personal exposures of inhabitants; by contrast with smoking habits, education, body mass, etc; they do not travel with the subject during follow-up. Cumulative exposures have not been considered, by contrast with smoking. Some long-term analyses have considered characteristics directly and found significant associations, notably "green" spaces and vehicular traffic density (VMT). The latter was considered extensively in the Veterans Cohort Study (the only cohort analysis to do so), where it was the most important predictor of mortality risk (as ln[VMT]) along with NO_x and elemental carbon (EC). The geographic distribution of ln(VMT) has been stable over decades; temporal trends are thus not at issue. VMT is a true geographic descriptor that could entail engine exhaust and lubricant residues, tire and road dust, or socioeconomic effects associated with undesirable residential locations. It is integrated over counties so that local changes in residence are not an issue nor are commuting patterns. VMT per se is not amenable to regulatory abatement and is likely to increase over time. However, the engine exhaust pollution should diminish over time with increased use of electric vehicles. In addition to neglecting personal exposures, epidemiology studies have not considered the ultimate fates of inhaled particles, most of which are retained in the lung (Churg and Brauer, 1997). Only ultrafine particles (UFP) are likely to translate into the bloodstream and travel to other organs (Wichmann et al., 2000).

UFPs are a tiny fraction of $PM_{2.5}$ and thus studies that attribute incidence cardiovascular, cancer, diabetes, or neurological effects to $PM_{2.5}$ are ipso facto problematic.

Appendix C. Publications by Lipfert and colleagues not considered in the ISA, by subject area.

Measurement error and uncertainties

These papers examine the effects of bias and noise in independent variables used in linear regression, especially correlated air pollutants. They show that the pollutant with the least error prevails in co-pollutant models. Random measurement error biases the slope of an exposure response function toward the null, which then biases the x-intercept toward the origin and obscures any threshold that may have otherwise existed. ”Measurement error” may be random (instrumental) or the result of mis-specification or mis-location of monitors.

F.W. Lipfert and R.E. Wyzga (1995), Uncertainties in Identifying "Responsible" Pollutants in Observational Epidemiology Studies, Inhalation Toxicology 7:671-89.

F.W. Lipfert and R.E. Wyzga, Air Pollution and Mortality: Issues and Uncertainties, J.AWMA 45:949-66 (1995).

F.W. Lipfert and R.E. Wyzga (1997), Air Pollution and Mortality: The Implications of Uncertainties in Regression Modeling and Exposure Measurement, J.AWMA 47 517-523.

F.W. Lipfert and R.E. Wyzga (1998), Effects of Exposure Error on Environmental Epidemiology, proc. International Symposium on the Health Effects of Particulate Matter, Prague. AWMA Publ. VIP-80, pp. 155-166.

F. W. Lipfert and R.E. Wyzga, Statistical Considerations in Determining the Health Significance of Constituents of Airborne Particulate Matter, J.AWMA. 49:PM-182-191 (1999).

F.W. Lipfert, The Use and Misuse of Surrogate Variables in Environmental Epidemiology, J. Environmental Medicine 1:267-278 (1999).

A new time-series model

Time-series studies of daily mortality predict acute responses on the first few days of exposure, usually persisting less than a week. Responses are limited to the elderly and are stronger among the most susceptible subjects. Similar risks have been associated with various air pollutants and are strongest for cardiac and respiratory deaths. Murray and Lipfert (2010) considered a new model that predicts the magnitude of an elderly subpopulation most at risk of imminent death on a daily basis, rather than the general population. In this model two conditions are required for an acute air pollution-related death: increased frailty (inability to maintain homeostasis) and increased pollution exposure. Extreme values of either parameter can result in death, thus precluding air pollution thresholds. Acute frailty is represented by membership in a small fluctuating sub-population (P_t) at high risk that is depleted by daily deaths (D_t) and replenished by new entries (N_t). D_t and N_t may be affected by current or previous environmental conditions. The ratio of P_t to D_t is a measure of survival time (i.e., daily life expectancy [DLE]) in the frail state. The Kalman filter is used to solve these equations. P_t fluctuates with season and averages ~0.08% of the elderly. Life expectancies of subjects in the at-risk pool are about 5-7 days and robust to alternative models and environmental fluctuations. Daily mortality risk estimates are similar to those from conventional time-series analyses, but information on the accompanying life expectancies provided by this model is new.

Murray CJ, Lipfert FW. Revisiting a Population-Dynamic Model of Air Pollution and Daily Mortality of the Elderly Population in Philadelphia. J Air Waste Manag Assoc. 2010 60:611-629.

Murray CJ, Lipfert FW. A new time-series methodology for estimating relationships between elderly frailty, remaining life expectancy, and ambient air quality. Inhalation Toxicology 2012 24:89-98.

Lipfert FW, Murray CJ. Air pollution and daily mortality: A new approach to an old problem. Atmos Environ 55; 467-74 (2012).

Murray CJ, Lipfert FW. Inferring frail life expectancies in Chicago from daily fluctuations in elderly mortality. Inhal Toxicol. 2013 Jul;25(8):461-79.

Other time-series papers.

These papers provided short-term risk estimates for numerous pollutants that have not been considered by others: a wide range of particulate measures in which TSP was the most important in Philaelphia, and a complete set of PM chemical components was consideeed kn Atlanta of which carbon compounds were the most important.

Lipfert, F.W., Morris, S.C., and Wyzga, R.E. (2000), Daily Mortality in the Philadelphia Metropolitan Area and Size-Classified Particulate Matter, J.AWMA 50:1501-13.

Klemm, R.J., Lipfert, F.W., Wyzga, R.E., Gust, C. Daily mortality and air pollution in Atlanta: Two years of data from ARIES. Inhal Toxicology 16 (Suppl 1):131-41 (2004).

The Veterans Cohort Study

The Veterans Cohort Mortality Study began as a cooperative venture with Washington University at St. Louis (WUSTL), who developed the cohort and originated the study. It is based on a cohort of about 70,000 male veterans who were recruited in 1976 and followed for 26 y This is an important period of study because of the substantial improvements in ambient air quality that were achieved following passage of the 1970 Clean Air Act. The cohort was 37.7% black and 81% had smoked at one time; they were recruited at VA 32 clinics nationwide. it is the first cohort study to examine long-term all-cause mortality risks associated with air pollution for a variety of pollutants by race. The study considered the overall follow-up period (1976-2001) and four sequential mortality periods (1976-81, 1982-88,1989-96, and 1997-2001). The WUSTL proportional hazards model included non-linear terms for age, smoking, body-mass index (BMI), blood pressure, and interaction terms. The first paper showed that the relative importance of $PM_{2.5}$ and SO_4 was contingent on the inclusion of contextual predictor variables in the model including climate, poverty and neighborhood characteristics in the proportional hazards model. Those variables were retained in subsequent analyses. Later papers examined $PM_{2.5}$ constituents, hazardous pollutants, and county-level traffic density, which was the most important predictor along with NO_x and elemental carbon. The 2018 paper examined the effects of cohort aging with respect to temporal trends and found the former to be more important with stronger risks in middle age. $PM_{2.5}$ had consistently negative (beneficial) effects; no effects of accumulated exposures were evident. The most recent (2019) paper found that black veterans were more heavily exposed to traffic, with significantly negative effects of $PM_{2.5}$ and significantly positive risks for whites similar to those found in other

cohorts. This explains the apparently anomalous (ngative) $PM_{2.5}$ effects for the entire cohort. It also supports the hypothesis that cross-sectional studies essentially consider differences among *places* per se (counties, zip-codes, etc.) rather than the personal exposures of residents. Traffic effects were found to be stable over the 26-y period; however, those actual risk agents remain unknown, comprising engine exhaust, noise, tire/road dust, undesirable residential locations, but not indoor air pollution.

Lipfert, F.W., Perry, H.M. Jr., Miller, J.P., Baty, J.D., Wyzga, R.E., Carmody, S.E. (2000) The Washington University-EPRI Veterans' Cohort Mortality Study: Preliminary Results, Inhalation Toxicology 12 (Suppl 4):41-73.

Lipfert, F.W., Perry, H.M. Jr., Miller, J.P., et al., 2003. Air Pollution, Blood Pressure, and Their Long-Term Associations with Mortality. Inhalation Toxicology 15, 493-512.

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Lipfert, F.W., Wyzga, R.E., Baty, J.D., Miller, J.P., 2006b. $PM_{2.5}$ Constituents and Related Air Quality Variables as Predictors of Survival in a Cohort of U.S. Military Veterans, Inhalation Toxicology 18:645-57.

F.W. Lipfert, R.E. Wyzga, Jack D. Baty, J. Philip Miller. Vehicular Traffic Effects on Survival within the Washington University - EPRI Veterans Cohort: New Estimates and Sensitivity Studies, Inhalation Toxicology 20:949-960 (2008a).

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Trend analyses

Lipfert FW (1998), Trends in Airborne Particulate Matter in the United States. Applied Occupational and Environmental Hygiene 13:370-384

Lipfert FW, Morris SC, Temporal and spatial relationships between age-specific mortality and ambient air quality in the United States: Regression results for counties, 1960-97, Occup Env Med 59:156-74 (2002).

This paper used population data to show how mortality risks associated with air pollution decline with age and are stronger when mortality and exposure are measured coincidentally during a given follow-up period.

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> Detailed analyses of indoor air quality data showing indoor infiltration rates and short- but not long-term relationships between indoor and outdoor concentration.

Lipfert FW. Long-Term Associations of morbidity with air pollution: A catalogue and synthesis. JAWMA 2018 68:12-26.

> The catalog comprises 417 long-term studies of cardiovascular, respiratory, cancer, diabetes, hospitalization, neurological, and pregnancy-birth endpoints with respect to $PM_{2.5}$, PM_{10}, TSP, carbon, ozone, sulfur, vehicular traffic, radon, and indoor air quality. Durations of exposure range from 60 d to 35 y. Most studies were cross-sectional over limited time spans with no consideration of lag or disease latency. 220 studies indicated significant adverse effects. Associations with cardiovascular indicators, lung function, respiratory symptoms, and low birth-weight were more likely to be significant than with disease incidence, heart attacks, diabetes, or neurological endpoints. Elemental carbon (EC), and NO_x were most likely to be significant for cardiovascular outcomes. For all diagnoses, the highest fractions of significant findings were for "other" pollutants including TSP, EC, and metals. $PM_{2.5}$ and PM_{10} had lower risk ratios. Overall, these studies support non-lethal physiological effects of various pollutants, more so for non-life-threatening endpoints and for non-criteria pollutants (TSP, EC, $PM_{2.5}$ metals).

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