Review and Critique of the U. S. Environmental Protection Agency's First External Review Draft of the "Integrated Science Assessment for Particulate Matter"

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Prepared for
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December 7, 2018

EXECUTIVE SUMMARY

This draft of the "Integrated Science Assessment for Particulate Matter" (ISA for PM) marks the beginning of the process to review the adequacy of the existing National Ambient Air Quality Standards (NAAQS) for PM. The draft discusses three size ranges of particles: "coarse" particles that have aerodynamic diameters between 10 and 2.5 micrometers (denoted $PM_{10-2.5}$); "fine" particles that have aerodynamic diameters below 2.5 micrometers (denoted $PM_{2.5}$); and "ultrafine" particles that have aerodynamic diameters between 0.01 and 0.1 micrometers.

In considering the establishment of NAAQS, EPA relies on three types of health effect studies: controlled human exposures (clinical), animal toxicology ("toxicology") and epidemiology studies. As in the last three PM reviews, EPA relies heavily on the epidemiological studies to support their paradigm that PM2.5 is causing a myriad of serious health effects including premature mortality at concentrations near and below the current PM2.5 NAAQS.

In order to provide the best available information to the Administrator of EPA, the ISA should present and discuss the evidence both for and against PM causing health effects at or near current atmospheric levels and the current standards. AIR, Inc. reviewed the Draft ISA with this objective in mind. In the following comments, we identify areas where the draft is incomplete or otherwise deficient. We restricted our review to the science that relates to and should inform the primary (health-based) standards for $PM_{2.5}$.

Before discussing the deficiencies in the Draft ISA, it is important to establish two points. The first is that there are unusually large uncertainties in establishing PM air quality standards. The second is that EPA downplays uncertainty when proposing regulations.

When the first $PM_{2.5}$ standards were set in 1996/7, the EPA acknowledged that there were unusually large uncertainties associated with establishing standards for PM compared to individual gaseous pollutants. Since 1997, there has been greatly expanded research on PM health effects guided by input from a blue-ribbon National Research Council Panel. Although that research has resulted in a large number of new studies over the last two decades, there is still a great deal of uncertainty and controversy as to how to interpret all of the various results. The

uncertainties primarily arise because the Agency is trying to regulate the complex mixture of many different chemical and physical aerosol components based only on their mass as particles using primarily observational data that is not conducive to evaluating causality. One of the major uncertainties EPA acknowledged during earlier reviews of the PM NAAQS was the lack of demonstrated mechanisms that would explain the mortality and morbidity effects implied by the epidemiological associations. A review of the toxicology material EPA used for the 2018 ISA reveals that, despite nearly two decades of expanded and focused research, there are still no data from controlled studies that indicate how on a toxicological basis anthropogenic PM at current ambient levels is causing the mortality effects implied by the epidemiological associations that EPA relies on.

The ISA continues to rely on assumptions that lead to the estimated benefits. Three are particularly relevant to the CASAC deliberations. The first is that "Inhalation of fine particles is causally associated with premature death at concentrations near those experienced by most Americans on a daily basis." The second is that "The concentration-response function for fine particles and premature mortality is approximately linear, even for concentrations below the public-health protective exposure levels established by the National Ambient Air Quality Standard (NAAQS)." The third assumption is that "All fine particles, regardless of their chemical composition, are equally potent in causing premature mortality." Our comments raise serious concerns about the validity of these assumptions.

The remainder of our comments focus on some major deficiencies in the ISA. The ISA fails to present evidence that the low doses of PM2.5 deposited in the human airways is capable of causing the health effects implied by the epidemiological associations. In addition, toxicological studies have not identified any component in the PM2.5 mixture that could be causing mortality at the concentrations typically observed in ambient US air.

Regarding the epidemiological studies, while EPA acknowledges that confounding can be a complicating issue, they fail to realize that it is of sufficient magnitude to account for some of the reported statistical relationships. Recent studies of model selection issues confirm that the results are model dependent and are not identifying causal relationships between PM2.5 and health effects.

INTRODUCTION

The U. S Environmental Protection Agency (EPA) initiated the next review of the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) with the issuance of the first external review draft of the Integrated Science Assessment for Particulate Matter[1] (ISA) in October 2018. PM air pollution is a complex mixture of solid and liquid particles that vary in number, size, shape, surface area, chemical composition, solubility, and origin. Historically, ambient PM air pollution has been regulated in the U.S. by setting national air quality standards for the total mass of particles (irrespective of their chemical composition). Over the years, the focus has changed from consideration of all particles that are suspended in the ambient air to

[1] U. S. Environmental Protection Agency, First External Review Draft of the Integrated Science Assessment for Particulate Matter, EPA/600/R-18/179, October 2018.

particles within specific size ranges. The draft discusses three size ranges of particles: “coarse” particles that have aerodynamic diameters between 10 and 2.5 micrometers (denoted $PM_{10-2.5}$); “fine” particles that have aerodynamic diameters below 2.5 micrometers (denoted $PM_{2.5}$); and “ultrafine” particles that have aerodynamic diameters between 0.01 and 0.1 micrometers.

Under the Clean Air Act, EPA is charged with identifying air pollutants that may reasonably be anticipated to endanger public health and welfare and to issue air quality criteria for those pollutants that accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of the pollutant in ambient air. For many years these criteria were called “Criteria Documents.” To date, except for PM, which is a mixture of many different chemical species, the air pollutants that EPA has regulated as “criteria pollutants” have been either specific gaseous compounds or an element of concern, such as lead.

In considering the establishment of NAAQS, EPA relies on three types of health effect studies: controlled human exposures (clinical), animal toxicology ("toxicology") and epidemiology studies. In all NAAQS reviews prior to the 1996 PM review, EPA relied most heavily on controlled human exposures, which establish health effect endpoints as a function of exposure and demonstrate causality, and the toxicology studies which provide insights as to the mode of the damage caused by an exposure. Epidemiology studies were used if they supported the findings in the other two types of studies because epidemiology studies can only identify statistical associations between air pollutant concentrations and health endpoint incidence and cannot be used to demonstrate causality (cause-effect relationships). In the past, the discovery of a moderate association between a chemical substance and a health endpoint simply meant that additional investigations were warranted, such as clinical and toxicological studies.

For the PM NAAQS review that ended in 1996, EPA subordinated its reliance on human exposure and toxicological studies because they showed no evidence of effects at concentrations near the level of the existing NAAQS. Instead, they relied primarily on epidemiology studies, which were finding very weak statistical associations between measures of PM, including PM10 and PM2.5, and mortality (death) at ambient concentrations well below the then existing PM10 NAAQS. EPA recognized that there were large uncertainties associated with the epidemiology studies because they cannot demonstrate cause and effect. Despite this realization, EPA promulgated new annual and 24-hour PM2.5 NAAQS based on the epidemiology findings.

Since 1996, two more PM NAAQS reviews have been completed and nearly two decades of additional research has been performed. Despite the fact that the additional research has failed to significantly reduce the uncertainties in the science, EPA promulgated more stringent 24-hr and annual NAAQS in 2006 and 2012, respectively, based on the epidemiology.

The criteria called for in the Act are now designated as an Integrated Science Assessment (ISA). The ISA should be a concise review, synthesis, and evaluation of the most policy-relevant science that communicates critical science judgments relevant to the NAAQS review. Thus, the ISA provides the scientific foundation for the review of the primary (health-based) and secondary (welfare-based) NAAQS for the air pollutant of concern.

In order to provide the best available information to the Administrator of EPA, the ISA should present and discuss the evidence both for and against PM causing health effects at or near current atmospheric levels and the current standards. AIR, Inc. reviewed the Draft ISA with this objective in mind. In the following comments, we identify areas where the draft is incomplete or otherwise deficient. We restricted our review to the science that relates to and should inform the primary (health-based) standards for $PM_{2.5}$. AIR prepared comments on the EPA's Draft Integrated Review Plan for Particulate Matter[2] in 2016. Many of those comments are still relevant to the current discussion.

Before discussing the deficiencies in the Draft ISA, it is important to establish two points. The first is that there are unusually large uncertainties in establishing PM air quality standards. The second is that EPA downplays uncertainty when proposing regulations. Each point is discussed in the following.

There are unusually large uncertainties involved with setting particulate matter (PM) standards that still persist

When the first $PM_{2.5}$ standards were set in 1996/7, the EPA acknowledged that there were unusually large uncertainties associated with establishing standards for PM compared to individual gaseous pollutants. The Agency went on to list nine major areas of uncertainty.[3] In 2005, EPA reiterated the fact that setting air quality standards for particulate matter involves unusually large uncertainties relative to setting standards for other single component pollutants.[4] The acknowledged uncertainties led the EPA and the scientific community to ask for and receive greatly expanded federal funding for PM air pollution research. Since 1997, there has been greatly expanded research on PM health effects guided by input from a blue-ribbon National Research Council Panel. Although that research has resulted in a large number of new studies over the last two decades, there is still a great deal of uncertainty and controversy as to how to interpret all of the various results. Samet,[5] in a 2005 paper, summarized his perspective on the activities of the National Research Committee on Research Priorities for Airborne Particulate Matter, notes that using large databases, relatively weak signals of the health effects of air pollution have been detected. He went on to indicate that although these small increases in relative risk signal an adverse health effect, there is uncertainty as to the long-term implications of the findings and the overall health impact. He particularly noted the slow progress in identifying the hazardous components of particulate matter. He also noted that with increasingly sophisticated and sensitive indicators of biological response, including various biomarkers, effects of air pollution exposure on biological systems that are of uncertain health relevance can

[2] AIR, Inc. Comments on EPA's Draft Integrated Review Plan for Particulate Matter, prepared for the Alliance of Automobile Manufacturers, August 2, 2016.
[3] U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information- OAQPS Staff Paper, EPA-452\R-96-013, July 1996 at pages VII-42 to VII-45.
[4] U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information- OAQPS Staff Paper, EPA-452\R-05-005, June 2005 at page 5-71.
[5] J. Samet, "The Perspective of the National Research Council's Committee on Research Priorities for Airborne Particulate Matter," *J. of Toxicology and Environmental Health*, Part A, 68, 1063-1067 (2005).

be detected.

The uncertainties primarily arise because the Agency is trying to regulate the complex mixture of many different chemical and physical aerosol components based only on their mass as particles using primarily observational data that is not conducive to evaluating causality. As Green et al. pointed out in 2002,[6] it makes no more sense to estimate the health effects of all particles in the air by their mass as it would to consider the health effects of all the gases in the air base on their contributions to mass. This ignores the science of toxicology.

Toxicology is known as the science of poisons, where a poison may be any substance which when acting directly through its inherent chemical properties is capable of destroying or seriously endangering life. Any substance, even food and water, may be harmful if absorbed or ingested in excessive amounts. The dose determines whether or not injury will occur, requiring the toxicologist to pay careful attention to the quantitative measurement of both dosage and effect, before the delivered dose is declared as "harmful." One of the major uncertainties EPA acknowledged during earlier reviews of the PM NAAQS was the lack of demonstrated mechanisms that would explain the mortality and morbidity effects implied by the epidemiological associations. A review of the toxicology material EPA used for the 2018 ISA reveals that, despite nearly two decades of expanded and focused research, there are still no data from controlled studies that indicate how anthropogenic PM at current ambient levels is causing the mortality effects implied by the epidemiological associations that EPA relies on.

To evaluate the risks posed by Superfund sites, which can contain numerous hazardous chemicals, or to assess the hazard due to an exposure to a mixture of hazardous air pollutants, EPA conducts a standard U.S. EPA health-risk assessment based on the relative toxicity of the mixture. Although EPA has not done this for $PM_{2.5}$, it would provide another reality check for the epidemiology results. However, such an assessment has been done by Valberg (2004).[7] In that assessment, the author used the chemical-specific, dose-response data typically used in U.S. EPA human health-risk assessments to evaluate the risk associated with a mixture of 27 separate chemical constituents typical of ambient $PM_{2.5}$ with a total $PM_{2.5}$ concentration equal to that of the then annual $PM_{2.5}$ NAAQS of 15 $\mu g/m^3$. The assessment relied on established, no-effect thresholds for noncancer health endpoints. The author found that the chemicals identified as constituents of ambient PM are present at concentrations considerably below the regulatory thresholds (for which no adverse health effects are anticipated for a lifetime of exposure) used in risk assessment. From the perspective of risk assessment, the author concluded that, using EPA's own risk assessment methodology, exposure to the concentrations of chemicals that constitute ambient $PM_{2.5}$ (e.g., sulfate, nitrate, and 25 other constituents) cannot be expected to cause death. Hence, the author noted that the health effects attributed to ambient PM in the NAAQS review appear to be at odds with what would be predicted from a standard U.S. EPA health-risk assessment for PM chemicals. The author discusses several possible explanations for this paradox, including the implausible possibility that the toxicity of ambient PM is unrelated to its chemical constituents, or that PM mass concentration is not the causal factor in the reported

[6] Green, LC et al. What's Wrong with the National Ambient Air Quality Standard (NAAQS) for Fine Particulate Matter ($PM_{2.5}$)? *Regulatory Toxicology and Pharmacology*, **35**, 327-337, 2002.
[7] Valberg, P.A. 2004. Is PM more toxic than the sum of its parts? Risk-Assessment toxicity factors vs. PM-mortality "effect functions", *Inhalation Toxicology*, 16(suppl.1):19–29.

associations. The current EPA ISA is silent on the existence of this paradox, much less on the possible explanation.

The assumption of equal toxicity by mass was also part of the focus of HEI's NPACT study,[8] which was initiated in 2005 and completed in 2013. Our reading of the NPACT reports is that they are not particularly helpful in resolving the controversy over the assumption of equal toxicity. There is not much consistency or coherence in the results. There are inconsistent and unexpected results in the studies as well as differences of opinion between the investigators and the HEI Review Committee as to the interpretation and significance of the results.

In addition, Harrison[9] in a 2013 paper entitled "Air pollution and human health: Where does the latest evidence lead us?" indicates:

> There has been intensive research aimed at elucidation of which of the characteristics of airborne particles (e. g. chemical composition, size association or source) is primarily responsible for the adverse health consequences of exposure, and the results of the recent NPACT study in the US and the RAPTES study in the Netherlands are reviewed and the conclusion drawn that no clear inference can currently be drawn as the ranking of toxicity of specific components, or even of size fractions.

Consequently, nearly two decades of intensive, focus research has failed to identify any constituent(s) of the $PM_{2.5}$ that could be responsible for a causal $PM_{2.5}$-mortality relationship.

PM mortality effects influence the Agency's actions

Despite the major uncertainties involved in establishing PM health effects, EPA's estimated benefits from various adopted and proposed regulations are dominated by PM benefits. The Office of Management and Budget's 2013 Report to Congress[10] notes:

> It should be clear that across the Federal government, the rules with the highest estimated benefits as well as the highest estimated costs, by far, come from the Environmental Protection Agency and in particular its Office of Air and Radiation. Specifically, EPA rules account for 58 to 80 percent of the monetized benefits and 44 to 54 percent of the monetized costs. Of these, rules that have as either a primary or significant aim to improve air quality account for 98 to 99 percent of the benefits of EPA rules.

The OMB report also indicates the large estimated benefits of EPA rules issued pursuant to the

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[8] Lippmann, M; Chen, LC; Gordon, T; Ito, K; Thurston, GD. (2013). National Particle Component Toxicity (NPACT) Initiative: Integrated epidemiologic and toxicologic studies of the health effects of particulate matter Components. HEI Report 177, Boston, MA; Vedal, S; Campen, MJ; McDonald, JD; Larson, TV; Sampson, PD; Sheppard, L; Simpson, CD; Szpiro, AA. (2013). National Particle Component Toxicity (NPACT) initiative report on cardiovascular effects. HEI Report 178, Boston, MA.

[9] Harrison, RM, Air pollution and human health: Where does the latest evidence lead us? *Air Quality and Climate Change*, **47**, 26-31, 2013.

[10] Office of Management and Budget, 2013 Report to Congress on the Benefits and Costs of Federal Regulations and Unfunded Mandates on State, Local, and Tribal Entities, May 2014, at pages 15-18.

Clean Air Act are mostly attributable to the reduction in public exposure to a single air pollutant: fine particulate matter.

The report continues on to discuss the key assumptions that lead to the estimated benefits. Three are particularly relevant to the CASAC deliberations. The first is that "Inhalation of fine particles is causally associated with premature death at concentrations near those experienced by most Americans on a daily basis." The second is that "The concentration-response function for fine particles and premature mortality is approximately linear, even for concentrations below the public-health protective exposure levels established by the National Ambient Air Quality Standard (NAAQS)." The third assumption is that "All fine particles, regardless of their chemical composition, are equally potent in causing premature mortality."

It's important to note that EPA changed the benefits methodology several years ago. OMB indicates:

> …it is worth noting that between FY 2001 and midway through FY 2009, all EPA's primary benefits estimates explicitly included an assumption of a threshold for premature mortality effects at lower levels—that is, health benefits were not assumed for exposure reductions below a hypothetical threshold of 10 $\mu g/m^3$ (although sensitivity analyses explored alternative models). Since mid-2009, EPA's primary benefits estimates reflect a no-threshold assumption.

Although the CASAC is not yet reviewing the Agency benefits methodology that accompanies various proposed rules, the PM-mortality link (with its accompanying assumptions) has become a "narrative" that the Agency uses to justify many of its air pollution-related actions. We urge the Agency and CASAC to focus the review on key areas that address the evidence in support of and the evidence against these three key assumptions. These assumptions also undergird the Human Health Risk and Exposure Assessment (REA) that is part of the NAAQS review so CASAC input will be critical to making judgments as to the weight that will be given to the REA.

DEFICIENCIES IN THE ISA

This review focuses on several major deficiencies in the ISA. These include shortcoming in the discussions on the interpretations of the dosimetry, toxicology and the epidemiological results.

Dosimetry

Information on the dosimetry of particles, that is the deposition, clearance, and retention of particles within the respiratory tract, is critical to understanding the health effects of inhaled particles because the cause of a biological response to PM is due to the dose deposited at the internal target site, rather than the external exposure. Information from dosimetry can answer key questions. The most important question is whether the doses of fine particles to target tissue in a 24-hour period or over a lifetime are high enough to cause the effects implied by the epidemiological associations.

The mass of particles deposited per unit of alveolar–interstitial (deep lung) tissue in humans inhaling particle concentrations as high as 50 μg/m^3 for 24-hours (the 24-hour PM2.5 NAAQS is 35 μg/m^3) is only in fractions of nanograms (10^{-9} gram) of particles per square centimeter.[11] For individual particle components that are of interest as potential causal agents, much lower deposition levels occur.[12] For example, sulfate deposits were only in the range of picograms (10^{-12} gram) per square cm of alveolar surface, and levels of elemental carbon, iron or trace elements were not higher than a fraction of a picogram per square cm of surface. For toxic metals, suggested as a probable cause of fine particle toxicity, the estimated 24-hour deposition levels were extremely low, not exceeding tens of femtograms (10^{-15} gram) per square cm of alveolar-interstitial surface. It is inconceivable that such small amounts of these materials could cause the effects implied by the statistical associations because these dosages are orders of magnitude lower than those that produced biological responses in toxicological studies. It is a challenge for toxicology to explain how such low doses of particles can be causing the health effects implied by the epidemiological associations.

Toxicology

As mentioned earlier, toxicology is known as the science of poisons, where a poison may be any substance which when acting directly through its inherent chemical properties is capable of destroying or seriously endangering life. In the present ISA, EPA fails to identify any constituent of PM2.5 that is capable of causing mortality at the concentrations observed in typical ambient U.S. air. In addition, the careful, systematic analysis conducted by Valberg (2004) further undermines the plausibility of a PM2.5-mortality causal relationship.

Epidemiology

The ISA fails to appreciate the influence that confounding and model selection can have on the results of air pollution epidemiology results.

Confounding

A confounder is an extraneous variable that correlates with both the dependent and independent variable. Such a relationship is termed a spurious relationship. In a risk assessment, it is important to control for confounding to isolate the risk of a particular hazard. All epidemiology studies must deal with the issue of confounding. The ambient air can contain trace amounts of hundreds of chemical species both in the gas and particulate phase. Most epidemiology studies only focus on PM2.5 mass, but PM2.5 contains measurable amounts of nearly every element that exists in the earth's crust. Individual elements can exist as different chemical compounds. Consequently, there are hundreds of potential confounders in the air and only a tiny fraction of them are even measured. Because of this, in a study of any one component of air pollution, other

[11] Snipes, M. B., A.C. James and A.M. Jarabek. 1997. The 1994 ICRP66 human respiratory tract dosimetry model as a tool for predicting lung burdens from exposures to environmental aerosols. *Appl. Occup. Environ. Hyg.*12: 547-554.

[12] Vostal, J. 2000. Statistical associations between ambient particulate matter and daily morbidity and mortality: Can we identify mechanisms responsible for these health effects? *Proceedings of the Air & Waste Management Association's 93rd Annual Conference & Exhibition*, Publ. VIP 97, Air & Waste Management Association, Pittsburgh, PA.

components that may be associated with health impacts should be controlled. Very few studies do this for even the ones that are measured. This means that the potential for confounding by other substances in the atmosphere can never be completely controlled and their effects ruled out.

In air pollution epidemiology, weather is also an obvious confounder. In addition, other temporal effects such as season, cyclic diseases, and day-of-the-week patterns must be controlled for. A prestigious Special Panel of the Health Effects Institute concluded however, that it is not known how to do this.[13] They stated: "Neither the appropriate degree of control for time in these time-series analyses, nor the appropriate specification of the effects of weather, has been determined." Many epidemiology studies of air pollution report associations between fine PM and various measures of human health, such as mortality and hospital admissions. However, when possible confounding by other factors is explicitly addressed, many of the studies find no association between PM and measures of human health.

Studies by Janes et al. (2007)[14] and Greven et al. (2011)[15] concluded that the reported associations between PM and mortality may actually be attributable to inadequately controlled confounding. They hypothesized that the association between national trends in fine PM and mortality is likely to be confounded by slowly time-varying factors, such as changes in industrial activities and the economy or improving health care. When these factors were removed, there was no evidence of an association between 12-month exposure to PM2.5 and mortality.

Model Selection

In epidemiology, statistical models are used to relate a health outcome to various factors that may contribute to the occurrence of that health outcome. Selecting an appropriate statistical model for epidemiological analyses of air pollution data is an extremely important process that can affect the outcome of the study in a very significant way. It can make the difference between finding a positive association, a negative association or no association. It involves making a number of choices which include:

- How is confounding by weather to be controlled? That is, what functional form should be assumed for the effects of weather variables, such as temperature and relative humidity?
- What weather variables should be used?
- What co-pollutants should be included and what averaging time should be used?
- What temporal effects need to be controlled and to what degree?
- What lag structure should be assumed? That is, how many days after exposure to a pollutant should one expect to see an effect on health?

There is little biological knowledge to inform these choices that must be made. Unfortunately,

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[13] Special Panel of the Health Review Committee. 2003. Commentary on Revised Analyses of selected studies. In: *Revised Analyses of Time-Series Studies of Air Pollution and Health*, HEI Special Report, pp. 255-291.
[14] Janes, H., F. Dominici and S.L. Zeger. 2007. Trends in air pollution and mortality – An approach to the assessment of unmeasured confounding. *Epidemiology*, 18:416-423.
[15] Greven S, Dominici F, Zeger S. 2011. "An Approach to the Estimation of Chronic Air Pollution Effects Using Spatio-Temporal Information," *Journal of the American Statistical Association* 106(494):396-406.

most investigators do not make these choices systematically and many choose the model that maximizes the effect estimates.[16] Because of the large number of possible models, the results that are reported could have occurred by chance.

Researchers that have examined this issue in depth conclude that when the uncertainties introduced by model selection are considered, the uncertainties "become so large as to question the plausibility of the previously measured links between air pollution and mortality."[17] Others have concluded that even if the true effect of pollution is zero, the estimated effect may be positive because it is impossible to control temporal trends or weather without accurate information from external sources that does not exist.

In a recent study on model selection, Cox (2016)[18] concluded that the resulting concentration-response (C-R) associations "typically reflect modeling choices and equally good choices can commonly lead to conflicting conclusions about the signs, significance, and magnitudes of C–R relations and regression coefficients." Another recent study by Young (2017)[19] concludes that the current EPA paradigm, "air quality is a killer, is not supported by statistical analysis that take multiple testing and multiple modeling into account and claims made in these papers may not replicate."

Cox and Popken (2015)[20] noted that models exist that show statistical associations between mortality and PM2.5 (and ozone) but a causal relation cannot be inferred. Subsequently in a review, Cox (2017)[21] came to the following conclusions:

- "The fundamental premise that C–R functions exist that can predict the public health effects caused by reductions in pollutant concentrations needs to be carefully reexamined and tested, as it does not appear to hold in general."
- "C–R functions that describe historical associations do not necessarily predict how changing C would change R. This is partly because associations may not represent manipulative causal relationships, as when positive associations between baby aspirin consumption and heart attack risk, or between nicotine-stained fingers and subsequent risk of lung cancer, do not allow a valid prediction that reducing one would reduce the other."
- "Almost all of the existing literature on PM2.5-mortality C–R functions deals with associations and not with causality."

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[16] Smith R., P. Guttorp, L. Sheppard, T Lumley and N.Ishikawa. 2001. *Comments on the Criteria Document for Particulate Matter Air Pollution*, NRSCE Technical Report Series #66, July 25, 2001. Available:http://www.nrcse.washington.edu/research/reports.html (as of 12-6-2018).

[17] Koop G. and L. Tole. 2004. Measuring the health effects of air pollution: to what extent can we really say that people are dying from bad air? *J. Environ Econ and Management*, 47:30-54.

[18] Cox LA Jr. Rethinking the meaning of concentration–response functions and the estimated burden of adverse health effects attributed to exposure concentrations. *Risk Analysis.* 2016 Sep;36(9):1770-1779

[19] Young, SS. Air quality environmental epidemiology studies are unreliable. *Regulatory Toxicology and Pharmacology*. 2017 86:177.

[20] Cox, LA Jr, Popken DA. Has reducing PM2.5 and ozone caused reduced mortality rates in the United States? *Annals of Epidemiology*. 2015 Mar;25(3):162-73.

[21] Cox LA Jr. Do causal concentration-response functions exist? A critical review of associational and causal relations between fine particulate matter and mortality. *Critical Reviews in Toxicology*. 2017 Aug; 47(7): 603-631.

- “The few papers that do attempt to model causality in C–R relations for PM2.5 exposure and mortality fail to distinguish among counterfactual, predictive, and manipulative causality. Most of these papers follow a counterfactual approach that relies heavily on unverified modeling assumptions about unobserved potential outcomes.”

Based on the above discussion, it is clear that the choice of the statistical model determines the outcome of the statistical relationship between PM and a particular health outcome. Clearly such relationships are not causal.