# Comments on US EPA's Proposed Rule for the Reconsideration of the National Ambient Air Quality Standards for Particulate Matter

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| | |
|---|---|
| AOD | Aerosol Optical Depth |
| ATS | American Thoracic Society |
| CASAC | Clean Air Scientific Advisory Committee |
| CI | Confidence Interval |
| C-R | Concentration-Response |
| ERS | European Respiratory Society |
| HR | Hazard Ratio |
| ISA | Integrated Science Assessment |
| NAAQS | National Ambient Air Quality Standards |
| PA | Policy Assessment |
| PM | Particulate Matter |
| $PM_{10}$ | Particulate Matter with Particles 10 µm in Diameter or Less |
| $PM_{2.5}$ | Particulate Matter with Particles 2.5 µm in Diameter or Less |
| SES | Socioeconomic Status |
| US | United States |
| US EPA | United States Environmental Protection Agency |

# Executive Summary

On January 27, 2023, the United States Environmental Protection Agency (US EPA) released the Proposed Rule on the "Reconsideration of the National Ambient Air Quality Standards for Particulate Matter" (hereafter referred to as the Proposed Rule) (US EPA, 2023). The US EPA Administrator proposes to lower the primary annual fine particulate matter (PM) (*i.e.*, particulate matter with particles 2.5 μm in diameter or less [$PM_{2.5}$]) standard from 12 $\mu g/m^3$ to 9-10 $\mu g/m^3$ (US EPA, 2023). The Administrator also proposes retaining the current primary and secondary 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$, the primary and secondary 24-hour coarse PM (*i.e.*, particulate matter with particles 10 μm in diameter or less [$PM_{10}$]) standard of 150 $\mu g/m^3$, and the secondary annual $PM_{2.5}$ standard of 15 $\mu g/m^3$ (US EPA, 2023).

The Administrator concluded that, supported by the results of recent accountability studies with starting $PM_{2.5}$ concentrations that are relevant to the current primary annual standard and studies that restricted their analyses to $PM_{2.5}$ concentrations below the current standard, the key US epidemiology studies provide evidence of adverse health effects occurring at concentrations below the current standard of 12 $\mu g/m^3$ (US EPA, 2023). However, US EPA did not review these key epidemiology studies in a systematic, unbiased, or transparent manner, and inappropriately discounted the substantial uncertainties in and limitations of these studies (*e.g.*, exposure measurement error, confounding, irrelevant exposure windows). Therefore, these studies do not provide adequate evidence of health effects occurring at concentrations lower than the current standard of 12 $\mu g/m^3$.

Even if such evidence were certain, US EPA also failed to acknowledge that the area annual design values are generally higher than the mean concentrations in these key studies, such that the lowest mean concentration reported in the monitor-based studies (*i.e.*, 9.9 $\mu g/m^3$) and hybrid model-based studies with population weighting (*i.e.*, 9.3 $\mu g/m^3$) are associated with a range of annual $PM_{2.5}$ design values of 10.9-11.9 $\mu g/m^3$ and 10.6-11.0 $\mu g/m^3$, respectively. These values exceed design values reflected in US EPA's proposed range (9-10 $\mu g/m^3$) for the annual standard. Similarly, as noted in the 2022 Policy Assessment (PA) for the reconsideration of the PM National Ambient Air Quality Standards (NAAQS) (hereafter referred to as the 2022 PA), the recommended increase in near-road monitoring will further increase the ratios of maximum annual design values to averaged concentrations. In turn, this will increase the potential that continued implementation of the current standard could effectively achieve average concentration levels in many areas that approach US EPA's proposed range for what is required to protect public health.

US EPA evaluated controlled human exposure studies and experimental animal studies of $PM_{2.5}$ in the 2019 Integrated Science Assessment (ISA) of PM (hereafter referred to as the 2019 ISA), the 2022 Supplement to the 2019 ISA (hereafter referred to as the 2022 ISA Supplement), the 2022 PA, and the Proposed Rule (US EPA, 2019, 2022a,b, 2023). The Agency acknowledged that these studies mostly evaluated $PM_{2.5}$ exposure levels much higher than ambient PM concentrations. In addition, some of the health outcomes observed in the controlled human exposure studies may not be adverse. These are also studies of small populations that may not be representative of the larger United States (US) population that the NAAQS are intended to protect. Regarding the experimental animal studies, there is inherent uncertainty in extrapolating results from animal models to humans. We agree with US EPA that the available controlled human exposure studies and experimental animal studies do not provide evidence regarding exposures to ambient levels of $PM_{2.5}$. We also conclude that these studies support the existence of thresholds for health outcomes associated with $PM_{2.5}$ exposure.

In the Proposed Rule, the Administrator concluded that the available literature did not call into question the adequacy of the current primary 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$ and proposed retaining that standard for now. In support of that decision, the Administrator noted that "the air quality concentrations in areas meeting the current standards are well below the $PM_{2.5}$ concentrations shown to elicit effects" (US EPA, 2023). Considering the uncertainties in and limitations of the scientific evidence and quantitative information on $PM_{2.5}$ exposure, we agree with the US EPA Administrator's current decision that the primary 24-hour $PM_{2.5}$ standard should be retained.

# 1 Introduction

In December 2020, based on the United States Environmental Protection Agency's (US EPA) review of the air quality criteria and the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM), US EPA Administrator Andrew Wheeler retained the primary and secondary NAAQS for fine and coarse PM (*i.e.*, particulate matter with particles 2.5 and 10 μm in diameter or less [$PM_{2.5}$ and $PM_{10}$], respectively) without revision (US EPA, 2020a).

In June 2021, US EPA announced that it would reconsider the 2020 decision to retain the PM NAAQS (US EPA, 2023). As part of the reconsideration process, in May 2022, US EPA released the Supplement to the 2019 Integrated Science Assessment (ISA) for PM (hereafter referred to as the 2022 ISA Supplement) and the Policy Assessment (PA) for the reconsideration of the PM NAAQS (hereafter referred to as the 2022 PA) (US EPA, 2019, 2022a,b).

On January 27, 2023, US EPA released the Proposed Rule on the "Reconsideration of the National Ambient Air Quality Standards for Particulate Matter" (hereafter referred to as the Proposed Rule) (US EPA, 2023). The Administrator proposes to lower the primary annual $PM_{2.5}$ standard from 12 $\mu g/m^3$ to 9-10 $\mu g/m^3$ and to retain the primary and secondary 24-hour $PM_{2.5}$ standard at 35 $\mu g/m^3$, the current primary and secondary 24-hour $PM_{10}$ standard at 150 $\mu g/m^3$, and the current secondary annual $PM_{2.5}$ standard at 15 $\mu g/m^3$ (US EPA, 2023).

To evaluate the adequacy of the current primary PM NAAQS, the Administrator considered the scientific evidence evaluated in the 2019 ISA and the 2022 ISA Supplement, as well as evaluations presented in the 2022 PA (US EPA, 2023). The Administrator considered the key epidemiology studies (including the key accountability studies), the available experimental animal and controlled human exposure studies, and air quality analyses, including the important strengths and limitations of these lines of evidence. In his evaluation, the Administrator placed the greatest weight on evidence regarding health effects that were determined to be causally or likely causally associated with short- and long-term $PM_{2.5}$ exposure in the 2019 ISA (US EPA, 2023).

Regarding the adequacy of the current primary annual $PM_{2.5}$ standard, the Administrator noted that "the evidence available in this reconsideration provides support for adverse health effect associations at lower ambient $PM_{2.5}$ concentrations than in previous reviews" (US EPA, 2023). He also stated that "a large number of key U.S. epidemiologic studies report positive and statistically significant associations for air quality distributions with overall mean $PM_{2.5}$ concentrations that are well below the current level of the annual standard of 12 $\mu g/m^3$… with concentrations ranging down as low as 9.9 $\mu g/m^3$ in U.S.-based monitor-based studies and 9.3 $\mu g/m^3$ in U.S.-based hybrid model-based studies" (US EPA, 2023). The Administrator acknowledged that the experimental studies (*i.e.*, controlled human exposure studies and experimental animal studies) mostly evaluate exposures well above ambient concentrations, and may measure outcomes that are not clinically significant. There are also issues with extrapolating results from animals or small human sample populations to the larger human population.

In the Proposed Rule, the Administrator concluded that the new literature did not call into question the adequacy of the current primary 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$ and proposed retaining that standard. In support of that decision, the Administrator noted that "the air quality concentrations in areas meeting the current standards are well below the $PM_{2.5}$ concentrations shown to elicit effects" (US EPA, 2023).

As discussed below, the available scientific evidence and risk-based information do not call into question the adequacy of the public health protection provided by the current primary annual and 24-hour $PM_{2.5}$ standards or indicate that lower standards will increase public health protection against adverse health effects associated with $PM_{2.5}$ exposure.

# 2 Primary Annual $PM_{2.5}$ Standard – Epidemiology Evidence

To evaluate the adequacy of the current primary annual $PM_{2.5}$ standard, the Administrator cited all available lines of scientific evidence, the previous US EPA risk assessments of $PM_{2.5}$ in the 2019 ISA and the 2022 ISA Supplement, and the analysis of the available evidence in the 2022 PA (US EPA, 2023). This approach is consistent with those of previous NAAQS reviews. However, the Administrator's decision regarding the adequacy of the current standard and his proposal to lower the standard are driven primarily by a review of the study-reported means and lower values (*i.e.*, the $25^{th}$ and $10^{th}$ percentiles of estimated exposures or health events) from the key epidemiology studies of $PM_{2.5}$. The key epidemiology studies included studies that used monitors to estimate $PM_{2.5}$ exposures, as well as studies that used hybrid modeling approaches and applied population weighting in calculating $PM_{2.5}$ exposure levels (US EPA, 2023).

In the Proposed Rule, the Administrator noted that "the evidence available in this reconsideration provides support for adverse health effect associations at lower ambient $PM_{2.5}$ concentrations than in previous reviews" (US EPA, 2023). He also stated that "a large number of key U.S. epidemiologic studies report positive and statistically significant associations for air quality distributions with overall mean $PM_{2.5}$ concentrations that are well below the current level of the annual standard of 12 $\mu g/m^3$… with concentrations ranging down as low as 9.9 $\mu g/m^3$ in U.S.-based monitor-based studies and 9.3 $\mu g/m^3$ in U.S.-based hybrid model-based studies" (US EPA, 2023). The Administrator noted that, supported by the results of recent accountability studies with starting $PM_{2.5}$ concentrations that are more relevant to the current primary annual standard and studies that restricted their analyses to $PM_{2.5}$ concentrations below the current standard, the key US epidemiology studies provide evidence of health effects occurring at $PM_{2.5}$ concentrations lower than the current standard of 12 $\mu g/m^3$ (US EPA, 2023).

However, as noted below, these studies have substantial uncertainties and limitations (*e.g.*, exposure measurement error, confounding, irrelevant exposure windows), and do not provide adequate evidence of health effects occurring at $PM_{2.5}$ concentrations lower than the current primary annual standard of 12 $\mu g/m^3$.

## 2.1 Key Monitor-Based Studies

In the Proposed Rule, US EPA focused on 21 key monitor-based studies that were conducted in the US that evaluated both short-term and long-term $PM_{2.5}$ exposures and their associations with morbidity and mortality (US EPA, 2023). These studies reported overall mean $PM_{2.5}$ exposure concentrations between 9.9 and 16.5 $\mu g/m^3$ (US EPA, 2023). As discussed below, US EPA also considered key studies that reported mean $PM_{2.5}$ concentrations corresponding to the $25^{th}$ and $10^{th}$ percentiles of exposures or health events.

### 2.1.1 Mean $PM_{2.5}$ Levels

The key US monitor-based epidemiology studies considered in the Proposed Rule reported mean $PM_{2.5}$ exposure concentrations between 9.9 and 16.5 $\mu g/m^3$ (US EPA, 2023).

As noted in the Proposed Rule, the area annual design values for $PM_{2.5}$ are generally higher than the mean concentrations reported in the monitor-based studies by 10-20% (US EPA, 2023). Therefore, the range of area annual design values associated with the lowest mean concentration (*i.e.*, 9.9 $\mu g/m^3$) reported in these studies would be 10.9-11.9 $\mu g/m^3$. These levels are higher than the Administrator's proposed primary annual $PM_{2.5}$ standard of 9-10 $\mu g/m^3$. CASAC member Dr. James Boylan also discussed this issue in his comments on the draft of the 2022 PA (Sheppard, 2022; US EPA, 2021a).

In addition, there are major limitations to relying on mean $PM_{2.5}$ concentrations to evaluate the adequacy of the current primary annual standard. US EPA justifies this approach in the 2022 PA by stating that there is the most confidence in the reported magnitude of $PM_{2.5}$ exposure-response associations around the center of the distribution, which corresponds to the bulk of the underlying data (as indicated by narrow confidence intervals [CIs]). However, statistically, influential points for an exposure-response association tend to be located at the data extremes (*i.e.*, outliers), where data are sparse and each data point is given a disproportionately large weight in a least square fitting (Bollen and Jackman, 1985). Considering that the incidence of health effects increases with increasing $PM_{2.5}$ exposure concentrations in cohort studies (as demonstrated by positive associations in linear models), the observed associations at the center of the data are more likely to be at least partially driven by the upper portion of the air quality distribution than observations found lower on the distribution. In other words, while cohort studies report health effects that occurred in *study populations*, for which the average $PM_{2.5}$ exposure concentrations are below the current primary annual standard, they do not necessarily reflect health effects that occur in *individuals* who live in areas with $PM_{2.5}$ concentrations below the current standard.

The key monitor-based studies also have major uncertainties and methodological limitations (*e.g.*, exposure measurement error, confounding, irrelevant exposure windows). In the Proposed Rule, US EPA noted:

> [T]he PA recognizes that uncertainties associated with the epidemiologic evidence (e.g., the potential for copollutant confounding and exposure measurement error) remain, although new studies evaluated in the ISA Supplement employ statistical methods such as alternative methods for confounder control, to more extensively account for confounders, which are more robust to model misspecification. (US EPA, 2023).

As discussed below in Section 2.5, these uncertainties and limitations call into question the basis for moving towards a more stringent primary annual $PM_{2.5}$ standard.

### 2.1.2 Mean $PM_{2.5}$ Concentrations Corresponding to the 25th and 10th Percentiles of Health Events

As part of the PM NAAQS reconsideration process US EPA also considered the mean $PM_{2.5}$ concentrations corresponding to the 25th and 10th percentiles of estimated exposures or health events, when these values were available in the key epidemiology studies, in the 2022 PA (US EPA, 2022b).

As shown in Figure 1 of the Proposed Rule (US EPA, 2023), none of the long-term monitor-based epidemiology studies reported mean $PM_{2.5}$ concentrations corresponding to the 25th and 10th percentiles of estimated exposures or health events. Three short-term $PM_{2.5}$ exposure studies reported both of these values: Franklin *et al*. (2007), Zanobetti and Schwartz (2009), and Bell *et al*. (2008). The lowest mean $PM_{2.5}$ concentrations (*i.e.*, averaged over the study period for each study city) corresponding to the 25th and 10th percentiles of health events reported in these studies are 11.5 and 9.8 $\mu g/m^3$, respectively, both of which are reported by Bell *et al*. (2008). While US EPA (2023) noted that these small number of studies can be "considered to provide insight into the concentrations that comprise the lower quartiles of the air quality distributions," any direct comparisons of the $PM_{2.5}$ concentrations corresponding to lower percentiles (*i.e.*,

25th and/or 10th) with the annual design values is more uncertain than comparisons with the mean concentrations. As noted in the Proposed Rule:

> As such, the PA concludes that focusing on concentrations somewhat below the means (*e.g.*, 25th and 10th percentiles), when such information is available from epidemiologic studies, is a reasonable approach for considering lower portions of the air quality distribution. However, the PA recognizes that the health data are appreciably more sparse and an understanding of the magnitude and significance of the associations correspondingly become more uncertain in the lower part of the air quality distribution. While health effects can occur over the entire distribution of ambient $PM_{2.5}$ concentrations evaluated, and epidemiologic studies do not identify a population-level threshold below which it can be concluded with confidence that PM-associated health effects do not occur (U.S. EPA, 2019a, section 1.5.3), using values below the 10th percentile would lead to even greater uncertainties and diminished confidence in the magnitude and significance of the associations. (US EPA, 2023)

We concur with these points made by the Administrator and conclude that the mean $PM_{2.5}$ concentrations corresponding to the 25th and 10th percentiles of health events from the monitor-based studies should not be considered in setting the $PM_{2.5}$ NAAQS.

## 2.2 Key Hybrid Model-Based Studies

The 2019 ISA and the 2022 ISA Supplement included a substantial number of hybrid model-based studies that had been conducted since the 2012 PM NAAQS review (US EPA, 2023). These studies "employ various fusion techniques that combine ground-based monitor data with air quality modeled estimates and/or information from satellites to estimate $PM_{2.5}$ exposures" (US EPA, 2023). In the current Proposed Rule, US EPA focused on 11 key epidemiology studies that used hybrid model-predicted $PM_{2.5}$ concentrations and that also applied aspects of population weighting. Similar to the monitor-based studies, US EPA also focused on these studies' reported mean $PM_{2.5}$ concentrations and concentrations lower than the mean (*i.e.*, concentrations corresponding to the 25th and 10th percentiles of estimated exposures or health events). As discussed below, while the hybrid model-based studies overcome certain limitations found in the monitor-based studies, these studies also have limitations that are similar to those of the monitor-based studies.

### 2.2.1 Mean $PM_{2.5}$ Levels

Overall, the key US epidemiology studies considered in the Proposed Rule that used hybrid model-predicted $PM_{2.5}$ concentrations and that applied aspects of population weighting reported mean $PM_{2.5}$ exposure concentrations between 9.3 and 12.2 $\mu g/m^3$ (US EPA, 2023).

As noted in the Proposed Rule, area annual design values for $PM_{2.5}$ are generally higher than the mean concentrations reported in the hybrid model-based studies with population weighting by 14-18% (US EPA, 2023). Therefore, the range of area annual design values associated with the lowest mean concentration reported in these studies (*i.e.*, 9.3 $\mu g/m^3$) would be 10.6-11.0 $\mu g/m^3$. These levels are higher than the Administrator's proposed primary annual $PM_{2.5}$ standard of 9-10 $\mu g/m^3$. In his comment on the draft of the 2022 PA (US EPA, 2021a), CASAC member Dr. Boylan also calculated the potential range of area annual $PM_{2.5}$ design values based on the mean $PM_{2.5}$ concentrations reported in the hybrid model-based studies with population weighting.

Dr. Boylan concluded:

> Based on this information, an annual standard in the range of 10.6-12.2 μg/$m^3$ is appropriate. In order to protect public health with an adequate margin of safety, an annual standard in the range of 10.0-11.0 μg/$m^3$ is recommended. In addition, many accountability studies that report public health improvements have starting concentrations within that range. (Sheppard, 2022)

The key hybrid model-based studies also have major methodological limitations (*e.g.*, exposure measurement error, confounding, irrelevant exposure windows). For instance, Di *et al*. (2017a) evaluated the relationship between long-term $PM_{2.5}$ exposure and total mortality in Medicare enrollees in the continental US from 2000 to 2012. While this study used a model that was validated and more flexible regarding complex nonlinear relationships than the models used in many other studies, it is limited by the quality of the input variables, such as the aerosol optical depth (AOD) data, as satellite-based AOD measurements can be biased by unresolved clouds, water vapor, and smoke. In addition, because the study used Medicare records as the source of data regarding cohort members, residential mobility was not accounted for and deaths from unnatural causes were not excluded, resulting in errors in the study's exposure and outcome assessments. Annual average $PM_{2.5}$ concentrations in the year prior to cohort members' deaths or censoring were evaluated in the study's concentration-response (C-R) analysis, but this was likely was not the relevant exposure window, due to the lack of latency time. Regarding adjustment for confounders, while Di *et al*. (2017a) included several individual-level covariates, important confounders such as smoking and body mass index were not available for the Medicare enrollee cohort. Other key hybrid model-based studies have similar limitations.

## Restricted Analyses

The Proposed Rule stated that, consistent with advice from CASAC, US EPA examined epidemiology studies that included "analyses that restrict annual average $PM_{2.5}$ concentrations" to concentrations that are lower than the current annual $PM_{2.5}$ standard, in order to assess the adequacy of the current standard (US EPA, 2023). The current Proposed Rule considered two key studies (Di *et al*., 2017b; Dominici *et al*., 2019) that both used hybrid model-based exposure assessments with population weighting. Regarding these two studies, the Proposed Rule noted:

> These restricted analyses report positive and statistically significant associations with all-cause mortality and report mean $PM_{2.5}$ concentrations of 9.6 μg/$m^3$. Thus, these two epidemiologic studies provide support for positive and statistically significant associations at lower mean $PM_{2.5}$ concentrations. The Administrator does note that uncertainties exist in these analyses (described in more detail in sections II.B.3.b and II.D.2.a above), including uncertainty in how studies exclude concentrations (e.g., at what spatial resolution are concentrations being excluded), which would make any comparisons of concentrations in restricted analyses difficult to compare directly to design values. (US EPA, 2023)

Furthermore, as stated by Papadogeorgou *et al*. (2019):

> [R]estricting the analysis to a subset of the data has some interpretational limitations. Considering a subgroup of the data effectively changes the population of interest. Specifically, it is likely that the subpopulation exposed to low levels of $PM_{2.5}$ does not have the same characteristics as the full study population. If the distribution of certain modifiers of the association between $PM_{2.5}$ and the outcome of interest is different among participants living in lower exposure levels (e.g., rural vs. urban residence, age, socioeconomic status,

etc.) compared to the characteristics in the full population, then the effect estimates from the restricted analysis are not necessarily directly comparable to those of the full analysis.

In other words, just because statistically significantly positive associations remained in analyses restricted to subpopulations exposed to lower $PM_{2.5}$ concentrations, this does not necessarily mean that the upper portion of the air quality distribution was not the driver for the observed associations in the full analyses. In addition, the distributions of potential confounders and effect modifiers in the subpopulation and the full study population could differ, undermining the direct comparability of the results from restricted analyses and those of the full analyses.

### 2.2.2 Mean $PM_{2.5}$ Concentrations Corresponding to the 25th and 10th Percentiles of Estimated Exposures or Health Events

Similar to the monitor-based studies, only three hybrid model-based studies reported the mean $PM_{2.5}$ concentrations corresponding to the 25th and/or 10th percentiles of estimated exposures or health events. However, while all three of the monitor-based studies reporting these values were studies of short-term $PM_{2.5}$ exposure, two of the three hybrid model-based studies reporting at least one of these values studied long-term $PM_{2.5}$ exposure, as shown in Figure 2 of the Proposed Rule (US EPA, 2023). Wang *et al*. (2017) reported a mean $PM_{2.5}$ concentration corresponding to the 25th percentile of estimated exposure of 9.1 $\mu g/m^3$, and Di *et al*. (2017a) reported mean $PM_{2.5}$ concentrations corresponding to the 25th and 10th percentiles of exposure estimates of 9.1 and 7.3 $\mu g/m^3$, respectively. Di *et al*. (2017b), who conducted a study of short-term $PM_{2.5}$ exposure, reported mean $PM_{2.5}$ concentrations corresponding to the 25th and 10th percentiles of health events of 6.7 and 4.7 $\mu g/m^3$, respectively.

As discussed in Section 2.1.2, US EPA noted that considering the small number of available studies reporting these values and the uncertainties related to the $PM_{2.5}$ concentrations lower than the overall mean concentrations, these studies do not provide adequate evidence regarding associations between $PM_{2.5}$ exposure and morbidity/mortality at lower concentrations. In addition, as discussed above, the hybrid model-based studies have several limitations, such as exposure misclassification, the use of an irrelevant exposure window, a lack of consideration of residential mobility, and issues with residual confounding. As such, the mean $PM_{2.5}$ concentrations corresponding to the 25th and 10th percentiles of estimated exposures or health events should not be considered in setting the primary annual $PM_{2.5}$ standard.

## 2.3 Accountability Studies

As part of US EPA's evaluation of the adequacy of the current primary annual $PM_{2.5}$ standard, the Administrator also considered evidence from $PM_{2.5}$ accountability studies, which examine "past reductions in ambient $PM_{2.5}$ and the degree to which those reductions resulted in public health improvements" (US EPA, 2022b). The Administrator specifically noted what he considered to be three key accountability studies that present analyses with starting $PM_{2.5}$ concentrations (*i.e.*, concentrations prior to the policy change or intervention) below the current primary annual standard of 12.0 $\mu g/m^3$: Corrigan *et al*. (2018), Henneman *et al*. (2019), and Sanders *et al*. (2020). The Administrator concluded that these three studies "indicate positive and significant associations with mortality and morbidity and reductions in ambient $PM_{2.5}$" and "suggest public health improvements may occur at concentrations below 12 $\mu g/m^3$" (US EPA, 2023).

We agree with the Administrator that these three accountability studies have made methodological improvements in terms of focusing on $PM_{2.5}$ and starting from a mean $PM_{2.5}$ concentration of 12 $\mu g/m^3$ (*i.e.*, the current primary annual standard) or lower, and can further inform the relationship between $PM_{2.5}$

exposure and health effects. However, accountability studies can have crucial methodological limitations that undermine their findings. Some of these methodological limitations are the same as those commonly found in more traditional epidemiology studies, and others are unique to this specific study design and the statistical approaches these studies use. In addition, some of the significant methodological limitations that remain in these studies were also noted in the previous PA for the PM NAAQS from 2020 (hereafter referred to as the 2020 PA), including the fact that they were not able to "attribute changes in ambient $PM_{2.5}$ concentrations to the interventions under evaluation" and/or "disentangle health impacts of the intervention from background trends in health" (US EPA, 2020b). As a result, the association between a reduction in $PM_{2.5}$ concentrations below the current standard and improvement in health outcomes observed in these studies is not fully supported. Unless all of the aforementioned methodological limitations can be sufficiently addressed, we conclude that accountability studies do not provide adequate evidence to support a lower primary annual $PM_{2.5}$ standard.

## 2.4 US Studies *vs*. Canadian Studies

While the 2019 ISA considered and included epidemiology studies of $PM_{2.5}$ conducted globally (US EPA, 2019), the 2020 PA focused on epidemiology studies of $PM_{2.5}$ conducted in the US and Canada (US EPA, 2020b), because these studies were considered "most relevant to informing the level, form, averaging time, and indicator of the NAAQS for PM" (US EPA, 2022a). Following this approach, the 2022 ISA Supplement was also limited to studies of $PM_{2.5}$ conducted in the US and Canada (US EPA, 2022a).

In the 2022 PA and the Proposed Rule, US EPA noted the differences in exposure environments and population characteristics in the US and Canada (US EPA, 2022b, 2023). As stated in the Proposed Rule:

> [W]hile information from Canadian studies can be useful in assessing the adequacy of the annual standard, differences in the exposure environments and population characteristics between the U.S. and other countries can affect the study-reported mean value and its relationship with the annual standard level. Sources and pollutant mixtures, as well as $PM_{2.5}$ concentration gradients, may be different between countries, and the exposure environments in other countries may differ from those observed in the U.S. Furthermore, differences in population characteristics and population densities can also make it challenging to directly compare studies from countries outside of the U.S. to a design value in the U.S. (US EPA, 2023)

Therefore, US EPA concluded that "interpreting the data (*e.g.*, mean concentrations) from the Canadian studies in the context of a U.S.-based standard may present challenges in directly and quantitatively informing questions regarding the adequacy of the current or potential alternative [to] the levels of the annual standard" (US EPA, 2023). The Agency further noted that while both US and Canadian studies were considered in reaching conclusions, it considered that "the U.S.-based epidemiologic studies are most informative for comparisons with the annual standard metric and for reaching conclusions on the current standard and for informing potential alternative levels of the standard" (US EPA, 2023).

In the comments on the 2022 ISA Supplement, CASAC consultant Dr. Clougherty also recommended removing the Canadian studies from the evaluation of exposure disparities and dose-response relationships between $PM_{2.5}$ and health effects, for the following reasons: "different social & economic context, context of health disparities very different, different patterns of historical discrimination by race and ethnic group, universal access to healthcare and education alter interpretability of SES [socioeconomic status] indicators for US regulatory context" (Sheppard, 2022).

Considering the differences in exposure environments, demographics, and access to healthcare and education between the US and Canada, we concur with Dr. Clougherty that the Canadian studies should be excluded from consideration in the Agency's evaluation of the adequacy of the current primary annual $PM_{2.5}$ NAAQS.

## 2.5 Uncertainties and Limitations

A relatively recent industry-sponsored workshop focused on bridging the gap between epidemiologists and risk assessors in an effort to improve the value of epidemiology research for use in decision-making. It included a diverse group of US EPA researchers, industry scientists, national and international academics, and government scientists. Following this workshop, Burns *et al.* (2019) and LaKind *et al*. (2020) developed a matrix for communicating risk assessment "asks" of epidemiology research that describes the characteristics of epidemiology studies that should be considered when using them for hazard identification, dose-response assessment, and exposure assessment in a risk assessment setting (Table 2.1). By extension, these "asks" are equally important to US EPA's reliance on epidemiology studies when determining whether the existing standards are adequate to protect public health. The key characteristics of epidemiology studies include confirming exposure levels and outcomes and determining the direction and magnitude of error surrounding exposure and dose-response assessments, among others. The epidemiology studies reviewed in the Proposed Rule do not fully meet the risk assessment "asks" outlined by Burns *et al.* (2019) and LaKind *et al*. (2020) or appreciably reduce uncertainty regarding the associations between $PM_{2.5}$ exposure and morbidity or mortality, particularly at exposure concentrations below the current primary annual $PM_{2.5}$ standard. Compared to the studies reviewed in the 2009 ISA (US EPA, 2009), the more recent cohort studies evaluated in the 2019 ISA (US EPA, 2019) and the 2022 ISA Supplement (US EPA, 2022a) are subject to similar methodological limitations, and thus do not meaningfully reduce the uncertainty of the evidence; this prevents causal inference at exposures below the current NAAQS. These methodological limitations and sources of uncertainty are discussed further below.

**Table 2.1 The Nine "Asks" of Epidemiology Research[a]**

| Step of Risk Assessment | "Asks" | | |
|---|---|---|---|
| Hazard Identification | Confirm outcome? | Confirm exposure? | Report methods fully and transparently? |
| Dose-Response | Include information on shape of the curve? | Harmonize exposure categories (definitions)? | Describe direction/ magnitude of error? |
| Exposure Assessment | Evaluate source-to-intake pathways? | Provide complete exposure data? | Report on quality assurance/quality control? |

Note:
(a) Adapted from Table 3 in LaKind *et al*. (2020).

### 2.5.1 Measurement Error

Exposure measurement error is a key source of uncertainty, not only because it affects the reported $PM_{2.5}$ concentrations at which associations with morbidity or mortality are observed, but it can also introduce bias to the observed associations if the direction or magnitude of error is associated with the outcome status. The assessment of $PM_{2.5}$ concentrations in epidemiology studies can be subject to considerable measurement error due to unaccounted-for residential mobility, temporal variation, or poor prediction model performance.

Another important source of exposure measurement error is the placement of the $PM_{2.5}$ monitors from which measurements are taken. As noted in the 2022 PA, in response to a key change in US EPA's monitoring requirements, "the addition of $PM_{2.5}$ monitoring at near-road locations was phased in from 2015 to 2017"

(US EPA, 2022b), largely after the study periods covered by the key epidemiology studies. Since near-road monitoring sites tend to capture higher $PM_{2.5}$ concentrations than those in surrounding areas, had the near-road monitors been placed during the study periods, the study-reported mean $PM_{2.5}$ concentrations would have been higher.

In addition, long-term cohort studies of all-cause or nonaccidental mortality often do not assess exposure timing or duration during etiologically relevant periods within individuals' lifetimes. In most of these studies, ambient $PM_{2.5}$ exposure is only measured for a few years, often contemporaneously with follow-up, leading to innumerable misalignments between exposures and disease processes that inevitably result in death. In effect, these exposure measurement periods are only small parts of individuals' lifetimes that are not contemporaneous with the natural history of any particular health condition that leads to death. Because different causes of death have different etiologies, they also have very different relevant exposure windows. In addition, some causes of death are also more likely due to acute, rather than chronic, conditions.

Given the potential existence of multiple sources of exposure measurement error, assuming the association is causal at higher $PM_{2.5}$ concentrations, it is possible that the observed associations with mortality or morbidity at lower mean $PM_{2.5}$ concentrations simply reflect true associations at higher $PM_{2.5}$ concentrations that were substantially underestimated in the studies. This is particularly important when considering there is limited evidence regarding health effects at lower mean $PM_{2.5}$ concentrations.

In addition, the Proposed Rule noted that the 2022 PA "emphasize[d] multicity/multistate studies that examine health effect associations, as such studies are more encompassing of the diverse atmospheric conditions and population demographic in the U.S. than studies focus on a single city or state" (US EPA, 2023). However, these studies also have limitations, as noted by CASAC consultant Dr. Jane Clougherty in her comments on the draft of the 2022 PA (US EPA, 2021a). Dr. Clougherty noted that she had "some hesitance regarding *co-pollutant adjustment* and *spatial scale* in the $PM_{2.5}$ epidemiology literature to date" (Sheppard, 2022 [emphasis in original]). She explained that:

> There is an assumption throughout the document [*i.e.*, the draft of the 2022 PA] that *larger studies constitute better epidemiology*, though this is not necessarily the case, as larger studies often have greater exposure misclassification, as compromises are made in estimating exposures across larger populations/regions.
>
> Further, these studies are often implemented at larger spatial scales (e.g., 1 km x 1 km or larger), which is much larger than the scale of variance for many important co-pollutants (i.e., NOx [nitrogen oxides] can vary at 100 m or less); as such, studies at larger almost necessarily imperfectly adjust for co-pollutants…. Though larger scales may reasonably capture spatial variation in $PM_{2.5}$ concentrations, they do not fully capture variation in important co-pollutants, so these studies may well not accurately adjust for co-pollutant exposures. (Sheppard, 2022 [emphasis in original])

### 2.5.2 Confounding

Although some of the recent studies have considered potential confounding by copollutants, others have not, which may render the observed associations between $PM_{2.5}$ exposure and health effects in such studies uncertain. However, copollutant evaluations are themselves subject to methodological issues, such as mismatching the copollutant exposure window and mortality, failing to account for collinearity or a nonlinear relationship with $PM_{2.5}$ exposure, and failing to account for temporal variation. In fact, the 2022 ISA Supplement found that there is some evidence of potential confounding by copollutants in some studies

(US EPA, 2022a), which is inconsistent with the studies evaluated in the 2019 ISA that showed statistically significant results in both single and copollutant models, indicating that confounding by copollutants was not a significant source of uncertainty in the associations between $PM_{2.5}$ exposure and health effects observed in these studies (US EPA, 2019).

Three assessments by different researchers (Janes *et al*., 2007; Greven *et al*., 2011; Pun *et al*., 2017) using Medicare cohort data from different time periods have each detected confounding in their datasets, conferring doubt on the reliability/validity of national-level effect estimates derived from this cohort and similar cohorts. Each study observed remarkable differences between their temporal (global) effect estimates and their spatiotemporal (local) effect estimates. In the absence of confounding by variables trending on the national level, these decomposed estimates would be approximately equal. Local effect estimates, which are not confounded by national trends such as healthcare and economic changes, have shown little to no evidence of an association between $PM_{2.5}$ exposure and mortality. While these studies suggested the presence of some unmeasured confounding from epidemiology studies, US EPA did not take these findings into consideration in its causal determinations for $PM_{2.5}$ exposure and health outcomes in the 2019 ISA and 2022 ISA Supplement (US EPA, 2019, 2022a), which provided the scientific basis for the 2022 PA and the Proposed Rule (US EPA, 2022b, 2023).

### 2.5.3 Statistical Model

The Cox proportional hazards model used in cohort studies cannot adequately control for strong time-varying confounding. A recent simulation, based on a realistic cohort of 500,000 adults constructed using the National Cancer Institute Smoking History Generator, indicates that the Cox model poorly controls for a time-dependent strong risk factor (*e.g*., smoking, which was used in this simulation), yielding unreliable relative risk estimates unless detailed, time-varying information is incorporated into the modeling. None of the studies identified as key in the 2022 PA incorporated these parameters in their modeling (US EPA, 2022b). As a result, the effect estimates from these studies are of questionable reliability, given the relatively modest association between $PM_{2.5}$ exposure and mortality (Moolgavkar *et al*., 2018).

### 2.5.4 $PM_{2.5}$ Exposure Threshold

In the Proposed Rule, US EPA noted:

> Studies evaluated in the 2019 ISA and the ISA Supplement examine this issue, and continue to provide evidence of linear, no-threshold relationships between long-term $PM_{2.5}$ exposures and all-cause and cause-specific mortality…. Generally, the evidence remains consistent in supporting a no-threshold relationship, and in supporting a linear relationship for $PM_{2.5}$ concentrations > 8 $\mu g/m^3$. However, uncertainties remain about the shape of the C-R [concentration-response] curve at $PM_{2.5}$ concentrations < 8 $\mu g/m^3$, with some recent studies providing evidence for either a sublinear, linear, or supralinear relationship at these lower concentrations (U.S. EPA, 2019a, section 11.2.4; U.S. EPA, 2022a, section 2.2.3.2). (US EPA, 2023)

Rhomberg *et al.* (2011) showed that exposure measurement error can lead to the underestimation of risks at higher exposure levels and the overestimation of risk at lower exposure levels. Exposure measurement errors, ranging from instrument imprecision to the practice of serially averaging measured constituent values over time and space, are pervasive in observational air pollution studies. These errors preclude the ability of these studies to detect a $PM_{2.5}$ threshold, if one were to exist. Given that such errors make determining the true shape of the $PM_{2.5}$ concentration-response function difficult, assessments of risks at low $PM_{2.5}$ exposure levels based on these curves are of dubious reliability.

Similarly, in his comments on the draft of the 2022 ISA Supplement (US EPA, 2022a), CASAC member Dr. Jeremy Sarnat noted:

> A theoretical question related to the shape of C-R curves (for mainly long-term exposure and mortality) is whether we might expect to see differential measurement error at lower observed PM concentrations. For studies based primarily on measured estimates of population exposure I could hypothesize why differential error may exist and lead to differences in the shape of the curve along its full observed range. (US EPA, 2021b)

Furthermore, in her comments on the same document, CASAC member Dr. Deborah Corey-Slechta stated:

> One topic that does come to mind, although not necessarily related to the current document or its ultimate purpose and which may be included in the 2019 PM ISA is the fact that exposure to air pollution is lifelong, beginning in utero. Obviously, this cannot be accommodated in terms of data or specific calculations but may be an important reminder with respect to the problem itself, given that right now we're not even focused on lifetime exposures. (US EPA, 2021b)

This is an important point. The long-term exposure studies of $PM_{2.5}$ that US EPA evaluated did not assess the risks of lifetime $PM_{2.5}$ exposures or determine how individuals' $PM_{2.5}$ exposures before the study period impact the interpretation of their results, even though it is hard to imagine these earlier exposures not playing a role if $PM_{2.5}$ exposure is indeed causal. Not only can this impact the detection of a threshold, but these earlier exposures may be confounders that impact the interpretation of associations between $PM_{2.5}$ exposure and health effects at lower exposure concentrations.

Taken together, there is a high degree of uncertainty at long-term $PM_{2.5}$ concentrations below the current annual standard in epidemiology studies that evaluated concentration-response relationships.

## 2.6 Conclusion

In the Proposed Rule, US EPA (2023) concluded:

> Regardless of whether an epidemiologic study uses monitoring data or a hybrid modeling approach when estimating $PM_{2.5}$ exposures, the PA recognizes that it is challenging to interpret the study-reported mean $PM_{2.5}$ concentrations and how they compare to design values. This is particularly true given the variability that exists across the various approaches to estimate exposure and to calculate the study-reported mean.

We concur with US EPA that comparing the mean $PM_{2.5}$ concentrations reported from the key epidemiology studies to the annual design values is challenging. In addition, we recognize that the key epidemiology studies on which the Administrator based his proposal to lower the current standard were not reviewed in a systematic, unbiased, or transparent manner. These studies have substantial uncertainties and limitations (*e.g.*, exposure measurement error, confounding, irrelevant exposure windows) that were not adequately taken into account in the Administrator's evaluation of the current standard. Therefore, these studies do not provide adequate evidence for health effects occurring at $PM_{2.5}$ concentrations lower than the current standard of 12 $\mu g/m^3$.

# 3 Primary Annual $PM_{2.5}$ Standard – Experimental Evidence

US EPA described experimental studies in the 2019 ISA, 2022 ISA Supplement, 2022 PA, and Proposed Rule (US EPA, 2019, 2022a,b, 2023). The Agency acknowledged that these studies mostly evaluated exposures well above ambient $PM_{2.5}$ concentrations. We agree with US EPA that these studies do not provide evidence regarding ambient $PM_{2.5}$ exposures. We also conclude that these studies provide evidence that there are thresholds for health outcomes associated with $PM_{2.5}$ exposure.

## 3.1 Controlled Human Exposure Studies

Regarding the available controlled human exposure studies of $PM_{2.5}$, the 2022 PA stated:

> Taken together, these controlled human exposure studies support biological plausibility for the serious cardiovascular and respiratory effects that have been linked with ambient $PM_{2.5}$ exposures and seen in epidemiologic studies (U.S. EPA, 2019, Chapter 6). However, while these studies are important in establishing biological plausibility, it is unclear how the results alone and the importance of the effects observed in these studies, particularly in studies conducted at near-ambient $PM_{2.5}$ concentrations, should be interpreted with respect to adversity to public health. (US EPA, 2022b)

We disagree with the Agency's conclusion that these studies' results provide support for the biological plausibility of the health effects observed at ambient $PM_{2.5}$ concentrations in the epidemiology studies. Only a few such studies are available, and they mostly evaluated exposure concentrations well above ambient concentrations. In addition, the exposure concentrations these studies evaluated and the health outcomes they observed are not consistent or coherent. They also all had very small samples sizes and do not represent the larger population of people in the US that the NAAQS is intended to protect.

In addition, some of the effects observed in these studies are either not adverse themselves or are not necessarily indicative of potential adverse effects. US EPA acknowledged and discussed this in the Proposed Rule:

> [I]mpaired vascular function can signal an intermediate effect along the potential biological pathways for cardiovascular effects following short-term exposure to $PM_{2.5}$ and show a role for exposure to $PM_{2.5}$ leading to potential worsening of IHD [ischemic heart disease] and heart failure followed potentially by ED [emergency department] visits, hospital admissions, or mortality (U.S. EPA, 2019, section 6.1 and Figure 6-1). **However, just observing the occurrence of impaired vascular function alone does not clearly suggest an adverse health outcome.** (US EPA, 2023 [emphasis added])

Regarding this issue, US EPA also referenced the American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the adverse effects of air pollutants (Thurston *et al*., 2017) in the Proposed Rule, stating:

> While the ATS/ERS statement concluded that chronic endothelial and vascular dysfunction can be judged to be a biomarker of an adverse health effect from air pollution, they also conclude that "the health relevance of acute reductions in endothelial function induced by air pollution is less certain" (Thurston et al., 2017). This is particularly informative to our consideration of the controlled human exposure studies which are short-term in nature (*i.e.*, ranging from 2- to 5-hours), including those studies that are conducted at near-ambient $PM_{2.5}$ concentrations. (US EPA, 2023)

Many of the cardiovascular and respiratory effects assessed in the controlled human exposure studies have threshold modes of action and do not occur at lower $PM_{2.5}$ concentrations. If the threshold is above ambient concentrations, then these studies do not provide support for these effects at ambient concentrations.

In light of these issues, US EPA should not consider the results of the controlled human exposure studies of $PM_{2.5}$ to support the biological plausibility of health effects reported in epidemiology studies at near-ambient or lower $PM_{2.5}$ concentrations.

## 3.2 Experimental Animal Studies

With respect to the available experimental animal studies of $PM_{2.5}$, the 2022 PA noted that, except for two studies that examined $PM_{2.5}$ concentrations close to ambient concentrations, most of the studies examined short-term exposures to concentrations ranging from 100 to >1,000 $\mu g/m^3$ and long-term exposures to concentrations ranging from 66 to >400 $\mu g/m^3$, which are far above ambient levels in the US (US EPA, 2022b). Of the two exceptions, one study reported impaired lung development in mice following exposure to an average concentration of 16.8 $\mu g/m^3$ of $PM_{2.5}$ for 24 hours/day for several months (Mauad *et al*., 2008), and the other study reported increased carcinogenic potential following exposure to an average concentration of 17.7 $\mu g/m^3$ $PM_{2.5}$ for 2 months (Cangerana Pereira *et al*., 2011, as cited in US EPA, 2022b). The 2022 PA noted that while these two studies reported "serious effects following long-term exposures to $PM_{2.5}$ concentrations close to the ambient concentrations reported in some $PM_{2.5}$ epidemiologic studies (U.S. EPA, 2019, Table 1-2), [these concentrations are] still above the ambient concentrations likely to occur in areas meeting the current primary standards" (US EPA, 2022b).

The Administrator noted in the Proposed Rule:

> With regard to the animal toxicological studies, the PA recognizes that, unlike the controlled human exposure studies that provide insight on the exposure concentrations that directly elicit health effects in humans, there is uncertainty associated with translating the observations in the animal toxicological studies to potential adverse health effects in humans. The PA notes that the interpretation of these studies is complicated by the fact that $PM_{2.5}$ concentrations in animal toxicological studies are much higher than those shown to elicit effects in human populations. Moreover, the PA recognizes that there are also significant anatomical and physiological difference[s] between animal models and humans. (US EPA, 2023)

The Administrator concluded, "noting uncertainty in extrapolating the effects seen in animals, and the $PM_{2.5}$ exposures and doses that cause those effects to human populations, animal toxicological studies are of limited utility in informing decisions on the public health protection provided by the current or alternative primary $PM_{2.5}$ standards" (US EPA, 2023). We agree with the Administrator's judgment regarding the overall evidence from the experimental animal studies of $PM_{2.5}$.

# 4 Primary 24-Hour $PM_{2.5}$ Standard

In the Proposed Rule, the Administrator concluded that the available literature did not call into question the adequacy of the current primary 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$ and proposed retaining that standard for now. In support of that decision, the Administrator noted that "the observations that the air quality concentrations in areas meeting the current standards are well below the $PM_{2.5}$ concentrations shown to elicit effects" (US EPA, 2023). However, because some CASAC members have proposed lowering the current primary 24-hour standard to between 25 and 30 $\mu g/m^3$, the Administrator will also take public comments on that proposal (US EPA, 2023).

Regarding the available epidemiology studies of short-term $PM_{2.5}$ exposure, the Administrator noted:

> While there are three studies available in this reconsideration that restricted 24-hour concentrations to concentrations below 25 $\mu g/m^3$ and while some members of CASAC pointed to these studies as the basis for their recommendation to revise the 24-hour standard, the Administrator preliminarily concludes that the results from these studies, particularly in light of the uncertainties associated with these studies… are an inadequate basis for revising the level of the 24-hour $PM_{2.5}$ standard. (US EPA, 2023)

The Administrator also noted that the risk assessment of long- and short-term $PM_{2.5}$ exposures and all-cause or nonaccidental mortality shows that:

> [E]stimated reduction in $PM_{2.5}$-associated risks is across a more limited population and is largely confined to a small number of areas located in the western U.S. Other areas included in the risk assessment were shown to experience risk reductions that were driven primarily by meeting a lower annual standard level (though the associated change in air quality also resulted in lower 24-hour standard concentrations). (US EPA, 2023)

In their review of the draft of the 2022 PA, some CASAC members recommended retaining the primary 24-hour $PM_{2.5}$ standard, primarily based on the US EPA risk assessment and evidence from controlled human exposure studies of $PM_{2.5}$. For example, in his comments on the draft of the 2022 PA, Dr. Boylan noted:

> EPA provides sufficient rationale to retain the current primary 24-hour $PM_{2.5}$ standard, without revision. The risk assessment not only accounts for the level of the standard, but also accounts for the form of the standard and the way attainment with the standard is determined (i.e., highest design value in the CBSA [core-based statistical areas]). The risk assessment indicates that the annual standard is the controlling standard across most of the urban study areas evaluated and revising the level of the 24-hour standard is estimated to have minimal impact on the $PM_{2.5}$-associated risks. Therefore, the annual standard can be used to limit both long- and short-term $PM_{2.5}$ concentrations.
>
> Epidemiologic studies provide the strongest support for reported health effect associations for the overall mean concentrations rather than near the upper end of the concentration distribution; therefore, there is limited epidemiologic evidence to determine the adequacy of the level of the 24-hour standard. The epidemiologic studies included in this document

> do not indicate that the reported health effect associations are strongly influenced by exposures to the peak concentrations in the air quality distribution.
>
> Finally, the $PM_{2.5}$ concentrations used in human clinical studies to show short-term exposure effects are well above those typically measured in areas meeting the current standards, suggesting that the current standards are providing adequate protection against these exposures. (Sheppard, 2022)

Considering the uncertainties in and limitations of the scientific evidence and quantitative information regarding short-term $PM_{2.5}$ exposure noted by both the Administrator and CASAC member Dr. Boylan, we agree with the US EPA Administrator that the primary 24-hour $PM_{2.5}$ standard should be retained.

# 5 At-Risk Populations

The Proposed Rule noted that at-risk populations "represent a substantial portion of the total U.S. population" and "[t]he information available in this reconsideration has not altered our understanding of human populations at risk of health effects from $PM_{2.5}$ exposures" (US EPA, 2023). These populations include children, older adults, individuals with pre-existing cardiovascular and/or respiratory diseases, individuals of Black and Hispanic race/ethnicity, and individuals of lower socioeconomic status (SES) (US EPA, 2023). However, the 2019 ISA indicates that "children and race were the only factors for which it was concluded that '*adequate evidence*' was available indicating that people of a specific lifestage and race are at increased risk of $PM_{2.5}$-related health effects" (US EPA, 2019 [emphasis in original]). For all the other risk factors, US EPA found the evidence to be suggestive of an association with an increased risk of $PM_{2.5}$-related health effects[1] (*e.g.*, pre-existing cardiovascular disease or respiratory disease, low SES) or inadequate to be able to assess that association (*e.g.*, older age) (US EPA, 2019). Highlighting environmental justice issues, the 2022 ISA Supplement focused on reviewing studies published since the 2019 ISA that examined disparities in $PM_{2.5}$ exposure or $PM_{2.5}$-related health risks based on SES and race/ethnicity (US EPA, 2022a). US EPA concluded in the 2022 ISA Supplement that the evidence from those studies "support the conclusions of the 2019 PM ISA," specifically that there is "suggestive" evidence that low SES is associated with an increased risk of $PM_{2.5}$-related health effects and "adequate" evidence that "race and ethnicity, specifically minority populations including Black populations, are at increased risk of $PM_{2.5}$-related health effects, in part due to disparities in exposure" (US EPA, 2022a).

With respect to children, the 2019 ISA stated that "[a]lthough stratified analyses do not indicate a difference in the risk of PM-related health effects between children and adults, there is strong evidence from studies focusing on children that demonstrate health effects only observable in growing children that [can be] attributed to $PM_{2.5}$ exposure" (US EPA, 2019). That is, while children may be susceptible to health outcomes that would not affect adults (*e.g.*, lung function growth), there is no evidence that the $PM_{2.5}$ exposure levels at which these effects occur are lower than the exposure levels at which other health effects can occur in children and adults. This indicates that the current primary annual and 24-hour $PM_{2.5}$ standards are adequate to protect children.

It is also notable that many of the epidemiology studies on which the evaluation of the current standard is based involved populations that the 2019 ISA indicated have suggestive evidence of being susceptible to $PM_{2.5}$ (US EPA, 2019). For example, studies of children, older adults, and people with pre-existing cardiovascular and respiratory diseases form the basis of causal conclusions in the 2019 ISA. In addition, three of the eight studies on which the $PM_{2.5}$ risk assessment presented in the 2022 PA was based (US EPA, 2022b) evaluated mortality risks in people over the age of 55 (*i.e.*, Thurston *et al.*, 2016) and 65 (*i.e.*, Di *et al.*, 2017a; Zanobetti *et al.*, 2014). Although the remaining five studies on which this risk assessment was based evaluated all ages (Baxter *et al.*, 2017; Ito *et al.*, 2013) and ages 30 and over (Jerrett *et al.*, 2017; Pope *et al.*, 2015; Turner *et al.*, 2016), the majority of the deaths observed in these studies occurred in older individuals.

In addition, while environmental justice issues are important and should continue to be studied, and there is clear evidence for disparities in $PM_{2.5}$ exposure associated with race and SES, the evidence to date regarding disparities in the risk of $PM_{2.5}$-related health effects associated with these factors does not support

[1] *i.e.*, "[The] evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines" (US EPA, 2019)

a similar conclusion. Specifically, none of the five studies included in the 2022 ISA Supplement (US EPA, 2022a) that evaluated the dose-response relationship between long-term $PM_{2.5}$ exposure and total mortality stratified by race/ethnicity (*i.e*., Awad *et al*., 2019; Lipfert and Wyzga, 2020; Parker *et al*., 2018; Son *et al*., 2020; Wang *et al*., 2020) support the conclusion that there is a disparity in $PM_{2.5}$-related mortality risk associated with race/ethnicity. Both Awad *et al*. (2019) and Lipfert and Wyzga (2020) reported stronger associations between long-term $PM_{2.5}$ exposure and mortality among Whites than among Blacks, while Son *et al*. (2020) and Wang *et al*. (2020) both reported associations of equal magnitude among Whites and Blacks (US EPA, 2022a). Regarding the fifth study by Parker *et al*. (2018), while the 2022 ISA Supplement stated that the "study reported a larger association, in terms of magnitude, among Black (HR: 1.05 [95% CI: 1.03, 1.09]) and White (HR: 1.02 [95% CI: 1.00, 1.05]) individuals and a null association among Hispanic individuals (HR: 0.98 [95% CI: 0.94, 1.03])" for all-cause mortality[2] (US EPA, 2022a), these hazard ratios (HRs) and CIs are not consistent with those reported in the study publication. Rather, Parker *et al*. (2018) reported no association between long-term $PM_{2.5}$ exposure and all-cause mortality among White (HR = 1.05, 95% CI: 1.00-1.11), Black (HR = 1.11, 95% CI: 0.97-1.28), or Hispanic individuals (HR = 0.97, 95% CI: 0.88-1.06). The results suggest that there were no statistically significant differences in the associations between long-term $PM_{2.5}$ exposure and all-cause mortality among different racial groups.

As with the key epidemiology studies of $PM_{2.5}$ exposure discussed in Section 2, US EPA did not systematically evaluate the quality of the studies evaluating $PM_{2.5}$ exposure and at-risk populations that the Agency reviewed in the 2022 ISA Supplement (US EPA, 2022a). For example, the study by Wang *et al*. (2020) is subject to several methodological limitations, primarily the potential for exposure measurement error, model misspecification, and multiple comparisons being performed, all of which could have biased the study's findings on racial disparities in mortality rates. Further, all five of the studies discussed above had very large sample sizes, ranging from approximately 660,000 to 53,000,000 (Awad *et al*., 2019; Lipfert and Wyzga, 2020; Parker *et al*., 2018; Son *et al*., 2020; Wang *et al*., 2020). As a result, any observed differences in the association between long-term $PM_{2.5}$ exposure and mortality across racial groups could have been due to overly sensitive statistical testing, rather than reflecting true underlying racial disparities in mortality associated with $PM_{2.5}$ exposure. Finally, there are few studies (maximum of two) available for each particular health outcome (*e.g*., overall cardiovascular mortality, hypertension, diabetes mortality), raising question about the certainty of the existing evidence.

[2] In addition, in Table A-16 of the 2022 ISA Supplement, US EPA reported a different risk estimate for all-cause mortality for white individuals (HR = 1.03, 95% CI: 1.02-1.03) (US EPA, 2022a). The risk estimates for the other two populations are the same as those provided in the main text.

# 6 Conclusions

Based on our review of the Proposed Rule, we conclude the following:

- The evidence does not support lowering the primary annual $PM_{2.5}$ standard.
  - The key epidemiology studies on which the Administrator based his proposal to lower the current standard were not reviewed in a systematic, unbiased, or transparent manner. These studies have substantial uncertainties and limitations (*e.g.*, exposure measurement error, confounding, irrelevant exposure windows) that were not adequately taken into account in the Administrator's evaluation of the current standard. Therefore, these studies do not provide adequate evidence for health effects occurring at $PM_{2.5}$ concentrations lower than the current standard of 12 $\mu g/m^3$.
  - The area annual $PM_{2.5}$ design values are generally higher than the mean concentrations reported in the monitor-based studies and the hybrid model-based studies that incorporated population weighting. The range of the area annual design values associated with the lowest reported mean $PM_{2.5}$ concentrations reported in these studies (*i.e.*, 9.9 $\mu g/m^3$ for the monitor-based studies and 9.3 $\mu g/m^3$ for the hybrid model-based studies with population weighting) would be 10.9-11.9 $\mu g/m^3$ and 10.6-11.0 $\mu g/m^3$, respectively. These levels are higher than the Administrator's proposed primary annual $PM_{2.5}$ standard of 9-10 $\mu g/m^3$.
  - Further, the recommended increase in near-road monitoring will further increase the ratios of maximum annual design values to averaged concentrations. In turn, this will increase the potential that continued implementation of the current standard could effectively achieve average concentration levels in many areas that approach US EPA's proposed range for what is required to protect public health.
  - While accountability studies can inform the relationship between $PM_{2.5}$ exposure and health effects, they can have crucial methodological limitations that undermine their findings, including some that are unique to this study design and the statistical approaches these studies use, and some common to epidemiology studies with a more-traditional study design (*e.g.*, exposure measurement error).
  - The experimental animal studies and controlled human exposure studies of $PM_{2.5}$ do not provide evidence regarding ambient $PM_{2.5}$ exposures.
- Considering the uncertainties in and limitations of the scientific evidence and quantitative information regarding short-term $PM_{2.5}$ exposure, we agree with the US EPA Administrator's current decision that the primary 24-hour $PM_{2.5}$ standard should be retained.

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