COARSE PARTICULATE MATTER COALITION

1025 Connecticut Avenue
Suite 1000
Washington, D.C.
(202) 828-1233
kurt@blasegroup.com

December 11, 2018

U.S. Environmental Protection Agency
EPA Docket Center (ORD Docket)
Mail Code: 28221T
1200 Pennsylvania Avenue NW
Washington, DC 20460

Submitted electronically through Regulations.gov

Re: Integrated Science Assessment for Particulate Matter (First External Review Draft), Docket ID No. EPA–HQ–ORD–2014–0859, 83 Fed. Reg. 53471(October 23, 2018)

Dear Docket Personnel:

The Coarse Particulate Matter Coalition (CPMC), an organization of industries dedicated to scientifically sound regulation of coarse particulate matter (PM10-2.5) in air, offers the following comments on the First External Review Draft of EPA's Integrated Science Assessment (ISA) for Particulate Matter.[1] CPMC's comments may be summarized as follows:

1. Coarse crustal PM. As documented in the draft ISA, nearly all of the health studies finding health effects from coarse PM exposure examined urban dusts contaminated by vehicle exhaust and other constituents common to urban roadsides. In contrast, other coarse PM is dominated by crustal material, which has been shown to be harmful only during dust storms at ambient concentrations well above the current PM standards. The next draft of the ISA should limit the coarse PM health findings to the dusts that were the subject of the health studies and should exclude coarse PM dominated by crustal material.

[1] Current members of the Coalition include the Corn Refiners Association, National Cotton Council, National Stone, Sand & Gravel Association, Rio Tinto Kennecott and the National Cattlemens' Beef Association.

2. Coarse PM causality. The draft ISA does not provide comprehensive, consistent and transparent application of EPA's causal criteria to the available coarse PM data. The "suggestive" causality findings for cancer and for long term cardiovascular, metabolic, nervous system and mortality effects from coarse PM exposure are not justified by the analyses presented in the draft ISA and should be revised to "inadequate" in the next draft.

These issues are discussed further below.

I. The Coarse PM Health Findings Should be Limited to the Dusts Analyzed In the Health Studies

The draft ISA finds that PM10−2.5 is almost entirely primary in origin, composed largely of crustal material, sea salt, and biological material, and also notes that national average PM10−2.5 concentrations have changed little over the past decade (p. ES-4). The ISA also finds that concentrations are highest in southwestern U.S. and are observed to be largely dominated by crustal material, but organic material can also represent a substantial contribution to mass, as well as biological material like bacteria, viruses, fungal spores, pollen, and plant debris (p. 1-12).

The only evidence for health effects associated with coarse crustal PM discussed in the draft ISA concerns dust storm events during which high concentrations were linked to increases in cardiovascular ED visits and hospital admissions (p. 6-248). However, as the draft ISA notes, these studies are limited by the potential for exposure measurement error and copollutant confounding (*id.*).

In contrast, the profile of urban roadside emissions presented in the draft ISA is quite different (pp. 2-70-71). The draft reports higher concentrations of some PM components near roads with heavy traffic than other urban locations. Carbonaceous aerosols exhibited substantial intra-urban variability in Detroit, MI and Cleveland, OH that was consistent with local sources, with EC higher at sites adjacent to freeways and busy surface streets. Site to site variability in OC was approximately 7% at distances from 0.5 to 4 km, but between 4−27% at distances 4 to 100 km. More finely speciated organic components differed by as much as 60% at the 0.5 to 4 km scale and up to 200% at the 4−100 km scale. PAHs and steranes along with OC and EC were found to be higher near roads with heavy traffic than in other urban locations. Differences of a factor of 2 to 3 between concentrations on major streets and at background locations in the same city in the Netherlands were also observed for chromium, copper, and iron, elements that were mainly present in the coarse fraction, as well as for black carbon and particle number count.

As discussed below, the vast majority of the new health effects studies for coarse PM, even if accepted at face value, are studies of urban roadside dust containing the contaminants discussed above. They are not studies of coarse crustal material

uncontaminated by roadside emissions. The next draft of the ISA should limit the coarse PM health findings to the urban dusts that were analyzed in the health studies, and should exclude coarse PM dominated by crustal material.

II. The Proposed Coarse PM Causality Finding for Cancer Should Be Revised To "Inadequate"

As discussed in the draft ISA, the proposed causality findings must be based on the criteria for such findings presented in EPA's General Preamble for ISAs, which includes aspects to consider in judging causality. These are shown in Table 1 below, reprinted from the General Preamble. They include: consistency, coherence, biological plausibility, exposure-response relationship, strength of the observed association, experimental evidence, temporality, specificity and analogy. As noted in the Preamble, "one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results and reach credible conclusions about the relative weight of evidence and the likelihood of causality. Rather, these aspects provide a framework for systematic appraisal of the body of evidence, informed by peer and public comment and advice, which includes weighing alternative views on controversial issues" (p.19). While not meeting one or more of the principles does not automatically preclude a determination of causality, these aspects provide a framework for assessing the evidence.

EPA's aspects for judging causality will be used throughout these comments in evaluating the proposed causality determinations in the draft ISA. As discussed below, the draft ISA does not apply them clearly and consistently to the various causality findings for coarse PM health effects.

To begin, thorough consideration of EPA's aspects for judging causality indicates that the proposed "suggestive" finding for coarse PM is inaccurate and should be replaced with a finding of "inadequate."

<u>Consistency</u>. This criterion provides that "an inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies." With respect to coarse PM and cancer, only two such studies are cited in the draft ISA: Puett et al and Raaschou-Nielsen et al. The cancer signals in both are consistently weak. As the draft ISA notes, both studies reported only an "imprecise" positive association, and the confidence intervals are broad (p. 10-83). The draft ISA also finds that "uncertainty remains with respect to exposure measurement error due to the methods employed to estimate PM10−2.5 concentrations (Section 3.3.2.3), specifically the use of PM10−2.5 predictions that have not been validated by monitored PM10−2.5 concentrations" (pp. 10-84-85).

Table I Aspects to aid in judging causality.

Aspect	Description
Consistency	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. Statistical significance is not the sole criterion by which the presence or absence of an effect is determined. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from one line of evidence (e.g., epidemiologic, controlled human exposure, animal, or ecological studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. There may be coherence in demonstrating effects from evidence across various fields and/or across multiple study designs or related health endpoints within one scientific line of evidence. For example, evidence on welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry, and paleontological/historical reconstructions).
Biological plausibility	An inference of causality is strengthened by results from experimental studies or other sources demonstrating biologically plausible mechanisms. A proposed mechanism, which is based on experimental evidence and which links exposure to an agent to a given effect, is an important source of support for causality.
Biological gradient (exposure-response relationship)	A well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times).
Strength of the observed association	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may or may not represent a substantial effect in a population.
Experimental evidence	Strong evidence for causality can be provided through "natural experiments" when a change in exposure is found to result in a change in occurrence or frequency of health or welfare effects.
Temporality of the observed association	Evidence of a temporal sequence between the introduction of an agent and appearance of the effect constitutes another argument in favor of causality.
Specificity of the observed association	Evidence linking a specific outcome to an exposure can provide a strong argument for causation. However, it must be recognized that rarely, if ever, does exposure to a pollutant invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes.
Analogy	Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

In addition, while the magnitude of the cancer association with PM2.5 was similar in the Puett et al. study, in Raaschou-Nielsen et al. the PM2.5 effect was larger and more indicative of a relationship with lung cancer incidence (p. 10-83). For Raaschou-Nielsen et al. a sensitivity analysis was not conducted for PM10−2.5 to assess the potential influence of exposure measurement error (such an analysis was conducted for PM2.5). An analysis by histological cancer subtype also was not conducted for PM10−2.5.

Accordingly, while the results of these two studies may appear consistent, the association is weak in both studies, the exposure data are suspect and there are several key differences between the studies.

Coherence. This aspect holds that "an inference of causality from one line of evidence (e.g., epidemiologic, controlled human exposure, animal, or ecological studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association." In this case, there are no such other lines of evidence. The draft ISA notes that "experimental studies are more limited in number compared with the evaluation of PM2.5 and consist of a controlled human exposure study and several in vitro animal toxicological studies demonstrating DNA damage, oxidative stress, and mutagenicity" (p. 10-85). While these studies may be relevant to mechanism (discussed below), they do not provide direct confirming evidence that exposure to coarse PM causes lung cancer.

Biological plausibility. This aspect provides that "an inference of causality is strengthened by results from experimental studies or other sources demonstrating biologically plausible mechanisms." The draft ISA finds that "very few studies evaluating the genotoxicity and carcinogenicity of PM10−2.5 have been published since the 2009 PM ISA" (p. 10-79). As discussed in the draft ISA, the results of these studies are mixed and often attributed to urban road dust.

Exposure-response relationship. Under this aspect "a well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure . . ." The draft ISA does not discuss any established exposure-response curve for coarse PM, and given the limitations of the available data it seems unlikely that an accurate relationship could be derived at this time.

Experimental evidence. This aspect states that "strong evidence for causality can be provided through 'natural experiments' when a change in exposure is found to result in a change in occurrence or frequency of health or welfare effects." No such evidence is discussed in the draft ISA.

Temporality. “Evidence of a temporal sequence between the introduction of an agent and appearance of the effect constitutes another argument in favor of causality.” No such temporal sequence is discussed in the draft ISA.

Specificity. This aspect provides that “evidence linking a specific outcome to an exposure can provide a strong argument for causation.” Here again, the evidence for coarse PM is very weak. Most of the PM cancer evidence discussed in the draft ISA involves PM2.5 exposures. As discussed above, the coarse PM studies are few, their results are weak and both of the epidemiological studies focused on urban road dusts.

Analogy. This aspect is not discussed in the draft ISA.

In sum: (1) the ISA discusses only two epidemiological studies of coarse PM, which produced weak and somewhat inconsistent results; (2) other than studies of biological plausibility, there are no confirming experimental studies; (3) the studies of biological plausibility are few, their results are mixed and often attributed to urban road dust; (4) no exposure-response relationship has been established; (5) there is no confirming experimental evidence; (6) no temporal sequence has been established; and (7) the vast majority of the PM cancer findings are not specific to coarse PM, the few specific results are weak and most of the studies focused on urban road dusts.

Under these circumstances, the Coalition believes that EPA’s causation criteria for “suggestive” associations have not been satisfied with respect to coarse PM and cancer. The next draft of the ISA should revise the classification to “inadequate.” If the “suggestive” classification is retained, it should be limited to the urban roadside dusts that were the subject of the studies.

Table 2: Draft ISA Coarse PM Cancer Analysis

Consistency	Two epidemiological studies, imprecise results, significant exposure uncertainty
Coherence	No direct experimental evidence of association*
Biological plausibility	Few studies, mixed results
Exposure-response	No relationship discussed, data likely inadequate
Experimental evidence	None discussed*
Temporality	No discussion
Specificity	Confounding PM2.5 exposures, studies focused on urban road dusts
Analogy	Not discussed

*As discussed in EPA's General Preamble for ISAs, "coherence" refers to animal or human exposure data that replicate or confirm epidemiological results. "Experimental evidence" refers to "natural experiments" where a change in exposure is found to result in a change in health effects.

III. The Proposed Coarse PM Causality Findings for Long-Term Cardiovascular, Metabolic, Nervous System and Mortality Should be Revised to "Inadequate"

Long-Term Cardiovascular Effects

Consistency. The draft ISA reports that "the evidence relating long-term exposure to PM10-2.5 to cardiovascular mortality remains limited. Overall, there is no consistent pattern of associations for cardiovascular mortality" (p. 6-272). As noted in Table 6-72, the studies also suffer from significant uncertainty regarding exposure measurement error.

Coherence. The draft ISA finds that "the toxicological evidence related to long-term PM10-2.5 exposures was overall lacking and represents a substantial data gap in the present collection of literature" (p. 6-272). One study reported "some indications" of impaired heart function, and potentially changes in BP. No changes in markers of inflammation or oxidative stress were reported (Table 6-72).

Biological plausibility. The draft ISA finds that "there are important gaps in biological plausibility in part, due to the overall lack of experimental evidence . . . evidence from experimental animal studies is of insufficient quantity to establish biological plausibility" (p. 6-272).

Exposure-response relationship. The draft ISA does not report any established exposure-response association, and given the limitations of the available data it seems unlikely that an accurate relationship could be derived at this time.

Experimental evidence. No such evidence is discussed in the draft ISA.

Temporality. No temporal sequence is discussed in the draft ISA.

Specificity. The draft ISA notes substantial uncertainty regarding copollutant confounding and the independent effect of coarse PM (Table 6-72). Also, most of the studies are large urban studies primarily involving road dusts.

In sum, the long-term cardiovascular health findings for coarse PM in the draft ISA do not appear to meet any of the causation criteria for "suggestive" associations. The next draft of the ISA should revise the classification to "inadequate." If the "suggestive" classification is retained, it should be limited to the urban roadside dusts that were the subject of the studies.

Table 3: Draft ISA Coarse PM Long-Term Cardiovascular Analysis

Consistency	No consistent pattern of associations, significant exposure uncertainty
Coherence	No direct experimental evidence of association*
Biological plausibility	Evidence insufficient to establish
Exposure-response	No relationship discussed, data likely inadequate
Experimental studies	None discussed*
Temporality	No discussion
Specificity	Confounding PM2.5 exposures, studies focused on urban road dusts
Analogy	Not discussed

*As discussed in EPA's General Preamble for ISAs, "coherence" refers to animal or human exposure data that replicate or confirm epidemiological results. "Experimental evidence" refers to "natural experiments" where a change in exposure is found to result in a change in health effects.

Long-Term Metabolic Effects

The draft ISA analysis of metabolic effects is cursory and gives very little detail with respect to the three studies used as the basis for the proposed “suggestive” finding. Only one (Puett et al.) is an epidemiological study of PM exposure and diabetes. The abstract for the Puett study states:

> “Overall, results did not provide strong evidence of an association between exposure to PM in the previous 12 months and incident DM; however, an association with distance to road (a proxy marker of exposure to traffic-related pollution) was shown among women.”

The other two studies were cross-sectional studies showing effects on glucose or insulin, but not diabetes itself (p. 7-61). Two of the studies showed correlations with copollutants as well (PM2.5, NO2) and all of the studies involved urban roadside dusts. Biological plausibility is described as “limited” and derived from the “potential” for deposition of PM10-2.5 to modulate the ANS, the immune system or disrupt glucose, lipid, and insulin homeostasis. Other aspects of the causation criteria are not discussed.

For these reasons the long-term metabolic health findings for coarse PM in the draft ISA do not appear to meet the causation criteria for “suggestive” associations. The next draft of the ISA should revise the classification to “inadequate.” If the “suggestive” classification is retained, it should be limited to the urban roadside dusts that were the subject of the studies.

Long-Term Nervous System Effects

With respect to long-term nervous system effects from coarse PM exposure, the draft ISA states:

> Although there is a limited number of studies overall, the evidence base includes well-conducted epidemiologic studies reporting associations with impaired cognition and anxiety in longitudinal analyses of women enrolled in the NHS (Power et al., 2015; Weuve et al., 2012). Studies of long-term exposure during pregnancy or childhood were not consistently associated with neurodevelopmental effects. There is uncertainty stemming from exposure assessment methods relying on the difference method to estimate PM10-2.5 concentration (Sections 2.4.2) and related uncertainties due to the potentially uncharacterized spatial variation in PM10-2.5 (Section 2.5 and Section 3.3.1.1). None of the available studies adjusted for copollutant exposures.

Accordingly, (1) the available epidemiological studies are subject to significant measurement uncertainty; (2) there is no conforming toxicological evidence; (3) evidence of biological plausibility is based on one study that produced uncertain results (p. 8-72); (4) copollutant exposures were not assessed; and (5) none of the other causation criteria for “suggestive” associations is addressed. The next draft of the ISA

Table 4: Draft ISA Coarse PM Long-Term Metabolic Analysis

Consistency	One study, "results did not provide strong evidence of an association
Coherence	No direct experimental evidence of association*
Biological plausibility	Limited evidence
Exposure-response	No relationship discussed, data likely inadequate
Experimental studies	None discussed*
Temporality	No discussion
Specificity	Confounding PM2.5 and NO2 exposures, studies focused on urban road dusts
Analogy	Not discussed

*As discussed in EPA's General Preamble for ISAs, "coherence" refers to animal or human exposure data that replicate or confirm epidemiological results. "Experimental evidence" refers to "natural experiments" where a change in exposure is found to result in a change in health effects.

should revise the classification to “inadequate.” If the “suggestive” classification is retained, it should be limited to the urban roadside dusts that were the subject of the epidemiological studies.

Long-Term Mortality

Consistency. The draft ISA finds that “since the completion of the 2009 PM ISA a number of recent cohort studies conducted primarily in the U.S. and Europe provide no consistent evidence for positive associations between long-term PM10−2.5 exposure and total (nonaccidental) mortality. In addition to the inconsistent results, all of the studies use the difference of PM10 and PM2.5 (measured at monitors or estimated from models) to estimate PM10−2.5, which continues to be a main uncertainty in the positive associations that are observed in some cohorts . . .” (p. 11-121). The Bentayeb et al. study, which is said to “provide the strongest evidence,” is an occupational study. The abstract for the study notes that “due to the limited sample size and the nature of our study (occupational), further investigations are needed in France with a larger representative population sample.”

Coherence. The draft ISA reports “limited information on biological plausibility and limited coherence across scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) for cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity and metabolic disease (Chapter 7)” (p. 11-121). However, the draft ISA cites no new experimental studies directly associating mortality with long-term coarse PM exposure.

Biological plausibility. See coherence discussion above.

Exposure-response relationship. The draft ISA does not report any established exposure-response association, and given the limitations of the available data it seems unlikely that an accurate relationship could be derived at this time.

Experimental evidence. No such evidence is discussed in the draft ISA.

Temporality. The draft ISA finds that “the lack of information on the spatial and temporal correlation between the various measurement approaches reduces the confidence in the associations observed across studies” (p. 11-121).

Specificity. The draft ISA finds “an additional uncertainty is related to potential copollutant confounding; positive associations observed in the Nurses’ Health Study (Puett et al., 2009), AHSMOG (McDonnell et al., 2000) and ESCAPE (Beelen et al., 2014a) cohorts were attenuated to the null when PM2.5 was included in the model. The strongest evidence for total mortality comes from the GAZEL cohort (Bentayeb et al.,2015) in France . . .This association remained positive in copollutant models with PM2.5, but was attenuated and less precise” p. 11-121). In addition, the studies primarily involve urban cohorts exposed to roadside dusts.

Table 5: Draft ISA Coarse PM Long-Term Nervous System Analysis

Consistency	Few epidemiological studies, inconsistent results, significant exposure uncertainty and spatial variation
Coherence	No direct experimental evidence of association*
Biological plausibility	One study, uncertain results
Exposure-response	No relationship discussed, data likely inadequate
Experimental studies	None discussed*
Temporality	No discussion
Specificity	No adjustment for copollutants, studies focused on urban road dusts
Analogy	Not discussed

*As discussed in EPA's General Preamble for ISAs, "coherence" refers to animal or human exposure data that replicate or confirm epidemiological results. "Experimental evidence" refers to "natural experiments" where a change in exposure is found to result in a change in health effects.

Table 5: Draft ISA Coarse PM Long-Term Mortality Analysis

Consistency	Epidemiological studies provide "no consistent evidence for positive associations," significant exposure uncertainty
Coherence	No direct experimental evidence of association*
Biological plausibility	"Limited information"
Exposure-response	No relationship discussed, data likely inadequate
Experimental studies	None discussed*
Temporality	Absence of spatial and temporal information reduces confidence in epidemiological results
Specificity	Copollutant confounding in epidemiological studies
Analogy	Not discussed

*As discussed in EPA's General Preamble for ISAs, "coherence" refers to animal or human exposure data that replicate or confirm epidemiological results. "Experimental evidence" refers to "natural experiments" where a change in exposure is found to result in a change in health effects.

In sum, the long-term mortality health findings for coarse PM in the draft ISA do not appear to meet any of the causation criteria for “suggestive” associations. The next draft of the ISA should revise the classification to “inadequate.” If the “suggestive” classification is retained, it should be limited to the urban roadside dusts that were the subject of the studies.

IV. Other Coarse PM Causality Findings Should be Limited to the Dusts Analyzed in the Health Studies

The discussions above concern the coarse PM causality findings that are proposed to be revised in the draft ISA. However, those that were retained from the last review also should be qualified by limiting them to the urban road dusts that were the subject of the relevant studies.

The 2009 Integrated Science Assessment (ISA) for PM noted that in the prior review, "the CASAC PM Panel was also in general agreement 'that coarse particles in urban or industrial areas are likely to be enriched by anthropogenic pollutants that tend to be inherently more toxic than the windblown crustal material which typically dominates coarse particle mass in arid rural areas'" (p. 1-9). The ISA goes on to discuss a number of new studies involving crustal material, but nearly all of them involve road dust, combustion sources or other external sources of potential contamination (see Table 6-17). The only reference to potential harm from exposure to crustal material is a discussion that refers primarily to studies of dust storms (p. 6-97). Accordingly, the Policy Assessment (PA) noted that in the last review new evidence of harm from exposure to crustal material was limited to concentration levels well above the current standard (p. 3-29).

This also was recognized by CASAC members. For example, in his individual comments on the second draft PA, Dr. Joe Brain stated:

> There is also a continuing cry for a more thoughtful assessment of particle composition. There is increasing evidence that the extent of particle toxicity relates to the composition and solubility of the particles. There is also concern about the most appropriate metric. Should standards really be mass-based or should they reflect numbers or surface area of particles? The composition issue is particularly relevant to discussions of coarse particles. How do we make the distinction between those derived from fossil fuel combustion and resuspended crustal dust? <u>There is consensus that resuspended crustal dust is less toxic than combustion products.</u> There are clear regulatory implications as well (emphasis added).

As discussed above, the dust storm studies continue to be the only health studies of crustal material that are referenced in the current draft ISA. With respect to the coarse PM causality determinations retained from the last review, as well as the proposed revisions discussed above, the ISA should make it clear that they are limited

to the urban roadside dusts that were the subject of the studies and do not include emissions composed primarily of coarse crustal material.

Conclusion

For the reasons discussed above, the next draft of the PM ISA should:

1. Limit the coarse PM health findings to the dusts that were the subject of the health studies, and exclude coarse PM dominated by crustal material; and

2. Provide comprehensive, consistent and transparent application of EPA's causal criteria to the available coarse PM data, which we believe will show that the proposed "suggestive" findings for cancer and for long term cardiovascular, metabolic, nervous system and mortality effects are not justified and should be revised to "inadequate" in the next draft.

We thank you for considering our comments.

Respectfully submitted,

Kurt E. Blase

Counsel for the Coarse PM Coalition