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VIA EMAIL

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U.S. Environmental Protection Agency
Office of the Administrator
Science Advisory Board Staff Office
1200 Pennsylvania Ave., NW (MC-1400R)
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RE: Comments of the American Petroleum Institute (API) on the Draft Charge to the Science Advisory Board Covid-19 Review Panel

The American Petroleum Institute ("API") respectfully submits the following comments on the U.S. Environmental Protection Agency's ("EPA" or "Agency") notice regarding the convening of a panel of experts to provide scientific and technical guidance on issues related to the COVID-19 Pandemic. API welcomes EPA's efforts to consider opportunities to engage in the current research as well as to consider future research activities that inform EPA's responses to SAR-CoV-2 and COVID-19.

1. INTEREST OF THE AMERICAN PETROLEUM INSTITUTE

API represents more than 600 member companies involved in all aspects of the natural gas and oil industry, including exploration and production, refining, marketing, and transportation of petroleum and petroleum products in the United States. Together with its member companies, API is committed to ensuring a strong, viable U.S. oil and natural gas industry capable of meeting the energy needs of our nation in an efficient and environmentally responsible manner

while continuing to ensure the responsible and beneficial use of our resources even as we are faced with an unprecedented public health crisis. To that end, we have a strong interest in helping EPA identify those areas of research that would be most impactful in improving the nation's efforts to prevent and treat COVID-19 infection.

According to the SAB Web page, The Science Advisory Board (SAB) COVID-19 Review Panel will hold a public teleconference to receive an agency briefing, review charge questions, and EPA's document titled: *"Identifying Research Needs to Address the Environmental and Human Health Impacts of COVID-19."* In addition, the Advisory Activity document "Review of COVID-19 Pandemic Scientific and Technical Issues to Inform EPA's Research Activities" will also be the subject of discussion. The document states, "COVID-19 issues are the top priority for the U.S. EPA, and it has been actively engaged and supporting response efforts to the SARS-CoV-2 Pandemic. As part of these efforts, the Agency has also been considering how current and future EPA research activities might enhance and inform EPA's current and any future responses to SARS-CoV-2. To support the SAB COVID-19 Review Panel, the Agency has developed a compendium summarizing current understanding and capabilities related to SARS-CoV-2. API appreciates EPA's effort to solicit technical input on the draft charge questions that are designed to assist the Agency in identifying research needs to address environmental and health impacts related to COVID-19. We welcome further opportunity to clarify our comments with the SAB COVID-19 Review Panel or with EPA if needed.

Our comments are broadly focused on the following two research categories titled:

- Environmental Factors affecting transmission and severity of COVID-19
- Human Health Risk Factors affecting transmission and severity of COVID-19

In response to the charge questions,

- We discuss study design challenges in the current literature and offer some potential solutions
- We offer a decision-making method that can be used to evaluate and prioritize studies
- We provide ideas for other areas of potential research

We believe that the Agency has an opportunity to address the question of if, how, and to what extent air quality impacts incidence, progression, and severity, including mortality, on infectious

diseases, particularly Covid-19. Additionally, the Pandemic presents a valuable opportunity to study the impact of a variety of policy and regulatory decisions that have impacted the public's exposure time-activity patterns, as well as changes in outdoor and indoor air quality. However, before any research moves forward, that COVID-19 related mortality data would need to be validated and representative.

2. COMMENTS AND RECOMMENDATIONS

Response to Charge Questions

We acknowledge the importance of the broad range of topics included in the research plan. Our responses here are focused on two research categories: Environmental Factors affecting transmission and severity of COVID-19 and Human Health Risk Factors affecting transmission and severity of COVID-19. We focus specifically on methodological challenges that can be anticipated and addressed early in the process to advance the current state of the science.

Charge Question 1:

Within each research category, please discuss whether there is sufficient clarity to indicate how addressing a research question might inform Agency activities related to the SARS-CoV-2 Pandemic? Specifically,

- **a. Which research questions within a category are particularly suited to EPA's mission and will have the most impact on EPA's role in responding to the SARS-CoV-2 Pandemic?**
- **b. Are there research questions that could more effectively be addressed by another Federal partner, the private sector, academia, or some combination?**

Research Question: Does exposure to air pollutants, including wildland fire smoke or other air pollutants (e.g., ozone, particulate matter, diesel exhaust, pollen) increase the susceptibility to respiratory viruses like SARS-CoV-2? Or exacerbate existing COVID-19 infection?

While the research question has merit, reliance on the existing body of COVID-19/air pollution literature (including recently published literature associating COVID-19 mortality with air pollution) is premature. The data used to inform this research is incomplete; therefore, the

literature findings are preliminary and cannot be used to draw policy inferences. We urge the Agency to review the studies within the context of the study's limitations. If a decision is made to proceed, the limitations need to be addressed (See Appendix 1 – Review of Existing Research-Wu et al., (2020))

Research question: Are there particular health risk factors (aside from preexisting conditions) that make certain individuals or subpopulations more sensitive or vulnerable to COVID-19, e.g., characteristics of the built environment, seasonal allergies, chronic exposure to aerosolized pollutants, demographic conditions, etc.?

To the extent that EPA can work with other federal agencies in providing insight into the effect of emissions on public health outcomes, EPA studies should incorporate or at least consider the role of non-environmental factors on COVID-19 health outcomes to determine the appropriate policy action. We encourage EPA to partner with other agencies to broaden the scope by considering other interactions or cumulative effects associated with lifestyle-related preexisting conditions and exposures. This type of research will not only inform the current COVID-19 Pandemic but have implications for other viral infections.

Furthermore, we encourage EPA to partner with infectious disease experts who will provide a better understanding of infectious disease patterns and transmission rates, including factors that influence disease progression parameters (such as incubation period, infectiousness, etc.).

Charge question 2: Within each research category, please identify if other research questions have not been identified by the Agency, that have the potential to refine or improve our understanding and further support its role concerning the Pandemic.

API recommends the following as other potential research areas.

Accountability Studies

API members see this as an opportunity to develop accountability and/or comparative studies. The current situation establishes a natural experiment scenario that can be used to assess environmental health dynamics. For example, this is a good time to evaluate the relationship between some of the social distancing/quarantine policy recommendations and subsequent impacts on outdoor air quality. There is growing quantitative data that suggests that outdoor air

quality has improved (due to lower economic activities, less driving). Research could focus on the impact of the change in ambient air quality on health status, for example, research that evaluates health status pre- and post- the changes in ambient air quality.

Better exposure characterization studies

One of the key limitations in the existing air pollution and COVID-19 studies is the failure to properly account for personal exposures. API members see this as an opportunity to further refine exposure measurement tools; for example, the use of technology, e.g., personal monitoring devices, the use of phone apps in tracing disease outbreaks.

Charge question 3: Within a research category, EPA roughly identified what research could be accomplished in the short-term, and what would be longer-term efforts. Within each research category, are there other considerations that might impact prioritization? How might research be prioritized across the landscape of research categories that have been identified?

Research quality used to inform prioritization

The quality of the research should be used to identify research prioritization. Research that is deemed to be preliminary or hypothesis-generating requires a longer time to mature before specific research questions can be asked.

The application of Risk and Public Health Decision Making Method to inform prioritization

The use of a checklist developed by Burns et al. (2019) can be used in determining if a study could potentially be used in risk assessment and ultimately incorporated into public health decision-making.[1] For example, we applied the tool to Wu et al., (2020) and identified several elements that were missing and limited the publication's strength for use in risk assessment for regulatory decision making (See Appendix 2 – Decision Making Method).

Are there any other important categories of research, focused on the Agency's role in responding to the SARS-CoV-2 Pandemic, that are not captured in the existing table? If so,

[1] Burns, C.J., LaKind, J.S., Mattison, D.R., Alcala, C.S., Branch, F., Castillo, J., Clark, A., Clougherty, J.E., Darney, S.P., Erickson, H. and Goodman, M., 2019. A matrix for bridging the epidemiology and risk assessment gap. *Global Epidemiology*, *1*, p.100005.

please discuss the current state of knowledge in the research category and identify what research would be relevant and inform EPA's efforts. Please provide some sense of prioritization and whether the effort is a short-or-long term research effort.

The SAB COVID-19 Review Panel document lists exposure to outdoor air pollutants as a long-term research question that could enhance knowledge and capabilities. Considering the Federal Interagency Committee on Indoor Air Quality supports EPA indoor air quality (IAQ) research program, could there be an analogous research question associated with indoor emissions? For example, the long-term research question associated with indoor emissions could be stated as "**Does exposure to indoor air pollutants, including indoor emissions, re-suspension, transport from outdoors, and indoor aerosol aging processes, increase the susceptibility to respiratory viruses like SARS-CoV-2? Or exacerbate existing COVID-19 infection**?"

In closing, API supports this SAB activity and looks forward to a report focusing on the critical work that can further public health. If you have any further questions or would like any more information regarding the recommendations discussed, please free to contact me at (202) 682-8480 or blakeu@api.org.

Sincerely,

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American Petroleum Institute

APPENDIX 1- EXISTING RESEARCH – Wu et al. (2020)

The results of a recent study posted online by Wu et al. is among the few to preliminarily associate COVID-19 mortality with long-term PM2.5 exposures[2]. It has not yet undergone peer-review. We caution the Agency and panel from relying solely on the findings from this and similar studies to determine where to allocate resources and time. A review of Wu et al. revealed some limitations that need to be addressed, especially, if the Agency chooses to pursue this line of research.

Note: The researchers recently updated their findings and dropped the associated increase in COVID-19 cases from 15% to 8%, within two weeks of study's publication. An action that suggests some fragility in the overall study results, and sets a precedent that the findings will likely continue to change due to the preliminary nature of the work.

Below, please consider some of our concerns related to Wu et al., paper.

- **The study design, both ecological and cross-sectional, does not allow for causal inference. Predominately due to the "ecologic fallacy," that is the potential lack of correspondence between associations identified in aggregate population groups (the county in this case) with the individual level**.
    - Although ecological studies are appropriate in the early phase of research when the baseline level of knowledge and understanding is limited, results should be viewed with caution and require confirmation from additional studies once (1) data are validated, and complete (which is not the current situation) and (2) more definitive study designs and/or refined exposure assessment and outcomes ascertainment methods can be utilized (e.g., use of individual-level electronic health record data that would validate the cause of death and underlying health conditions and potentially provide individual-level confounder data.)
- **In the original publication released April 5, Wu et al. did not sufficiently explore the role that the number of hospital beds is playing in the analysis of PM2.5 and COVID-19 mortality**.

[2] Wu, X., Nethery, R. C., Sabath, B. M., Braun, D., & Dominici, F. (2020). Exposure to air pollution and COVID-19 mortality in the United States. *medRxiv*.

- Perhaps the number of beds is, to some extent, a surrogate for death, because most reported COVID-19 deaths occurred in hospitals – inpatient beds. Similarly, the number of beds might be an indicator of healthcare quality. The more beds that are available, the higher the quality of care could be for COVID-19 patients. Therefore, the number of beds could be causal in the COVID-19 patient outcomes. At this time, we simply do not know what the relationship is between number of hospital beds, estimated county-level PM2.5 concentrations, and COVID-19 mortality. The relationship between PM2.5 and COVID-19 mortality was highly sensitive to the number of hospital beds, and as such, is worthy of further exploration.

- **Compositional Confounding**
  - Ample empirical evidence exists showing that areas with high PM2.5 also have a high prevalence of socioeconomic status (SES)-related characteristics and associated outcomes (e.g., low educational attainment, low income, obesity, cardiovascular disease) and even genetic similarity. The technical term for this situation is 'compositional confounding,' which has also defied statistical adjustment, especially in cross-sectional and ecological studies with aggregate-level data such as in Wu et al. 2020. The development of methods to address this form of confounding is much needed.
- **Poor correlation between ambient air concentration and true individual-level PM2.5**
  - Despite their state-of-the-art exposure assessment methodologies, neither van Donkelaar et al. (2019)[3] nor Di et al. (2019)[4] can overcome the extensive research that demonstrates the poor correlation between ambient air concentrations and true individual-level PM2.5 exposure. The inherent lack of agreement between ecological and individual level exposure can lead to exposure misclassification with limited statistical remedy.

[3] Van Donkelaar, A., Martin, R. V., Li, C., & Burnett, R. T. (2019). Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. *Environmental science & technology*, *53*(5), 2595-2611.
[4] Di, Q., Amini, H., Shi, L., Kloog, I., Silvern, R., Kelly, J., ... & Wang, Y. (2019). An ensemble-based model of PM2.5 concentration across the contiguous United States with high spatiotemporal resolution. *Environment international*, *130*, 104909.

- **Lack of information on residential location and time-activity patterns creates the potential for exposure misclassification**
    - This lack of information increases the potential for exposure misclassification with the length of time used for estimating PM2.5 exposure. In addition, the place of death is used as the location to assign PM2.5 exposure rather than the location of residence, further increasing the potential for exposure misclassification.
- **Nearly 80% of the counties did not report any COVID-19 deaths**
    - Of all US counties included in the analysis, 77% of the counties did not report any deaths as of April 4, 2020 (the closing date for the current study). The reason none of these counties had any COVID-19 deaths is because they hadn't had any reported cases of COVID-19 by then. Although negative binomial regression is specifically suited to handle "zero counts" (i.e., counties with no deaths), it is not clear what implications having 77% of U.S. counties with no COVID-19 deaths means for the results observed and their interpretation (especially as new cases emerge and deaths increase across the US).

APPENDIX 2 - DECISION MAKING METHOD

Using the Burns et al. (2019) checklist allows research planners to quickly assess if a study protocol can be used in risk assessments or public health decisions. The following applies the method to Wu et al.[5]

Hazard identification

- While the authors confirm which outcome is of interest (COVID-19 mortality), they don't fully confirm exposure characterization. The evidence that is needed to suggest whether those who died from COVID-19 were exposed to the estimated PM2.5 concentrations is lacking.
- While the Agency has implied that they will not address the issue of pre-existing conditions, knowing if the confounders (comorbidities) were controlled for is helpful. If someone had any other preexisting condition that increased their susceptibility to COVID-19, this would be a significant source of confounding. The presence of these comorbidities (e.g., obesity, high blood pressure) isn't necessarily the result of exposure to PM2.5 but could directly impact the outcome for COVID-19 patients.

Dose-response

- The authors do not attempt to explicitly show whether counties with lower estimated PM2.5 concentrations showed lower COVID-19 mortality rates as compared to counties with higher estimated PM2.5 levels. It would be valuable to see the range of estimated PM2.5 concentrations for counties with no confirmed COVID-19 cases, and how they compare to the PM2.5 levels in counties with COVID-19 cases.
- No plots to show linear associations between PM2.5 and mortality are shown.
- Temporality, the strength of the association, and specificity were not appropriately explored.

[5] Burns, C.J., LaKind, J.S., Mattison, D.R., Alcala, C.S., Branch, F., Castillo, J., Clark, A., Clougherty, J.E., Darney, S.P., Erickson, H. and Goodman, M., 2019. A matrix for bridging the epidemiology and risk assessment gap. *Global Epidemiology*, *1*, p.100005.

- Wu et al. did not report the *zero-sub* model? This model accounts for an excess of zeros by counties not yet eligible for COVID-19 deaths (e.g., the 77.8% of counties that don't have any confirmed cases). This information would be valuable to contribute to the overall discussion.
- As far as concordance with previous studies, since this Pandemic is unprecedented, there are no alternative datasets to compare against to check for comparability in the data.

Exposure assessment

- The authors present very little information that characterizes a COVID-19 patient's exposure to estimated PM2.5 concentrations. They don't provide any information on the source or rate and transport of PM2.5. This information should be included in the limitations of the study.
- What is the proportion of actual measured monitor data for PM2.5 estimates? Wu et al. used satellite measurements and modeling results, in addition to measured monitor data to estimate PM2.5 concentrations for their analysis. Satellite and modeling results introduce uncertainty in the estimates, and though the authors mention the results were extensively cross validated, they don't cite how this validation was done.