Clean Air Scientific Advisory Committee (CASAC)

A Federal Advisory Committee to the U.S. Environmental Protection Agency

April 22, 2022

EPA-CASAC-22-003

The Honorable Michael S. Regan
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Consultation on the EPA's *Integrated Review Plan for the National Ambient Air Quality Standards for Lead. Volume 2: Planning for the Review and the Integrated Science Assessment (March 2022)*

Dear Administrator Regan:

The 2021 Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel, hereafter referred to as the Panel, met on April 8, 2022, to provide a consultation on the EPA's *Integrated Review Plan for the National Ambient Air Quality Standards for Lead. Volume 2: Planning for the Review and the Integrated Science Assessment (March 2022)*. The Panel generally found the Draft IRP Volume 2 to be a useful roadmap for the development of the Integrated Science Assessment.

The Science Advisory Board Staff Office has developed the consultation as a mechanism to provide individual expert comments for the EPA's consideration early in the implementation of a project or action. A consultation is conducted under the normal requirements of the Federal Advisory Committee Act (FACA), as amended (5 U.S.C., App.), which include advance notice of the public meeting in the Federal Register.

No consensus report is provided to the EPA because no consensus advice is given. Individual comments from the Panel are provided in Enclosure A.

We thank the EPA for the opportunity to provide advice early in the review process. The Committee does not expect a formal response from the EPA.

Sincerely,

/s/

Dr. Elizabeth A. (Lianne) Sheppard, Chair
Clean Air Scientific Advisory Committee

Enclosure

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names or commercial products does not constitute a recommendation for use. The CASAC reports are posted on the EPA website at: https://casac.epa.gov.

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
Lead Review Panel (2021)

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Dr. Elizabeth A. (Lianne) Sheppard, Rohm and Haas Professor in Public Health Sciences and Professor, Department of Environmental & Occupational Health Sciences and Department of Biostatistics, Hans Rosling Center for Population Health, University of Washington, Seattle, WA

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Dr. James Boylan, Assistant Branch Chief, Air Protection Branch, Environmental Protection Division, Georgia Department of Natural Resources, Atlanta, GA

Dr. Judith C. Chow, Nazir and Mary Ansari Chair in Entrepreneurialism and Science and Research Professor, Division of Atmospheric Sciences, Desert Research Institute, Reno, NV

Dr. Deborah Cory-Slechta, Professor, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Dr. Christina H. Fuller, Associate Professor, Department of Population Health Sciences, Georgia State University School of Public Health, Atlanta, GA

Dr. Philip E. Goodrum, Principal Toxicologist, GSI Environmental Inc., Fayetteville, NY

Mr. Perry Gottesfeld, Executive Director, Occupational Knowledge International, San Francisco, CA

Dr. Daven Henze, Professor, Mechanical Engineering, University of Colorado Boulder, Boulder, CO

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Dr. Joel G. Pounds, Retired, Linden, MI

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Dr. William Stubblefield, Professor, Department of Environmental and MolecularToxicology, Oregon State University, Corvallis, OR

Dr. Kathleen Vork, Staff Toxicologist, Office of Environmental Health Hazard Assessment, Air Toxicology and Risk Assessment Section, California Environmental Protection Agency, Oakland, CA

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Enclosure A

Individual Comments from Members of the CASAC Lead Review Panel on EPA's *Integrated Review Plan for the National Ambient Air Quality Standards for Lead. Volume 2: Planning for the Review and the Integrated Science Assessment (March 2022)*

Mr. George Allen

Overall the IRP is well written and addresses the key topics for the ISA. Section 2 presents a useful summary of the scope of the ISA and the policy-relevant issues that the ISA will support for the Policy Assessment document for both the primary and secondary standards.

Section 3 provides details on the scope and scientific questions for the ISA. Page 3-1 at the bottom says "…specific policy-relevant questions related to the available scientific evidence that have been identified for consideration in the Pb ISA are described in the section 4." Does this mean the questions presented in Section 3.3 of this IRP? Section 4 is References. The questions presented in Section 3.3.1 for air quality sources, transport, and fate, and Section 3.3.2 for exposure, toxicokinetics, and biomarkers are appropriate.

Causality determinations as shown in Tables 3-1 and 3-2 for the last review are an important component of an ISA, as are any changes from the previous review in either direction, providing a summary of any new evidence for each category since the 2011 literature cutoff. The NASEM is nearing completion of their review of frameworks to assess causality of health and welfare effects of air pollutants in EPA's Integrated Science Assessments. While I don't expect that review to recommend substantial changes to the weight of evidence approach EPA has been using for many years, it may be worth noting that the results of that review will be incorporated into this ISA as appropriate.

The material presented in Section 3.3.3.2 Other Science Questions: Health effects, uncertainties, and biological plausibility is appropriate and thorough. The question on page 3-11 "To what extent is new evidence available regarding mechanisms for nervous system effects associated with lower blood Pb levels (i.e., <5 µg/dL in young children)?" is a very appropriate topic for this ISA. Presumably the 5 µg/dL value used here is based on the CDC's previous population-based blood lead reference value for screening of young children that was lowered to 3.5 last fall to reflect ongoing decreases in blood lead levels. While this CDC value is not a health-based guideline, it does reflect the ongoing concern regarding health effects even at low levels.

Although not directly relevant to this NAAQS review, the expected EPA proposal of an endangerment finding for leaded AvGas later this year that was announced last January is closely related to the exposure and health issues that are part of this review, and it would be useful to include information on that process.

Section 3.3.4 is a brief summary of Pb-related health effects for at-risk populations or life-stages, including children and those with pre-existing disease). This is an important component of the ISA. This section states that "… emphasis will be placed on the health effects for which there is a causal or likely to be a causal relationship with exposure to Pb." Outcomes that are "Suggestive of a Causal Relationship" should also be covered in this section to some extent.

Section 3.3.5 covers ecological (welfare) effects. The questions listed in Section 3.3.5.2 are thorough and appropriate.

Dr. James Boylan

Included in the ISA are causality determinations that are then used in the risk and exposure assessment (REA) and policy assessment (PA) documents. The causal determination framework proposed by EPA is based on weight-of-evidence and professional judgement leading to conclusions than can't be replicated by other scientists.

For example, the 2018 draft ISA for PM found that there was a "likely to be a causal" relationship between long-term $PM_{2.5}$ exposure and nervous system effects; between long-term ultrafine particulate (UFP) exposure and nervous system effects; and between long-term $PM_{2.5}$ exposure and cancer. However, the CASAC letter dated April 11, 2019 to Administrator Wheeler stated, "…the CASAC finds that the Draft ISA does not present adequate evidence to conclude that there is likely to be a causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects; between long-term ultrafine particulate (UFP) exposure and nervous system effects; or between long-term $PM_{2.5}$ exposure and cancer." This is an example of two different groups of scientists looking at the same evidence and coming to different conclusions on the causal relationships. In the 2019 final ISA for PM, EPA agreed that the causal relationship between long-term ultrafine particulate (UFP) exposure and nervous system effects should be changed from "Likely to be Causal Relationship" to "Suggestive of, but not Sufficient to Infer, a Causal Relationship". This is an example of the same group of scientists looking at the same evidence and coming to a different conclusion.

The 2019 CASAC recommendation that a "more explicit, systematic, and transparent process" be used for determining causal relationships resulted in the National Academies of Sciences, Engineering, and Medicine (NASEM) committee on "Assessing Causality from a Multidisciplinary Evidence Base for National Ambient Air Quality Standards," which is currently in deliberations (https://www.nationalacademies.org/our-work/assessing-causality-from-a-multidisciplinary-evidence-base-for-national-ambient-air-quality-standards). EPA should review the findings of the NASEM committee and incorporate any recommended changes into their causal determination framework prior to developing the draft ISA for Pb.

Dr. Judith Chow

The Integrated Review Plan (IRP) for lead (Pb) is well written and summarizes policy relevant issues for the current reviews with a plan for the Integrated Science Assessment (ISA) for NAAQS lead. The following subjects merit more discussion:

- Particle Size Distribution:

Volume 1 states that the rationale to retain Pb-TSP as the indicator is based on the assertion that "…the differences in particulate Pb captured by the TSP and PM_{10} monitors may be a factor of two in some areas, and all particle sizes contribute to Pb in blood and associated health effects" (Page 3-7, Section 3.3, The Primary Standard, Volume 1 IRP). The specific question listed in Section 3.3.3 on "Source to Concentration- Air Quality Atmospheric Science, Fate and Transport" asks "What new evidence is available regarding the use of monitors to characterize Pb in different particle size fractions (e.g., TSP, PM_{10}), and the relationships between them, accurately?" It is true that a Pb-PM_{10}-based standard may not effectively detect ultra-coarse particles. However, the lower size fractions (including nanoparticles and ultra-fine particles) from anthropogenic sources such as lead smelters, aviation engine exhaust and consumer products may pose greater health risks owing to their greater penetration into human airways. A broader range of particle sizes (~3 nm to 30 μm) needs to be characterized to better understand inhalation properties and dose-response relationships.

- Spatial and Temporal Variations:

As of March, 2022, only 10 areas in the U.S. were classified as nonattainment for the NAAQS Pb (U.S. EPA, 2022), including 4 counties in Southeast Missouri that have experienced the world's largest known lead concentrations (Appold and Garven, 1999). As Pb concentrations vary by geology, ore deposits, and mining processes, their environmental pathways in airsheds and waterways need to be examined. The National Research Council report (Bouwer et al., 2017) on strategies for Pb-source attribution associated with mining activities at Superfund sites highlights Pb environmental dispersals and provides a good overview of Pb sources, transport, and exposures.

As coarse particles (> 2.5 μm) have high gravitational settling velocities and can deposit onto surfaces within minutes to hours after suspension, they are unlikely to transport long distances by direct wind action (except for tornadoes). Dust suspension and deposition within the neighborhood scale (< 4 Km) needs to be examined. The statement in Section 3.2 on "Scope of the Lead ISA", notes that "Effects observed at or near Pb concentrations measured in ambient soil, sediment, and water for which local contamination is not thought to be a primary contributor will be emphasized" (Page 3-5, Volume 2, IRP). This needs to be clarified.

References

Appold, M.S., Garven, G., (1999). The hydrology of ore formation in the Southeast Missouri district: Numerical models of topography-driven fluid flow during the Ouachita Orogeny. Economic Geology and the Bulletin of the Society of Economic Geologists, 94(6), 913-935.

Bouwer, E.J., Barton, M.D., Betterton, E.A., Blum, J.D., Brantley, S.L., Chow, J.C., Fendorf, S.E., Hazen, R.E., Johnson, C.E., Manton, W.I., Miller, J.R., O'Day, P.A., Toll, J., White, W.H., Mantus, E.K., Wassel, R., Karalic-Loncarevic, M., Rose-Crawford, R., Dawson, T., (2017). Consensus study report: Investigative strategies for lead-source attribution at superfund sites associated with mining activities. The National Academies Press, Washington, DC. https://www.nap.edu/download/24898

U.S.EPA, (2022). Lead (2008) designated area/state information. U.S. Environmental Protection Agency, Washington DC. https://www3.epa.gov/airquality/greenbook/mbtc.html

Dr. Deborah Cory-Slechta

In general, the proposed plans seem sufficient, and the proposed questions relevant.

However, in regard to toxicokinetics and biomarkers, it may be time to re-evaluate/re-think aspects of this. It is increasingly evident that metals such as Pb, that are contaminants of air pollution, particularly the ultrafine particle component, travel directly up the olfactory and trigeminal nerves into the brain. While there is limited data on brain Pb levels, it has been shown in other cases that blood levels of a metal do not reflect its brain concentrations, since these particles are by-passing the blood brain barrier. It may be that such a re-evaluation is not possible, but kinetic models do not recognize this. It is potentially critical with respect to air Pb concentrations. If blood Pb does not reflect changes in actual brain concentrations, it may be that the use of blood Pb is not a valid marker for changes in brain Pb. For example, the intranasal instillation of Fe2O3 nanoparticles to rats over 7 days increased the Fe brain levels while significantly reducing the serum Fe levels. Such discrepancies between the brain and serum levels are also seen in neurodegenerative diseases that include elevated brain Fe—e.g., PD. While data for airborne Pb may not be sufficient, this is a potential issue that should at least be considered.

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Askri, D.; Ouni, S.; Galai, S.; Arnaud, J.; Chovelon, B.; Lehmann, S.G.; Sturm, N.; Sakly, M.; Seve, M.; Amara, S. Intranasal instillation of iron oxide nanoparticles induces inflammation and perturbation of trace elements and neurotransmitters, but not behavioral impairment in rats. Environ. Sci. Pollut. Res. Int. 2018.

Costa-Mallen, P.; Gatenby, C.; Friend, S.; Maravilla, K.R.; Hu, S.-C.; Cain, K.C.; Agarwal, P.; Anzai, Y. Brain iron concentrations in regions of interest and relation with serum iron levels in Parkinson disease. J. Neurol. Sci. 2017, 378, 38–44.

Szabo ST, Harry GJ, Hayden KM, Szabo DT, Birnbaum L. Comparison of Metal Levels between Postmortem Brain and Ventricular Fluid in Alzheimer's Disease and Nondemented Elderly Controls. Toxicol Sci. 2016 Apr;150(2):292-300. doi: 10.1093/toxsci/kfv325. Epub 2015 Dec 31. PMID: 26721301; PMCID: PMC4881830.

Dr. Christina H. Fuller

Overall this document provides an appropriately detailed integrated review plan (IRP) for the National Ambient Air Quality Standard Lead (Pb). The IRP as presented in Volume 2 should produce the necessary scientific information in order to create an appropriate Integrated Science Assessment (ISA).

Recommendations:

I have two sets of major comments that I recommend be implemented in the IRP.

First, I recommend a change to 3.3.3.2 Other Science Questions to Associations with Health Outcomes. The assessment of and reduction in the incidence of adverse health effects is a main aim of the review process, so elevating Health Effects to a higher level makes sense. Then both uncertainties and biological plausibility can fit under this heading.

Next, the plan detailed in Section 3.3.4 At-Risk Lifestages and Populations and Public Health Impact should be spread across other sections of the document. Keeping this section on its own may result in a less rigorous assessment of the scientific literature as it pertains to at-risk lifestages and populations. Integration of At-Risk populations should be well-integrated into the process and not an aside. At-risk populations are identified as such either because they are disproportionately exposed to Pb or that they are susceptible to adverse effects due to some factor or experience. Therefore, (1) identifying information detailing disproportionate exposures affecting some populations would be best placed in Section 3.3.1 Source to Concentration. (2) Gathering data on susceptibility should be placed in the re-named section 3.3.3.2 Associations with Health Outcomes (formerly named 3.3.3.2 Other Science Questions). In addition, (3) discussion of the mechanisms that result in increased health effects among at-risk populations should be placed in 3.3.3.2 Biological Plausibility.

Suggestions:

Section 3.3.2 Exposure, Toxicokinetics, Biomarkers

- Include “and interpretation” to the following sentence of bullet number 6. What new evidence is there regarding the use **and interpretation** of different biomarkers to assess Pb exposure (Pb in blood, bone, urine, hair nails, or teeth?)

Section 3.3.4 At-Risk Lifestages and Populations and Public Health Impact

- Lines 9-10 of this section. Please clarify which race/ethnic populations had increased risk for Pb-related health effects as shown in the 2013 Pb ISA. Stating “being of a certain race/ethnicity” is too vague and should be specified. As noted above, the information contained in this section should be moved to more appropriate sections of the document.

Dr. Philip Goodrum

General Comments

Overall, the IRP Volume 2 document provides a solid framework of topics and questions for the committee to provide meaningful input. References to epidemiological study data are clear, but there is no specific information given with respect to the mechanistic models that are of interest. Given USEPA's ongoing evaluation of the All Ages Model, it would be helpful to understand if USEPA has a specific interest in this tool at this time.

Specific Comments

Section 3.3.2	Bullet 2	The question uses the term *body burden* of Pb (in bone or blood), which, if expressed as an absolute concentration, can be examined from the perspective of different reference levels (e.g., 5 µg/dL or 3.5 µg/dL for a blood lead level (BLL)). In this bullet, or as a separate bullet, the same question should be posed relative to the delta (change) in BLL. The two risk metrics - absolute BLL and incremental change in BLL - have both played a role in evaluations of empirical data and model predictions on interpreting relationships between exposure, BLL, and health outcomes; they remain relevant for many of the charge questions in this document.
Section 3.3.2	Bullet 2	Importantly, the new developments with the biokinetic model should include any verification studies to evaluate model performance relative to epi study data.
Section 3.3.2	Bullet 2	Will the USEPA All Ages model (version 2) be considered in this exercise?
Section 3.3.2	Bullet 4	Connect with discussion of mixtures in Section 3.3.3.2. Accounting not only for how to account for air Pb within a multi-pathway mechanism for body burden, but also how to account for the influence of baseline relative to other stressors: co-contaminants magnitude and relative time course of such exposures (similar peaks, duration, body burdens). Also, the change in baseline of co-contaminants and how that affects change in Pb exposure-response relationship - do exposures need to be co-occurring, or staggered in time?

Section 3.3.3.2	p. 3-11, bullet 1	not only mixture effects, but influence of co-contaminants on dose-response. Will baseline be defined beyond BLL, but also as other constituents? If yes, what is evidence to support the definition of exposure (external dose or internal dose) for such co-contaminants?
Section 3.3.3.2	p. 3-11, bullet 2	The introduction to Uncertainties refers to consistency between epi findings and toxicological effects in terms of observed effects and biological pathways. In addition to effects and pathways (which are components of hazard identification), also relevant is coherence in exposure-response relationships.
Section 3.3.3.2	p. 3-11, bullet 2	The question asks, "To what extent are the observed associations between biomarkers and health outcomes attributable to exposure to Pb rather than co-exposures to other toxic metals or environmental contaminants?" The question presupposes there is no interaction ("…attributable to …Pb..rather than co-exposure to other toxic metals..". Consider revising "…rather than…" to "…influenced by co-exposure…."
Section 3.3.3.2	p. 3-11, bullet 2	It is not obvious what decision process will be used to identify relevant co-contaminants. One approach might be to consider chemicals that share a common adverse outcome pathway with Pb; however, given the rather long list of health outcomes (Table 3-1), this approach would not be very discriminatory (i.e.., most priority pollutants share one or more of the same outcomes as sensitive health effect endpoints). This may become a relevant data gap that the committee is charged with discussing, and perhaps providing input/suggestions for an effective decision process.
Table 3-1	pp. 3-8 and 3-9	I agree with the points made during the April 8 webinar regarding deficiencies in the use of IQ scores as a primary metric of neurotoxicity/cognitive function deficits. Bullets following the table are sufficiently open ended to allow for input by the committee; for example, "Does the evidence base…call into question the causality determinations made in the 2013 ISA?"

Section 3.3.5.2	p. 3-16, multiple bullets	I agree with the points made during the April 8 webinar regarding consideration of mixtures / co-exposures when evaluating studies of Pb bioavailability, particularly from studies involving evaluations of tissue levels of receptors exposed at contaminated sites. I would recommend we extend this concept to include interpretation of toxicity /health effects. This applies to both terrestrial and aquatic systems.

Mr. Perry Gottesfeld

Policy Relevant Issues:

1) This is not clear or perhaps a word is missing here:
   p. 2-4 "To what extent are the air-related risks remaining upon just meeting the current Pb standard important from a public health perspective?"

2) The policy question that I do not see outlined in this section is: How does this CASAC review process take account of ongoing EPA activities that directly impact the policy-relevant issues of the NESHPA standard under this review including:

   a. EPA proposed NESHAP standard for Lead Acid Battery Manufacturing;
   b. EPA Draft Strategy to Reduce Lead Exposures and Disparities in U.S. Communities;
   c. EPA plan to issue a proposed endangerment finding for piston-engine aircraft that run on leaded fuel in 2022;

3) The framing of policy questions may be key to evaluating health information in light of the lower blood lead level targets adopted since the last CASAC review. In particular, how does the ambient air standard correspond with other federal guidance on childhood lead poisoning prevention? Given the lower CDC Blood Lead Reference Value (3.5 ug/dl) does the existing standard adequately protect children by maintaining blood lead levels below this action level?

4) Sections 2.1 and 2.2 mention that there will be an evaluation of the averaging time for the air standard but it does not mention the applicability of the existing standard for short-term emissions from construction activities that may result in higher emissions for several days or weeks. Such activities may include removal of road marking paints, maintenance of steel structures, and exposures during abrasive blasting of lead paint. In addition, studies of lead emissions from short term use of lead in gasoline during NASCAR events may be relevant.

5) Section 3.3.2 outlines questions regarding lead exposure but does not directly question if there are differences in airborne lead exposure that may account for some part of the disparities in blood lead levels between racial and income groups. The document refers to race/ethnicity as a risk factor and "biological factor" but fails to ask the question if air emissions differ for race/ethnicity based on geographic residence/ neighborhood patterns. Aside from housing, whatever geographic and environmental factors influence lead exposure patterns by racial/ethnic background?

6) Section 3.3.2 considers contributions from different sources. To what extent does the past and ongoing use of lead chromate and other lead pigments in "industrial" paints on roadways, bridges, and other steel structures contribute to ambient airborne lead during

construction/ demolition activities? (See Lee et al. 2016 and Le Galley et al. 2013 and White at al. 2014) What are the contributions from these sources in long-range (transboundary) transport?

7) Section 3.3.3 discusses causality determinations and notes the term "externalizing behaviors" used during the previous ISA that groups multiple behaviors. However, it may be worth considering if there is evidence for a separate causality determination for violent behaviors? Do more recent studies including Emer et al. 2020 provide support for evaluating causality for violent behaviors aside from externalizing behaviors?

8) Additional issues that were raised during the April 2022 meeting that should be further investigated include:

    a. Ways to account for metal mixture exposures that include lead;
    b. Contributions from wildfire smoke;
    c. An unpublished report linking AVgas emissions around an airport in California with elevated blood lead levels and if this study properly accounts for blood lead levels below the limit of detection for the test methods used. (see: Leaded Aviation Gasoline Exposure Risk at Reid-Hillview Airport in Santa Clara County, California).

References

Dietrich, M., Wolfe, A., Burke, M., & Krekeler, M. P. (2019). The first pollution investigation of road sediment in Gary, Indiana: anthropogenic metals and possible health implications for a socioeconomically disadvantaged area. Environment international, 128, 175-192.

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Hollingsworth, A., & Rudik, I. (2021). The effect of leaded gasoline on elderly mortality: Evidence from regulatory exemptions. American Economic Journal: Economic Policy, 13(3), 345-73.

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LeGalley, E., Widom, E., Krekeler, M. P., & Kuentz, D. C. (2013). Chemical and lead isotope constraints on sources of metal pollution in street sediment and lichens in southwest Ohio. Applied Geochemistry, 32, 195-203.

White, K., Detherage, T., Verellen, M., Tully, J., & Krekeler, M. P. (2014). An investigation of lead chromate (crocoite-PbCrO4) and other inorganic pigments in aged traffic paint samples from Hamilton, Ohio: implications for lead in the environment. Environmental earth sciences, 71(8), 3517-3528.

Dr. Daven Henze

The Integrated Review Plan (IRP) for the National Ambient Air Quality Standards for Lead, Vol 2, provides a comprehensive overview of the plans for the development of the Integrated Science Assessment (ISA). Overall, the IRP lays out a plan that is well structured, mindful of past scientific issues associated with assessment of the health impacts of Pb, and well designed to evaluate how knowledge has evolved since the previous review cycle. As a planning document, it is appropriately high-level, and as such will provide flexible guidance for the ISA. I do have specific comments for areas where some additional focus or emphasis is warranted for inclusion within the ISA. Though it is likely that these considerations could fit in some way within the scope of the IRP as currently written, I've provided comments on such aspects below, along with a few other minor suggestions and requests for clarification.

One aspect of uncertainty that I didn't see explicitly mentioned is discussion of the extent to which regions with high air Pb emissions, or high ambient Pb concentrations, may also regions where the population exposure to multimedia Pb (e.g., paint, water) would be high regardless of an air-based source. Accounting for this type of correlation would contribute to mechanistic understanding of the air/blood Pb ratios. Places where this might be considered within the IRP include the high-level science questions on page 2-4. This point is perhaps within the scope of paragraph 4, section 3-3, but it would perhaps be useful to see it considered more explicitly. In Section 3.3.2, 2nd bullet: Is there also new evidence for causes of correlation of blood Pb with ambient air Pb?

I also wonder the extent to which the ISA will examine disproportionate exposure to Pb and corresponding health impacts in specific demographic communities. For example, a suggested follow up to sub-bullet 5 on page 2-4 could be: Are there any communities who are disproportionately sensitive to Pb exposure (besides children), or are there any communities who are disproportionately exposed to Pb?

Section 3.3.4 gets at the first half of this question, as it addresses it from the standpoint of populations being otherwise at-risk. However it could also be useful to see this discussion expanded to consider disproportionate distributions of Pb sources and ambient concentrations, as has been identified for other criteria pollutants such as NO2.

I was somewhat concerned by the focus on reducing the uncertainty in the understanding of health effects of low-levels of Pb exposure in combination with the removal of Pb TSP measurements from NCORE sites. While the latter may be justified within the context of known effects at the time of the previous review, it would not seem to help address the scientific goals of understanding effects at lower levels. I would also like to see the question of Pb's distribution in TSP compared to PM2.5 and PM10 elevated. With these factors in mind, I would consider adding the following points:

- As an additional consideration for the questions on pages 2-4, 2-5 (and in section 2.2 as well):
    - To reduce uncertainties in the evidence of effect at exposure levels lower than previously observed, how critical is it to have sustained measurements of ambient low-levels of Pb TSP in at-risk populations throughout the US? This may more specifically focus on the relationship between Pb in ambient air and children's blood at low levels, and the ability to assess this given the loss of Pb TSP measurements at NCORE sites.
- For the list on page 2-5 (and in section 2.2 as well):
    - What is the relationship between Pb levels in TSP compared to PM10 and PM2.5, and what uncertainties are present in using measurements of the latter as proxies for the former?
- 3.3.1, questions on Sources, Fate & Transport…
    - There are a lot of references to "new evidence" however an additional consideration is a more recent lack of evidence, given reduction in Pb monitoring. Could there be a question along the lines of "To what extent is evidence gathering hindered or supported by changes in Pb monitoring programs"? I'm concerned that SLAM sites, being focused around large sources, may not be useful for reducing uncertainty in the evidence of Pb exposure health impacts for sensitive populations, who may not live directly next to the largest sources.

General: the scoping section talks frequently of integration of previous assessments with more recent evidence, which is great. For example, consider the paragraph spanning pages 3-4 and 3-5. In addition to integrated summary of the current state, it would also be valuable to present the current state of knowledge in the context of changes since the previous ISA, to more readily ascertain how knowledge and uncertainty has evolved. This is because a lot of the science questions stated in section 2 are framed in the context of evolving knowledge (e.g., language such as: "Does the current evident alter our conclusions from the last review regarding…." "Does the newly available evidence alter or further inform our understanding of…"). While this may be the plan anyways, it could be useful to state this explicitly.

Section 3.3.3.2, Uncertainties: This section seemed a bit short in the broader context of assessing uncertainties, but many of the previous science questions specifically target uncertainties of one form or another, so that is probably OK. One point though that does stand out is the question related to seasonal trends. What is the interest in this? Would seasonal trends point to other co-founding factors, or to specific sources? Is there a reason there is an interest in seasonal trends alone rather than diurnal, daily, or annual? I understand the attainment metric is seasonal, but for the ISA the science scope should fundamentally consider the importance of trends across a wide variety of scales, to evaluate the appropriateness of the current metric, were that to be the intended goal here. Or maybe questions related to trends should be in another section.

Editorial:

- One of the sub-bullets on 2-4 is also a main bullet (2nd one), which is just a bit odd. Maybe only a single level of bullets is needed for this list.
- The EPA administrator could be referred to as “they” or “Administrator” rather than “he” in a few locations in Vol 1 and 2 of the IRP where the text is discussing a non-specific administration.

Dr. Howard Hu

- Overall, good outline.
    - How about anti-social behavior/violence/criminality as an outcome? (Note: I am working with Ellen Kirrane, Rachel Shaffer, and others in the EPA IRIS office and other colleagues on a systematic review of this topic).

- Specific comments
    - Page 2-3: Regarding populations that may be at increased risk of health effects --- How about pregnant women/prenatal exposures? The stated focus on "young children and on early childhood exposures" should probably be extended to prenatal exposures given evidence indicating that they may have impacts on intelligence that are distinct from and add to postnatal impacts.
    - Page 2-5: I'm not that familiar with Pb-TSP as an indicator.
    - Page 3-7: discussion of exposure, toxicokinetics, and biomarkers is good
        - Given that (a) as a biomarker of cumulative exposure, bone lead levels (measured non-invasively using XRF) has turned out to be better than blood lead levels at predicting a number of outcomes; but (b) measurement of bone lead remains an expensive, time-consuming process, are there ways of modeling or predicting bone lead levels? (short answer: yes).
    - Page 3-8: Summary of causality determinations: pretty good. BUT:
        - Reduced renal fx is "suggestive"? Evidence may be better than "suggestive".
        - Repro and Developmental effects: "Causal", but causal for what specific adverse outcomes?
        - Need to discuss impacts on intelligence that are separate from childhood exposures, e.g., mobilization of lead from maternal bone, etc.
        - How about lifespan exposure-outcomes, e.g., the evidence from animal studies that early life exposures may predispose to late-life expression of outcomes consistent with Alzheimer's? No proof yet, but the question has been raised?
        - Effects on bone and teeth: "likely causal relationship", but what specific outcomes are we talking about.
        - Cancer: likely causal? Haven't seen much in terms of epi evidence. This may be where animal evidence (which is strong) and human evidence may diverge.
        - Do each of these need to go through a systematic review process? If so, which type?
    - Page 3-11: recent v. past---an important issue. A critical example relates to the recent Lanphear study in Lancet Public Health on BLLs and CV mortality. What do the BLLs actually represent? Need to parse out whether they represent recent/on-going exposures v. mobilization of lead from skeletal stores, and

therefore are a proxy for cumulative exposures. The implications of one v. the other are huge.

- Page 3-12: important acknowledgment of at-risk lifestages and populations, but the discussion is confined to potential vulnerabilities related to children, certain race/ethnicities, poor nutrition. But there also is growing evidence of genetic susceptibilities involving fairly common allelic variants. Also growing evidence of sex-based differences in epi studies (the animal toxicology evidence for this is acknowledged in 3-10); and vulnerabilities related to co-morbidities, such as type II diabetes.

Dr. Chris E. Johnson

The IRP is very good. It has clearly been informed by the previous NAAQS processes and discussion related to previous Integrated Science Assessments (ISAs). It captures the principal objectives of the ISA well, with few omissions. It is a good road map for the analysis that lies ahead.

Section 2.1, Questions, pp. 2-3, 2-4

Are there indicators or tests of cognitive function that are better than IQ for the purpose of establishing a relationship between Pb in blood/bone and intellectual development or functioning?

Section 2.2, Questions, pp. 2-8, 2-9

Does newly available evidence alter or inform our understanding of the resuspension and transport of previously deposited particles?

Have "critical loads" methodologies, and the data required to use them, advanced sufficiently to consider using this approach to inform the development of a secondary standard for Pb?

Section 3.3.2, p. 3-10

It seems certain that the CDC will recommend a blood Pb reference level lower than the 5 ug/dl that has been used to estimate a corresponding air Pb value for regulatory purposes. Will the ISA and/or the Risk/Exposure Assessment incorporate an assessment of the relationships between blood Pb and air Pb, and blood Pb and cognitive function at lower blood Pb levels?

The impact of a given air Pb exposure level is layered on top of other factors and exposures. Specifically, we know that there are significant health disparities related to socio-economic and racial/ethnic factors. The ISA refers to these as "risk factors" or "biological factors," but is there an intent to examine differences in response relationships in different populations?

There have been notable successes in reducing the exposure of young children to Pb in air, soil, and paint chips. This a good thing. It also hints that it may be important to look more closely at the risks associated with Pb exposures for pregnant women. There is some evidence in the literature that Pb is a risk factor for both pre-term birth and preeclampsia. It would be worth including questions focused on this period of human development in the ISA.

Section 3.3.4, p. 3-12

It may be worth adding a question related to workplace/school/day care exposures, especially in "common" occupations and spaces.

Section 3.3.5.2, p. 3-16

Fifth bullet under both "Terrestrial Ecosystem Effects" and "Aquatic Ecosystem Effects": What is meant by the second question in these bullets? Specifically, is there a particular sort of "response," or directionality of response, that is the focus of investigation?

Section 3.3.5.2, p. 3-16

Is there new evidence regarding the actual or potential mobilization and transfer of "legacy" Pb from terrestrial to aquatic ecosystems?

Dr. Susan Korrick

I think there are several areas where the Draft IRP (Vol 2) could expand/refine its focus. These are areas that have come to light since the last review (2013 ISA; 2011 literature cut off) and/or are important to consider going forward to optimally review the NAAQS for lead as, over time, lower level lead exposures are generally observed. These areas fall into 5 broad categories and are relevant to the primary (human health-based) standard:

1. <u>The definition of at-risk populations re. susceptibility to adverse health impacts of lead exposure</u>.

    a. Extensive and robust literature supports a focus on young children (and neurodevelopment) as the most susceptible population (and health outcome) upon which regulations should be based. However, I think it is important to also consider the role of exposures during pregnancy given the potential for prenatal lead exposures to be important to subsequent child neurodevelopment. As early childhood lead exposures have generally declined, this is likely to become an increasingly important exposure window vis-à-vis risk of adverse child neurodevelopment. Also, differences in minute ventilation (increased) and physiology during pregnancy may enhance uptake of airborne lead in this group. Of note, I concur with other committee members' comments that prenatal lead exposures have an independent (as compared to postnatal/early childhood exposures) impact on child development and, as such are important to consider.

    b. The Draft IRP (Vol 2) enumerates non-chemical risk factors that could potentially alter lead's health impacts – these include genetics, epigenetics, sex, race/ethnicity, co-morbid conditions (e.g. diabetes, obesity), and nutrition (see Draft IRP pages 3-10, 3-12). It is helpful to acknowledge that race/ethnicity measures are social, not biological, constructs. More importantly, previously observed altered susceptibility to chemical exposures based on race/ethnicity is now understood to be a likely consequence of psychosocial stressors associated with being in a minority group, not race/ethnicity. These stressors result from the experience of structural racism, discrimination, etc. Race/ethnicity is often a poor proxy for such measures. As the literature update allows, it will be useful to update the approach to characterizing non-chemical factors (particularly race/ethnicity) that are potential determinants of susceptibility to lead toxicity. During our CASAC Pb Review deliberations it was noted that EPA is very aware of this principle and is applying it to its review of other criteria air pollutants. However, in the Draft IRP (Vol 2), it was not clear that this principle was being applied to the Pb review so it will be helpful to make that explicit going forward.

    c. As an extension of "b" above, it is increasingly clear that there are community and/or geography-based sources of environmental health disparities (e.g., as evidenced by Flint, Michigan's water crisis). In communities where non-airborne

sources of lead exposure are elevated (e.g., the lead exposure from drinking water distribution infrastructure in Flint), an incremental increase in lead exposure from airborne sources may be more detrimental than in communities for which baseline lead exposures are lower. The "supra-linear" dose-response relationship observed for some lead-related outcomes (e.g., lead-associated decrements in childhood IQ are greater for a given incremental increase in blood lead at lower, as compared to higher, blood lead levels), may argue against this concern. But I think there is enough uncertainty on this point, that identifying high risk populations based on community environmental health disparities is important to consider.

d. As was mentioned in our CASC Pb Review deliberations, there is increasing evidence that children who are already doing poorly on developmental measures (e.g., poor school performance) are more adversely impacted by Pb exposure than peers with normative development. This phenomenon can be ascertained with analytic techniques such as quantile regression. This observation highlights the value of considering children with developmental difficulties as another "at risk" population.

2. Biomarkers of lead exposure

a. The choice of lead exposure biomarkers can be critical to assessing the relevance of exposure timing (prenatal, postnatal, adult, etc.) and duration (e.g., acute versus chronic) on health outcomes. E.g., blood lead has a half-life of months, as compared to bone lead with a half-life of years to decades, depending on the bone site. In addition, deciduous tooth lead can be used to ascertain lead exposure in a number of specific prenatal and early childhood exposure windows. Although the literature on childhood exposure and neurodevelopment is critical, as environmental sources of lead exposure are mitigated, I suspect that chronic low-level exposures may be relevant to health risk. Thinking creatively about how to integrate risk of long-term, chronic exposure will be valuable to characterizing lead impacts. Similarly, when low-level exposure is of interest, it is even more important to carefully consider what are the critical exposure windows corresponding to critical health measures (see comments 1a, 3a).

3. Exposure monitoring

a. As was discussed in our CASC Pb Review deliberations, the importance of (increasingly common) short-term exposure events (e.g., wildfires) as well as other intermittent high exposure risk events (e.g., demolition of steel structures or removal of road markings containing lead paint) should be considered as a source of airborne Pb exposure with substantial potential health risks.

4. Latencies between lead exposure and health outcomes

    a. Admittedly, it is challenging to assess health impacts for which there is a long latency between exposure and outcome. But ongoing work supports the potential importance of prenatal and early life lead exposure to subsequent risk of neurodegenerative disorders of aging. Given our aging population and the substantial costs associated with neurodegenerative disorders (re. morbidity, health care, and lost productivity), such outcomes are of increasing relevance to identifying an "adequate margin of safety" regarding the public health impacts of lead exposure. As noted during our CASAC Pb Review deliberations, studying outcomes with long latency to onset after exposure (e.g., prenatal Pb exposure as a risk factor for aging associated cognitive decline) is conditioned on reaching old age so is susceptible to biases that lead to underestimation of associations. It will be important to manage this issue when considering critical health outcomes with long latencies between exposure and onset.

5. Exposure mixtures

    a. State-of-the-art statistical methods are now available to consider impacts of chemical exposure mixtures, even where there are strong correlations among the chemicals (see Draft IRP Vol 2 footnote on page 3-11). These include, e.g., Bayesian Kernel Machine Regression (BKMR), Weighted Quantile Sum regression (WQS), and Quantile-based g-Computation. I think there is an increasing body of robust literature assessing dose-response relationships between lead and health outcomes in the context of real-world mixture exposures. In some cases, lead impacts may be enhanced by the chemical mixture, in others not, but updating the lead literature using exposure mixtures analyses will be valuable.

6. Neurodevelopmental outcomes

    a. There has been a recent paradigm shift in how we assess child neurodevelopment; this is somewhat related to item 1b. Specifically, the use of IQ as a measure of child neurodevelopmental function is considered problematic given concerns about biases in its measurement as well as its historical use to fallaciously promote discrimination and racial/ethnic biases. That said, reliance on IQ has a number of advantages as it has been widely used as an outcome, there is a large body of past literature in which IQ data are available, it is presumed to be a well understood omnibus measure of cognitive function, and it has been used to predict longer term measures of health and productivity. In this complex context, considering other neurocognitive or behavioral measures is important.

Minor Comments/Questions:

1. Page A-1 of the Draft IRP Vol 2 outlines the draft organization of the Pb ISA but does not list neurologic effects (in adults and children) as a separate appendix. Is this outcome embedded under another category (e.g., "Reproductive and Developmental Effects" or "Effects on Other Organ Systems")? I think it's important enough to have its own appendix.

2. In the Draft IRP, Vol 1, approach to the ISA literature search, a clarification would be useful. I appreciate the sophisticated, comprehensive, and thoughtful approach to updating the literature for the new ISA. Given that analyses assessing exposure to chemical mixtures (see above comment 4a) are increasingly common in the epidemiology literature, if lead is not mentioned explicitly as part of the title or abstract of a reference (e.g. terms like "metal mixtures" might be used), what is the strategy for trying to identify relevant exposure mixtures studies?

3. I didn't understand the comment on page 3-10 of the Draft IRP, Vol 2: "Specifically, do recent studies expand…understanding…at the lower range of Pb exposures…particularly in young children for whom observed relationships are less likely to be confounded by Pb exposures earlier in childhood?"

Dr. Bruce Lanphear

Does currently available scientific evidence and exposure- and risk-based information support or call into question the adequacy of the public health protection afforded by the current Pb primary standard?

To what extent has new information altered scientific conclusions regarding the relationships between Pb in ambient air and Pb in children's blood?

Airborne lead remains an important source of lead exposure in the United States. In a study published since the last ISA review, Jennifer Richmond-Bryant and other US EPA scientists found that children's blood lead concentrations rose sharply at airborne lead concentrations (TSP) below 0.15 $\mu g/m^3$ and then decelerated at concentrations > 1.0 $\mu g/m^3$ (Richmond-Bryant, 2014). Richmond-Bryant's study indicates that, for a given exposure, children's blood lead concentrations would decline considerably more by lowering airborne lead concentrations < 0.15 $\mu g/m^3$ than by lowering airborne lead concentrations > 1.0 $\mu g/m^3$. This study indicates that the current primary lead standard fails to protect the public – including children – from lead exposure.

The major sources of airborne lead in the United States include piston-engine aircraft, lead battery recycling operations, and incinerators. The EPA estimated that over 450 tons of lead were emitted by piston-engine aircraft annually, or about 70% of all lead emissions (EPA, 2017). New studies implicate leaded aviation fuel as an important source of lead exposure for communities who live near general airports (Zahran, 2017; Zahran, 2021).

In a study of 448 airports and over 1 million children in Michigan, Sammy Zahran found that children who lived near a general airport had significantly higher blood lead levels after accounting for age of housing stock and industrial sources (Zahran, 2017). Compared with children who resided > 4 km from an airport, children who lived < 1 km, 1–2 km, and 2–3 km were 25.2%, 16.5%, and 9.1% more likely to have a blood lead exceeding 5 µg/dL, respectively. The increase in blood lead concentration was larger for toddlers and children who lived downwind from the airport. Children who lived nearer airports were also more likely to live in households receiving public assistance (Zahran, 2017). If airborne lead monitors around Michigan airports did not exceed the primary lead standard, it indicates that the current primary lead standard fails to protect the public, including a vulnerable subpopulation.

In 2021, Sammy Zahran was asked to conduct a study of childhood lead exposure at Reid-Hillview airport in Santa Clara County, California. Zahran and his team used blood lead tests of 17,000 children collected from January 1, 2011 to December 31, 2020 by the California Department of Public Health. Zahran found that 2% of toddlers who lived > 0.5 miles from the airport had a blood lead > 3.5 µg/dL. In contrast, 5.7% of toddlers who lived within 0.5 miles of the airport had a blood lead > 3.5 µg/dL and 10.5% of toddlers who lived within 0.5 miles of the airport and were downwind of the airport had a blood lead > 3.5 µg/dL during heavy traffic (Zahran, 2021). If the air monitors surrounding the Reid-Hillview airport did not consistently

exceed the existing primary lead standard, it indicates that the existing standard fails to protect children from lead toxicity.

Does the currently available information call into question the identification of Pb-TSP as the indicator for Pb?

New evidence on the size of lead particles in exhaust from aircraft emissions and automobile emissions – which are much smaller than TSP and may be transported directly to the brain via the olfactory nerve – indicate that Pb-TSP is unlikely to be an adequate indicator of lead exposure. Moreover, up to 20% of lead in aircraft emissions is in the vapor phase (also known as alkyl or organic lead) that can be readily inhaled or dermally absorbed (page 2-10, EPA, 2013).

The EPA estimated that sixteen million Americans – including three million children – live within a kilometer of a general airport. Lead particles found in aircraft emissions are smaller than those found in automobiles emissions. Exhaust particles in piston-engine aircraft emissions are "irregular particles measuring 13 nanometers with a 4 nm microcrystal of lead dibromide surrounded by a halo of hydrocarbons". In contrast, exhaust particles from automobile burning leaded fuel averaged 35 nm in diameter and contained five to ten 4 nm beads of lead" (Griffith, 2021).

Small particles of manganese and lead, which are readily absorbed, may be transported directly to the brain via divalent metal transporters found in the olfactory nerve (Thomason 2007). Zeliha Kayaalti found that people with the CC genotype of DMT 1 had significantly higher blood lead concentrations than those with AA and CA genotypes ($p = 0.036$) (Kayaalti, 2015). Lead that is in the vapor form would also be readily inhaled and transported directly to the brain.

Using a validated land use model, Erika Rasnick estimated monthly air lead concentrations of $PM_{2.5}$ for 263 children from birth to age 12 years and assessed their relationship with parent-reported behavioral problems at 12 years (Rasnick, 2021). Using distributed lag analysis, Rasnick estimated the effect of airborne lead on behavioral problems adjusting for maternal education, community-level deprivation, blood lead concentrations (to account for internal lead stores), greenspace, and traffic related air pollution. Rasnick identified sensitive windows for airborne lead concentrations during mid- and late childhood for increased anxiety and atypicality scores, while sensitive windows for increased aggression and attention problems were identified immediately following birth. At age 12 years, a 1 ng/m^3 increase in airborne lead – concentrations ten-times lower than the National Ambient Air Quality Standard set by the U.S. Environmental Protection Agency – was associated with a 3.1-point (95% CI: 0.4 – 5.7) increase in anxiety scores.

To what extent does the newly available evidence alter our understanding of the concentration-response relationships between Pb in children's blood and reduced IQ <u>or cognitive abilities</u>?

New studies confirm that exceedingly low levels of lead adversely impact children's cognitive abilities. In a large study of Chicago school students (n=58,658), Ann Evens confirmed that the

dose-response relationship for cognitive or academic abilities exhibits a decelerating curve (Evens, 2015). Using blood lead concentrations measured in early childhood, she found that a 5 μg/dL increase in blood lead concentration was associated with a 32% increased risk of reading failure (RR = 1.32, 95%CI = 1.26, 1.39) on standardized tests in 3rd grade children. The effect of lead on reading was non-linear with steeper failure rates at lower blood lead concentrations. Evens estimated that 13% of reading failures in Chicago school children were attributable to blood lead concentrations of 5 to 9 vs. 0 to 4 μg/dL.

Using quantile regression, Sheryl Magzamen found in 4th grade children (n=1,076) in two Milwaukee school districts at the children from two urban school districts that lead exposure was associated with an 18-point decrease (95% CI: 48.7, 3.3) at the 10 quantile of reading scores and a 7.5-point decrease (95% CI: 15.5, 2.1) in at the 90th percentile (Magzaman, 2015). Thus, lead appears to adversely impact vulnerable children who are already struggling with reading to a greater extent than children who read well.

Lead-associated IQ deficits continue beyond childhood. Aaron Reuben found that participants (n=565) with higher blood lead concentrations at 11-years of age had further decrements in intellectual abilities by 38 years of age. After adjusting for participants' childhood IQ score, their mothers' IQ score, and socioeconomic background, each 5 μg/dL higher concentration of blood lead measured in childhood was associated with an additional 1.6-point lower full-scale IQ score (95% CI: −2.5 to −0.74; P<.001) (Reuben, 2017). Reuben also found that children with higher blood lead concentrations were less likely to attain the same social standing as their parents (Reuben, 2017).

Lead-associated deficits persist beyond childhood. Michael McFarland quantified the IQ loss of Americans from 1940 to 2015 using NHANES (McFarland, 2022). McFarland estimated an average deficit of 2.6 IQ points for people born between 1951 and 1980, totaling 824 million IQ points. The average deficit (5.9 IQ points) was larger for people born between 1966 and 1970 (McFarland, 2022).

Is there new evidence on health effects beyond neurocognitive endpoints in children that suggests additional sensitive populations should be given increased focus in this review?

In the 2013 ISA review, the committee concluded that lead exposure was "suggestive of a causal relationship". New studies published since that review support a causal relationship for lead exposure and birth outcomes.

Lead is a risk factor for preeclampsia, a disorder of severe hypertension in pregnant women. In a meta-analysis – a study of several high-quality studies – Arthur Poropat found that higher concentrations of lead in the blood of pregnant women was a risk factor for pre-eclampsia (Poropat, 2017). For every 1 μg/dL (10 ppb) increase in blood lead in pregnant women, the risk of pre-eclampsia rose by 1.6% (Poropat, 2017).

Lead is a risk factor for preterm birth (Taylor, 2014; Li, 2017; Vigeh, 2011). In a pregnancy and birth cohort study in Bristol, England, pregnant women with a blood lead > 5 μg/dL (> 50 ppb) were 1.9-fold more likely to give birth preterm (Taylor, 2014). In the China-Anhui Birth Cohort Study with a mean blood lead of 1.5 μg/dL, Jun Li found that the risk of PTB was elevated in those with moderate (1.18-1.79 μg/dL; OR=2.33, 95% CI:1.49, 3.65) and high (≥1.61 μg/dL; OR=3.09, 95% CI: 2.01, 4.76) serum lead concentrations compared with women who had lower exposure (<1.18 μg/dL) (Li, 2017). In an Iranian cohort of 348 pregnant women with a geometric mean blood lead of 3.5 μg/dL, Mohsen Vigeh found using logistic regression that higher blood lead concentrations, measured between 8 to 12 weeks gestation, were associated with an elevated odds of preterm birth (OR=1.41, 95% CI: 1.08, 1.84) (Vigeh, 2011).

Does the currently available information call into question the current averaging time?

In a natural history study, Linda Bui examined the impact of short-term lead exposure on birth outcomes in 147,673 births following NASCAR's decision to eliminate leaded gasoline (Bui, 2021). After leaded fuel was no longer used, newborns of mothers residing within 4,000 meters of the racetrack gained an average of 104 grams and 0.36 weeks longer duration of pregnancy. The probability of low birth weight declined by 4.1%, preterm births by 2.7%, and small for gestational age by 4.1% (Bui, 2021). The authors concluded that the EPA's National Ambient Air Quality Lead Standard, which is based on a 3-month moving average, failed to protect against risks from short-term exposures.

Is there new evidence on health effects beyond neurocognitive endpoints in children that suggests additional sensitive populations should be given increased focus in this review?

New evidence shows that exceedingly small increments in lead exposure result in delays in conception. In a study of 501 couples who desired to become pregnant, Germaine Buck-Louis found that it took 15% longer to achieve pregnancy if the men had higher blood lead concentrations; the geometric mean blood lead concentrations among men with delayed pregnancy was only 0.24 μg/dl higher than men who achieved earlier pregnancy (Buck Louis, 2012).

The US EPA concluded that lead is a causal risk factor for coronary heart disease (US EPA, 2013). In laboratory studies, chronic lead exposure causes HTN and enhances atherosclerosis by inactivating NO, increasing H_2O_2 formation, inhibiting endothelial repair, impairing angiogenesis, and promoting thrombosis (US EPA, 2013; Vaziri, 2008). Studies published since the last ISA review confirm that lead is a leading, if largely overlooked risk factor for coronary heart disease (McElvenny, 2015; Aoki, 2016; Chowdhury, 2018; Lanphear, 2018; Wang, 2019).

Fifteen prospective cohort studies conducted in Europe (4) and the United States (11) examined blood lead concentrations and cardiovascular mortality; all found that lead was a risk factor for CVD mortality (Navas-Acien, 2021). Three of these studies (data from two of these cohorts overlapped) and a meta-analysis have been published since the last IAS (McElvenny, 2015; Aoki, 2016; Chowdhury, 2018; Wang, 2019). In the meta-analysis in the British Medical Journal,

Rajiv Chowdhury and his team examined over 90,000 people in eight studies. Comparing the lowest tercile with the highest tercile, Chowdhury found that blood lead concentration was a risk factor for coronary heart disease (RR = 1.85, 95% CI: 1.27, 2.69) (Chowdhury, 2018).

The global burden of cardiovascular disease attributed to lead only include effects mediated through blood pressure and the risk for CHD deaths is assumed to begin at blood lead > 5 ug/dL (Shaffer, 2019). Newer studies indicate that no apparent threshold exists and indicate that lead is a risk factor for atherosclerosis (Vaziri, 2008; Navas-Acien, 2021; Lanphear, 2018). Using NHANES Mortality Follow-up, Lanphear found that lead was the leading risk factor for CHD mortality in the United States, accounting for 185,000 deaths annually (Lanphear, 2018).

Does the current evidence continue to support blood Pb level as a useful indicator of Pb exposure and dose for purposes of characterizing Pb health effects, with well-recognized strengths and limitations?

The amount of lead circulating in blood is a valid and practical biomarker of lead exposure. Using the amount of lead circulating in blood to estimate cumulative lead exposure is analogous to measuring a person's monthly salary to estimate their overall wealth; bone lead concentration is a better indicator of cumulative lead exposure. Studies that rely on whole blood for measuring lead exposure will underestimate lead's impact on death, disease, and disability. Still, lead measured in whole blood is a valid and practical biomarker and is the optimal biomarker for estimating the adverse consequences of lead exposure in large epidemiologic studies.

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Dr. Joel G. Pounds

As anticipated, the Integrated Review Plan for the NAAQS for Lead, Volume 2: Planning for the Review and the Integrated Science Assessment is logical, thorough, and appropriate. No concerns are noted.

Suggestion: The human microbiomes are increasingly recognized as important in the physiology, health, and disease. In particular, the role of the gut and respiratory tract microbiomes are recognized as important in modulating the function and dysfunction of the brain and other target organs of lead toxicity. See, for example, Tooley (2020), Mohajeri *et al.* (2022), and Man e*t al.* (2017).

Moreover, several recent studies since the last NAAQS review describe dysbiosis and alterations in microbiome metabolite levels following lead exposure in experimental animals (see Liu *et al*. 2021) and more recently, in humans (Zeng *et al.* 2020). While these studies do not directly support the conclusion that the microbiome is a critical target for very low levels of human lead exposure, these studies do identify the microbiome as a potential and important target of lead toxicity. It is likely that additional studies will be published in the coming months during the ISA process.

Thus, I recommend that the ISA Review Team include a directed analysis of the Pb-microbiome literature related to lead exposure. Such an analysis will facilitate development of hypotheses and experimental designs for future studies and establish the ISA as forward looking by addressing the microbiome as a potential target for lead and other environmental toxicants.

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Mohajeri *et al*. Relationship Between the Gut Microbiome and Brain Function. Nutr Rev. 76:481-496. 2018.

Tooley, K.L. Effects of the Human Gut Microbiota on Cognitive Performance, Brain Structure and Function: A Narrative Review Nutrients: 12:1-17, 2020.

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Dr. Brisa Sánchez

Major issues:

- The volume should consider the role of racial segregation, and environmental justice throughout

  In 2.1:
  - The list of policy-relevant questions should include the role of racial residential segregation, income segregation, and racialized income segregation as relevant exposure risks.

  In 3.3.2:
  - The third bullet should separate race out of the list of biological factors (race is a social construct).
  - Individual-level race differences in exposure should not be divorced from racial residential segregation and racialized economic segregation. These structural factors confound the role of individual-level race.
  - New evidence on the role of racial residential segregation and exposure and/or health effects should be considered.

  In 3.3.4:
  - Line 14 from the top, amend "being of a certain race/ethnicity and poor nutrition", to include racial residential segregation

- In page 2-3, it is stated that examining biomarkers other than blood Pb may be useful. Yet, the scope of the ISA (pg. 3-4, line 6) focuses only on the relationship between blood Pb and air Pb. Please justify this narrow focus for the ISA or expand to review the literature regarding air Pb and other Pb biomarkers.
- In 3.3.4, it is desirable to explicitly include life stages related to women's health – pregnancy period, menopause, etc.
- Use gender-inclusive language when not directly quoting other texts, i.e., replace "his" or "him" with "they" or "the Administrator"

Minor issues:

- Second bullet on page 3-12, under 3.3.4: it would be clearer to explicitly include a life stage following this word and separate the meaning from populations, e.g., "life stage (e.g., fetal period) or populations (e.g., those with pre-existing diseases such as diabetes).

- Page 2-1, immediately above the section 2.1:
  - It would be useful to orient the reader by including a sentence that establishes that the primary standard is made in connection with human health, and the secondary standard is made in connection to public welfare more generally, including ecosystem, etc.
  - If possible, also clarify briefly/remind the reader what happens if the primary and secondary standards differ. Does one supersede the other or is the minimum adopted?
- It is unclear why are the "CAA provisions" referenced explicitly (pg 2-7) when describing the requirement of the secondary standard, but not the primary standard?
- The bulleted sentence in page 2-4 is confusing/unclear. Is "depend" missing between "remaining" and "upon"?
- Typo on figure 2-1, last bullet on "evidence-based considerations" box: "then" should be "than"

Dr. Brian S. Schwartz

I believe the review must be completed and strongly situated in the world in which we currently live, specifically, in the context of changes to be anticipated in the coming years regarding climate change, changes in energy policy, decarbonization of the transportation sector, and urban renewal and gentrification. We have already seen air lead levels increase significantly associated with urban redevelopment in several northeastern and other U.S. cities because this has occurred in areas with legacy soil lead contamination, from lead smelters and other abandoned industrial operations (e.g., see here: https://www.inquirer.com/news/inq/philadelphia-lead-soil-fishtown-construction-dust-20170618.html). Energy and climate policy in the coming years is likely to increase the motivation for redensification and urban renewal. Old buildings with lead paint will be torn down, soils with legacy lead contamination will be disturbed, and increased air lead levels could be a result. Changing climate will also contribute to the drying of soils, which could further increase air lead levels, especially in urban areas with high legacy soil lead levels. Notably, these risks may fall disproportionately on communities of color and with low socioeconomic status. Drying of soils and ecosystems could also make ecosystems much more susceptible to the toxic effects of lead, a large set of potential secondary standards outcomes. Finally, with the expected increases in wildfires due to warming, changes to the hydrologic cycle, and soil drying, this is also an important potential source of contributions to air lead levels in a range of possible settings.

The EPA has relied heavily in its deliberations, understandably, on the relation between air lead levels and blood lead levels, and in turn, between blood lead levels and child intelligence quotient measures. I would recommend careful consideration of exposure, dose, latency, and duration issues that could suggest that other longer-latency, longer exposure periods, and chronic disease outcomes may guide us to different policy choices. For example, the current indicators are generally reliant on early life exposures, a short-term lead biomarker (30-day clearance half-time of lead from blood), short duration exposure (a few to around 10 years), and a short latency health effect (within a few years). I think cumulation of lead for much longer periods of time can increase the risk of a larger and more varied set of health outcomes that occur in mid- to later life, including reproductive, cardiovascular, behavioral, neurobehavioral, cognitive, and neurodegenerative outcomes. Blood lead is a less useful predictor of these health outcomes than is cumulative dose. There is a large literature on tibia lead levels as a surrogate biomarker for lifetime lead dose, and how the area under the curve of blood lead levels vs. time is a possible surrogate for this. What is interesting about this range of outcomes is that there is built in bias towards the null in published studies reporting on the relation between lead dose and any health outcome in later life.

I recommend that the notion of susceptibility be considered very broadly. It should be first emphasized that race/ethnicity is not a biologic construct but rather represents risk of a number of adverse social determinants of health that increase exposure risk, toxicokinetic risk, and toxicodynamic risk. Differences in genetic polymorphisms, co-exposures, co-morbidities, diet, physical activity, housing, and microbiota, for example, can all contribute to differential dosing

and/or modify the toxic effects of lead, and many of these occur disproportionately in communities of color and with low socioeconomic status.

Dr. William Stubblefield

Overall, this document provides an adequately detailed *Integrated Review Plan* (IRP) for the evaluation of the National Ambient Air Quality Standards for Lead (Pb). The approach, as detailed in Volume 2 for the conduct of the IRP, should provide an appropriate framework for identifying, obtaining, and evaluating the scientific information needed to develop an appropriate *Integrated Science Assessment* (ISA).

Recommendations

Most of my attention has been directed toward the evaluation of the secondary Pb standard given my background and expertise. I identified three specific items for consideration, i.e., data to be considered, bioavailability concerns, and questions associated with metals mixtures, each are discussed below:

Data for consideration

The quality and accuracy of the ISA will require a comprehensive evaluation of the extant literature and available data; given that I was somewhat concerned to see that barriers to the types of data considered to be considered. Page 3-6 of the IRB states that *"Generally, studies on mine tailings, biochar, industrial effluent, sewage, ship breaking, bioremediation of highly contaminated sites, and ingestion of Pb shot, fishing tackle or pellets are not within the scope of the ISA due to high concentration of Pb and lack of a connection to an air-related source or process."* I can understand why this might be an issue and ideally having Pb data that only exists due to airborn Pb concentrations would be ideal. However, these are likely to be the type of data that are available, and they will help to inform the evaluation of environmental concentrations likely to result in adverse ecological impacts. The importance of this information is acknowledged on page 2-8 (bullet 4) in the series of questions that states: *"Does the newly available evidence indicate new exposure levels at which ecological systems or receptors are expected to experience effects?"* Addressing this question can be done regardless of the source of the Pb (airborne, effluent discharge, etc); therefore, the available data should not automatically be truncated based on the source of the Pb.

Data availability may continue to be an issue. Section 3.3.5.1 discusses the limited amount of "new" data that were identified in the 2013 ISA; for example, Page 3-15 states that "*Generally, in the previous review, there were fewer studies available for saltwater organisms compared to terrestrial and freshwater biota, and therefore the evidence was often inadequate to relate Pb exposure to specific endpoints in coastal environments.*" Current national Ambient Water Quality Criteria (AWQC) for Pb are based on the data presented in the 1985 EPA document; at that time there were acute toxicity data for 13 marine species and 1 chronic toxicity study. Most of these data were developed at EPA ORD labs (Gulf Breeze, FL and Narragansett, RI) and were never available in the peer-reviewed literature—only in internal memos and reports. More recently, 2007 a European Union Risk Assessment was conducted for lead metal and lead

compounds (https://echa.europa.eu/voluntary-risk-assessment-reports-lead-and-lead-compounds), this report found that chronic data were only available for four additional marine species. EPA must recognize that the development of new data chiefly arises as a result of regulatory questions or enforcement actions that encourage industry or other entities to generate additional data to address these concerns, or the data can come about as a direct result of research conducted or sponsored by EPA or other state and federal governmental groups. It should come as no surprise that there are limited "new" environmental toxicology data for Pb, this does not mean that there are no concerns, it just means that no one has looked.

Bioavailability

Page 2-8 (i.e., bullet 3) raises a question that states: "*Does the newly available evidence alter or further inform our understanding of the bioavailability of Pb in different types of ecosystems and media and the extent to which it affects toxicity or potential for effects?"*

The current national Ambient Water Quality Criteria (AWQC) for Pb are based on a water hardness (only) correction (US EPA 1984). The state-of-the-science regarding our understanding of the environmental parameters affecting the bioavailablilty and toxicity of Pb has improved substantially since 1984 and both biotic ligand models (BLM) and multiple linear regression (MLR) models are available for Pb in freshwater. These models consider the effects of pH and dissolved organic carbon, in addition to water hardness, resulting in a more accurate and predictive model with less uncertainty. A full discussion of the acute and chronic Pb MLR models and the BLM is provided in DeForest et al. (2020) and will be available at https://www.epa.gov/wqc/metals-crada-phase-1-report. Much of the data used to develop these models (and to expand the range of species considered in the species sensitivity distributions (SSD) used to derive water quality standards) resulted in response to European regulations, i.e., REACH. All of the data are available via the peer-reviewed literature or have been peer-reviewed separately by EPA, so they should be available for the ISA effort. Similarly, a soil threshold calculator is now available for a number of metals including Pb (https://www.arche-consulting.be/tools/threshold-calculator-for-metals-in-soil). The input parameters used in the model are dependent upon the metal under consideration, and are soil parameters like pH, % organic matter, % clay and eCEC. Underpinning empirical data are available for the models; again this should all be available for the ISA effort.

Mixtures

Section 3.3.5.2 does a good job of identifying areas where new information would be useful in addressing some of the questions posed. One area that was identified in Section 3.3.3.2 under human health, was the question: "*What new evidence has become available to help discern health effects of exposure to Pb within mixtures - including mixtures with other toxic metals, other pollutants in ambient air, or other environmental exposures - versus Pb alone (e.g., additive, synergistic, or antagonistic effects)?"* This question is equally important, if not more so, from an ecological perspective, and probably should be incorporated in Section 3.3.5.2 in both the terrestrial and aquatic sections. Metals mixtures (including Pb) are an area where a

greater understanding of interactive effects on toxicity would be beneficial, in the real world we seldom find Pb as a single contaminant.

References

DeForest, DK, Tear L, Brix KV. 2020. Comparison of multiple linear regression models and biotic ligand models for predicting acute and chronic lead toxicity to freshwater organisms. Technical Report prepared for International Lead Association, Durham, NC, USA.

US Environmental Protection Agency. 1984. Pb Ambient water quality criteria for lead—1984. EPA 440/5-84-027. Washington, DC.

US EPA. 2022. Metals Cooperative Research and Development Agreement (CRADA) Phase I Report: Development of an Overarching Bioavailability Modeling Approach to Support US EPA's Aquatic Life Water Quality Criteria for Metals. (EPA-822-R-22-001) Office of Water. March 2022

Dr. Kathleen Vork

In spite of significant progress in reducing exposure to lead in ambient air, there continues to be evidence of an ongoing problem of childhood lead exposure reaching or exceeding previous reference levels set by the CDC (i.e. 5 to 10 ug/dL). There are new tools for identifying sensitive and highly exposed subpopulations and updated models and new exposure pathway coefficients to consider in a health risk assessment such as the health risk assessments that informed agency decisions in 2008.

Some of this new information was provided in response to the Agency's request for new information published in Federal Register Vol. 85, No. 130/Tuesday, July 7, 2020. Documents provided were believed to address several relevant topics:

- Lead (Pb) toxicokinetics and toxicokinetic modeling
- exposure assessment methodologies
- research on fate and transport of Pb in environmental media
- air-related Pb pathways of human exposure, including inhalation of ambient air or ingestion of food, water or other materials, including dust and soil, containing Pb that has deposited from ambient air

Given new exposure coefficients and updated models for assessing lead exposure, respiratory tract deposition and clearance, uptake, distribution and elimination, expanded scenarios for health risk assessments could shed additional light on the adequacy of the current Standard. For example, it could be informative to include the following new information:

- additional pathways – swallowed mass from inhaled particles, mother's milk
- differences in air-blood lead relationships between particles mostly in the inhalable versus the respirable particle range
- GI absorption fractions for inhaled lead aerosol that is swallowed

Post CASAC lead panel meeting comments on topics discussed at the April 8th meeting with additional references:

Assessment of pharmacodynamics of lead-calcium interactions on the brain.

- Radulescu A and Lundgren S. 2019. A pharmacokinetic model of lead absorption and calcium competitive dynamics. Sci Rep 9:14225. doi 10.1038/s41598-019-50654-7.

Health effects from metal mixtures

- Linares AM, Unrine JM, Thaxton Wigging A, Tantalean JC, Radulescu VC. 2021. Blood's concentration of lead and arsenic associated with anemia in peruvian children. J Environ Public Health 2021:7283514. doi 10.1155/2021/7283514.

Analysis of lead and other metals in PM2.5 measurements of ambient air during and after wildfire in 2018 that burned through the town of Paradise Ca.

- Payne Sturges et al 2021 California Air Resources Board, Camp fire air quality data analysis
  Camp Fire Air Quality Data Analysis

Additional human exposure pathways potentially affected near lead emissions and transfer coefficients

- OEHHA 2012, Chapter 1 schematic of Exposure Assessment pathways
  I. Introduction (ca.gov)

Inhalation transfer coefficients for adult lead exposures over a broad range of particle sizes.

- A manuscript undergoing review and resubmission that may be available in 2022.

Dr. Marc Weisskopf

In general, the plan looks appropriate. My only comment relates to the issue of selection biases, perhaps more pronounced for chronic outcomes of later life (although definitely possible in early life and birth cohort studies). Specifically, I think it is worth some attention to issues of who gets into a study and who drops out. To the extent that long-term exposures to lead matter for a health outcome, but also possibly influence who gets into a study or drops out of a follow-up study—for example if the lead exposure leads to adverse health effects, adverse health is known to predict non-participation in studies and drop out—these can bias findings among those in the study relative to the larger population. These biases are almost always such that they drive true causal effects towards the null in the observable data. While it is not always possible to know to what extent this is happening, it is worth clarifying this possibility as it would suggest that estimates of effects from studies subject to this are conservatively low. We have a few papers describing this issue, but most relevant for the lead ISA is Weisskopf et al., Environ Health Perspect., 123(11):1113-22, 2015. Although not specifically about lead, the principles of this issue are also detailed in the context of birth cohort studies in Raz et al., Am J Epidemiol., 187(11):2292-96, 2018 and Leung et al., Environ Health Perspect., 129(4):47001, 2021.