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Thomas Luben, Ph.D.
National Center for Environmental Assessment
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EPA Docket Center (ORD Docket, Mail Code: 28221T)
U.S. Environmental Protection Agency,
1200 Pennsylvania Ave., NW.
Washington, DC 20460

Dear Dr. Luben,

We are writing to convey comments from the California Air Resources Board (CARB) and the California Office of Environmental Health Hazard Assessment (OEHHA) on the U.S. Environmental Protection Agency's (U.S. EPA) recently released External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants, hereafter referred to as the draft Ozone Integrated Science Assessment. We appreciate the opportunity to comment on this high quality document, as it is crucial to continue to objectively and comprehensively review the available scientific evidence on the effects of ozone in order to adequately protect public health and welfare.

CARB and OEHHA both fall under the purview of the California Environmental Protection Agency. CARB is charged with protecting the public from the harmful effects of air pollution and developing programs and actions to fight climate change; staff include epidemiologists and other scientists, engineers, economists, lawyers and policy makers. OEHHA's mission is to protect and enhance the health of Californians and the environment through scientific evaluations that inform, support, and guide regulatory and other actions. OEHHA scientists, including epidemiologists and toxicologists, recommend health-based levels of criteria air pollutants and other toxicants and conduct epidemiological investigations of these pollutants. CARB and OEHHA take very seriously their responsibility of carefully assessing the science surrounding policies that have major public health implications.

The overall conclusions for most of the adverse ozone impacts reported on for health and ecological endpoints appear to be well-considered and well-justified. These include determining the relationship between short- and long-term ozone exposure

and metabolic effects to be “likely to be a causal relationship”, in contrast to making no determination in the 2013 draft Ozone Integrated Science Assessment. However, we question several other proposed causality determinations, and suggest further analysis and literature review. For some endpoints, there appears to be an over-emphasis on findings from controlled human studies in healthy adults, insufficient consideration of effects on more vulnerable segments of the population, under-weighting of evidence from experimental studies, and/or missing publications that could add to the evidence for causality. On these grounds, we question the change in determination from “likely to be a causal relationship” in the 2013 Ozone Integrated Science Assessment to “suggestive of, but not sufficient to infer, a causal relationship” in the current draft Integrated Science Assessment for short-term ozone and cardiovascular disease effects and total mortality. For some additional hazard traits, there is substantial evidence of effect that warrants reconsideration of the “suggestive” evidence categories assigned in the draft Ozone Integrated Science Assessment. These include long-term ozone exposures and total mortality, specific categories of pregnancy and birth outcomes, and central nervous system effects.

All of U.S. EPA’s proposed causality determinations for ecological effects appear to be sound and well justified. These include the findings of “likely to be a causal relationship,” for the adverse impacts of ozone on plant-insect signaling, tree survival and herbivore growth and reproduction and the findings of a “causal relationship” for negative impacts of ozone on terrestrial biodiversity, agricultural yield and plant reproduction and growth. These determinations conveying the significant adverse ecological effects of ozone will provide a robust scientific background as U.S. EPA reviews the secondary National Ambient Air Quality Standard (NAAQS) for ozone.

Detailed comments on the draft Ozone Integrated Science Assessment are provided to supplement this letter with a number of technical points for consideration by the U.S. EPA as it considers revision to the document.

Comments on Process Changes to the NAAQS Process

The last review of the Ozone National Ambient Air Quality Standards, completed in 2015, was a model of scientific integrity that relied on the comprehensive and technically sound 2013 final Ozone Integrated Science Assessment to inform the ozone standard. Review of the current draft Ozone Integrated Science Assessment will be compromised due to the lack of scientific expertise on the Clean Air Scientific Advisory Committee (CASAC) and the extraordinarily foreshortened NAAQS review process. These changes reflect a thorough disregard for the scientific process once inherent in U.S. EPA’s NAAQS reviews.

In its previous ozone NAAQS review, U.S. EPA convened a thirteen member expert panel comprised of epidemiologists, toxicologists, ecologists, atmospheric chemists,

and atmospheric modelers to review draft Ozone Integrated Science Assessments, the Risk and Exposure Assessments and the Policy Assessment. This panel was well qualified to provide valuable input on these different elements of U.S. EPA's NAAQS review process.

Conversely, the current draft Ozone Integrated Science Assessment will be reviewed by CASAC members who lack the expertise to fully review the Integrated Science Assessment, such as epidemiologists. Expertise from multiple epidemiologists is critical since the draft Ozone Integrated Science Assessment comprises a large and complex body of epidemiological evidence and causality determinations between ozone exposure and adverse health effects heavily rely on the strength of epidemiologic studies. Additionally, there are no ecologists on the Committee. For a draft Ozone Integrated Science Assessment that has changed one and made four new causality determinations since the 2013 Ozone Integrated Science Assessment, this is an egregious oversight. This process compromises, and will continue to compromise, U.S. EPA's ability to adequately consider and weigh all the scientific evidence in updating the Ozone NAAQS.

In its previous Ozone NAAQS review, U.S. EPA released multiple drafts before finalizing its documents: three external review drafts of the Integrated Science Assessment prior to the final document, and two drafts each of the Risk and Exposure Assessment and Policy Assessment, before final versions were released. This iterative process resulted in a successive series of documents that assured that U.S. EPA's decisions were based on the best available science.

In this current review, only one draft each of the Ozone Integrated Science Assessment and the Policy Assessment were released for public review, with the Policy Assessment released prior to the finalization of the Integrated Science Assessment. The Integrated Science Assessment forms the scientific basis for the Policy Assessment; thus, it is illogical to produce a draft Policy Assessment without first establishing a sound Integrated Science Assessment from which to draw evidence. We urge U.S. EPA to revise the draft Ozone Integrated Science Assessment based on a thorough review and comment from the scientific community, and to release a second draft for further scrutiny, before finalizing the Ozone Integrated Science Assessment. Then, and only then, should the Policy Assessment be developed upon the foundation of the final, fully vetted version of the Integrated Science Assessment, to ensure that it is grounded in the best available science.

CARB and OEHHA appreciate the opportunity to comment on the draft Ozone Integrated Science Assessment. As noted earlier, you will find detailed supplemental comments in the attachment to this letter. However, we object to the abbreviated nature of the review process as well as the failure to convene a scientific panel with sufficient expertise to adequately review the draft Ozone Integrated Science

Dr. Scott Jenkins
December 2, 2019
Page 4

Assessment. Given U.S. EPA's stated intention to return its focus to protecting public health and its fundamental obligations under the Clean Air Act to set air quality standards that protect all citizens, we expect U.S. EPA will take all appropriate actions to establish adequate health-protective NAAQS grounded on sound analyses, as done previously. We are ready to work with the U.S. EPA to help ensure it does so, and to develop effective State plans to attain those NAAQS. If you need additional information, please contact Elizabeth Scheehle, CARB Chief of the Research Division at (916) 322-7630 or Elizabeth.Scheehle@arb.ca.gov, or Vince Cogliano, OEHHA Deputy Director for Scientific Programs at Vincent.Cogliano@oehha.ca.gov.

Sincerely,

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California Office of Environmental Health
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Supplemental Comments from CalEPA ARB and OEHHA
December 2, 2019 Comment Letter

The California Air Resources Board and the Office of Environmental Health Hazard Assessment provide these additional, more detailed comments as a supplement to those made in the December 2, 2019 comment letter on the U.S. Environmental Protection Agency's (U.S. EPA) recently released External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants.

General comments

Causality determinations

Cardiovascular effects

The determination for short-term ozone exposure and cardiovascular effects was changed from the 2013 Integrated Science Assessment category of "Likely to be a causal relationship" to "Suggestive of, but not sufficient to infer, a causal relationship". We question this change as there appears to be an over-emphasis of findings from controlled human studies in healthy adults, insufficient consideration of effects on the more vulnerable segments of the population, under-weighting of evidence from experimental studies, and/or lack of consideration of important publications. The mechanistic evidence for systemic inflammation and oxidative stress is relatively consistent across the epidemiologic, exposure assessment, and toxicologic studies.

Total mortality

The scientific evidence supporting the relationship between short-term ozone exposures and total mortality has not been diminished and only strengthened since the 2013 Integrated Science Assessment which found the relationship "likely to be a causal relationship." The basis for the determination in the current document that the evidence is "Suggestive of, but not sufficient to infer, a causal relationship" is unclear and not well supported. However we acknowledge the category Total Mortality (Non-accidental) makes determining biological plausibility difficult since there are a myriad of mechanisms that cause deaths. Alternative determinations to consider would be to use the categories of Respiratory Mortality and Cardiovascular Mortality instead.

The Integrated Science Assessment is missing an important short-term ozone mortality meta-analysis study by Bell et al. (2014). This very experienced and highly respected group of epidemiologists found significant positive relationship among older populations between short term ozone exposure and mortality. The meta-analysis was a formal pooling of 73 mortality studies, and therefore, should be given substantial weight. This study provides further support to findings of increased mortality in the most vulnerable populations. Taken together with the discussion of studies in the

current Integrated Science Assessment leads one to strongly question U.S. EPA's finding that the evidence was only suggestive for short-term ozone exposure and mortality.

For long-term exposures, U.S. EPA states on page 6-41 "The strongest evidence for the association between long-term ozone exposure and total (non-accidental) mortality continues to come from the analyses of patients with pre-existing disease from the Medicare cohort..." Effects occurring among the most vulnerable are important indicators of potential causal associations, as are the persistence of effects after adjustment for confounders, and dose response showing increased effect at higher levels of exposure, also seen for this endpoint. These findings underscore the need to reconsider the evidence for vulnerable populations and those more highly exposed in reaching the overall evidence conclusion in the Ozone Integrated Science Assessment. U.S. EPA should consider a finding of "likely to be a causal relationship" for long-term ozone exposure and mortality.

Reproductive effects

The Integrated Science Assessment presents substantial evidence for long-term ozone exposure and several outcomes: pre-term birth, fetal growth, birthweight and body length. In this Integrated Science Assessment, reproductive (male and female fertility effects) and developmental effects (multiple sub-categories) were separated, a departure from the previous assessment that is sound. However, there are likely a number of mechanisms involved in the variety of outcomes addressed in the sub-categories of the developmental effects portion (maternal health during pregnancy, fetal growth, birth weight, body length, preterm birth, birth defects, fetal and infant mortality, and effects of exposure during developmental periods). Strong findings for any specific negative developmental outcome supports a need to consider developmental impairment as an ozone hazard and care should thus be taken to consider the strength of the evidence for individual outcomes. A catch-all determination of "suggestive of, but not sufficient to infer, a causal relationship" in the Integrated Science Assessment does not appear to reflect the range of the findings and their significance.

Specifically, if assessed individually, the summary for fetal growth, birth weight and body length at birth (section 7.1.3.3.3) concludes that there is both epidemiologic and toxicological evidence in rodents to support conclusions regarding adverse effect from ozone exposure. Similarly, in regards to preterm birth, "all (epidemiologic) studies that examined ozone exposures during the 1st and 2nd trimesters reported associations elevated from the null" (section 7.1.3.4.1). Although there were no toxicological studies specific to preterm birth, there is very strong epidemiologic evidence coupled with some toxicological evidence from pregnancy conditions that can sometimes lead to preterm birth. Thus, for these two subcategories, the Integrated Science Assessment discusses the evidence in compelling terms, and lays the basis for a

possible “likely to be causal” conclusion, and thus careful reconsideration of the conclusion is needed for these specific endpoints. Moreover, we suggest an examination of studies missing from the review tables. These studies are listed below in Section 4, “Additional Publications to Review.”

Central Nervous System

The evidence for long-term ozone exposure also supports reconsideration of the suggestive evidence conclusion to a possible “likely to be a causal relationship” label for central nervous system (CNS) effects as a whole. CNS effects observed in ozone studies encompass a number of outcomes discussed in the Integrated Science Assessment, including short-term cognitive and behavioral effects (including depressive symptoms and impaired memory and learning), short-term neuroendocrine effects, and effects on rates of emergency room and hospital admission for diseases of the nervous system or mental health (short-term). Adverse effects from long-term ozone exposure include brain inflammation and morphology, effects on cognition, motor activity and mood, and, finally, neurodevelopmental effects.

Despite the varying outcomes from both long-term and short-term studies, the current Integrated Science Assessment only supplies a conclusion of “suggestive of, but not sufficient to infer, a causal relationship” for both short-term and long-term CNS categories. In the current Integrated Science Assessment, which groups long-term ozone effects on brain inflammation and morphology (toxicological only), cognition, motor activity, mood and neurodevelopmental effects, there appears enough evidence to carefully consider the elevation of the current Integrated Science Assessment conclusion to “likely to be a causal relationship” given that “toxicological studies provide coherence for these findings.” (Section 7.2.2.4.3), even if there are few epidemiological studies. Recently, a few epidemiological studies pertaining to suicide and other mental health outcomes have emerged that may strengthen the evidence for an effect and should be considered in this Integrated Science Assessment, and these should be also considered (please see Section 4 below).

Other general comments

Wording of Causal Determinations

In this draft Integrated Science Assessment, the causal determination categories changed from the 2013 Integrated Science Assessment’s “suggestive of a causal relationship” to “suggestive of, but not sufficient to infer, a causal relationship.” The reason for the change needs to be clearly described in the Evaluation of the Evidence section (section IS.1.2.4). Additionally, these determinations should be made consistently throughout the entire document. In Table IS-1 and Table ES-1, the term “suggestive of a causal relationship” for the current assessment category is occasionally used.

Inconsistent Footnotes of Causal Determinations

Table ES-1, Table IS-1, and Figure IS-6 each summarize causal determinations for ozone and health effects. However, their footnotes are slightly different. For instance, in Table ES-1, "c: Denotes change in causality determination from 2013 Ozone Integrated Science Assessment", the c footnote is missing in the short-term total mortality section. As another example, Table IS-1 says "b: denotes new causality determination," for short-term total mortality while Figure IS-6 says "*: change in causality determination from 2013 Ozone Integrated Science Assessment." Given 2013 Ozone Integrated Science Assessment did not subcategorize reproductive effects, the footnote of Figure IS-6 should change to "+: new causality determination."

Missing Units of Ozone Concentration Increase in Tables

Unlike the figures (all long-term exposures in this Integrated Science Assessment) that clearly indicate a standard increase in ppb ozone concentration for the results, the tables do not include this information. We suggest adding a column indicating the ppb increase in ozone that the results are based on. If the tables are based on a standard increase, that information needs to be added to the footnote for each table. Also, since most studies report multiple results, the table would benefit by a notation indicating the table, figure, page number or personal communication for the result.

Inconsistent Study Locations

Study locations of epidemiological studies are inconsistently described across health outcomes in the draft Integrated Science Assessment. Some outcomes include all populations worldwide, while others only include studies conducted in U.S. or Canada. This implies that the robustness differs across health outcomes. Inconsistent findings throughout the world and inconsistent findings in the U.S. have different implications, and this point should be discussed.

The PECOS tool was not applied in the 2013 Integrated Science Assessment, and evidence of causality for most health outcomes relied on findings worldwide. Therefore, the causal determinations are not directly comparable since some health outcomes in the current Integrated Science Assessment are restricted by location.

For mortality specifically, the PECOS criteria are quite different for the study populations between short- and long-term studies (P6-3 vs. P6-26). The PECOS criteria states that the short-term studies must be conducted in US or Canada, but the long-term studies can be anywhere.

At-Risk Populations

Populations at risk (or vulnerable populations) are discussed in Section IS.4.4, but are omitted from other sections. Table IS-11 includes evidence for populations at increased risk to the health effects of ozone, and should be mentioned in the Executive Summary. In the previous Integrated Science Assessment in 2013, there is a

designated chapter for this topic, “Chapter 8: Populations Potentially at Increased Risk for Ozone-related Health Effects,” but there is no chapter or appendix covering this topic in this draft Integrated Science Assessment. The same should be done for this Integrated Science Assessment or populations at risk should be discussed for each health outcome. Currently, some appendices discuss at-risk populations in the effect modification section, but other appendices did not mention them.

Overlapping Studies between Sections on Health Effects

Appendix 3 (Respiratory), Appendix 4 (Cardiovascular), Appendix 5 (Metabolic), and Appendix 7 (Other Health Endpoints: Lung Cancer Mortality) – all include mortality studies. Appendix 6 Total Non-accidental Mortality also includes more of these same mortality endpoints.

- Cardiovascular [Table 6-4 short-term exposure; Table 6-7 long-term exposure, within which are listed by study subcategories IHD, CHD, Stroke, CBVD, Cardiometabolic, Diabetes, Dysrhythmias, HF; Figure 6-10 long-term exposure, Cardiovascular and subcategories]
- Respiratory [Table 6-5 short-term exposure; Table 6-8 long-term exposure, within which are listed by study subcategories COPD, Pneumonia and flu; Figure 6-9 long-term exposure, Respiratory and subcategories]
- Other Mortality [Table 6-9 cancer-specific, reduction in life expectancy, in-hospital]
- Range of Categories and subcategories [6-11 long-term exposure with and without adjustment for PM_{2.5}]

The morbidity sections (e.g., cardiovascular, respiratory) should be restricted to morbidity outcomes and not discuss mortality outcomes. PECOS criteria restricting study geographic areas for analysis in this Integrated Science Assessment are dependent on causality determinations on health endpoints. These determinations may differ between morbidity and mortality studies even if the health category is the same. This strict separation between morbidity and mortality outcomes helps avoid confusion on choosing appropriate studies to review for this Integrated Science Assessment.

Specific Comments by Section

Appendix 1: Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone

- The focus of this Appendix is on background ozone. Although the contribution of background ozone is becoming more important as anthropogenic emissions are reduced, local and regional anthropogenic emissions are still the major contributors to ozone issues. This is especially true in the more polluted nonattainment areas. These considerations should be more clearly addressed.
- There are relatively large uncertainties and great spatio-temporal variations in VOC emissions from biogenic and wildfire sources.
- NO_x from fertilized soils should be considered to be anthropogenic emissions.
- This Appendix should include more discussion on the impact of emissions and meteorology on ozone in the west coast including California.
- Generally, the methods and conclusions on background ozone estimation seem reasonable.

Appendix 2: Exposure to Ambient Ozone

- Page 2-14 (Line 20-22). The description of the time spent indoor/outdoors for different races may be a bit circular. Perhaps a statement to clarify how Asians and Blacks compare versus the total population would be helpful.
- Page 2-21 (Line 4-5) – The statement “such as air purifiers” gives the impression that all air purifiers produce ozone. The term “such as certain ozone generating air purifiers” would be more accurate.
- Page 2-21 (Line 4-5) - Also In addition to air purifiers, there are a number of consumer products as well which can generate ozone, so the statement could be modified to “such as certain ozone generating air purifiers and consumer products” Reference for consumer products: (Zhang et al (2017) Indoor Air 27(2) 386-39) <https://onlinelibrary.wiley.com/doi/full/10.1111/ina.12307>

Appendix 3: Health Effects – Respiratory

- There are a number of key sentences that are repeated a number of times. This may be the way the document is structured, but it is repetitious.
- The association of the long-term impacts as likely to be causal is based on the epidemiology studies. However there were and continue to be some concerns for potential copollutant confounding. The animal studies do provide some strong support and biological plausibility. Overall, more emphasis could be placed on the animal toxicity studies.
- For respiratory mortality, only studies conducted in the US or Canada should have been reviewed according to the PECOS criteria. However, on page 3-106, European studies are discussed.

- The Turner et al. (2016) publication discusses co-pollutant adjustment for respiratory mortality. This discussion should be included in the Integrated Science Assessment.
- Suggestion: Publications discussing joint effects may merit further discussion. For example, in addition to Winqvist et al (2014) and Xiao et al (2016) and Darrow (2014):
- (background from prior Integrated Science Assessment period) Mauderly JL, Samet JM. Is there evidence for synergy among air pollutants in causing health effects? Environ Health Perspect. 2009 Jan;117(1):1-6. doi:10.1289/ehp.11654. Epub 2008 Aug 22. Review. PubMed PMID: 19165380; PubMed Central PMCID: PMC2627851.
- Please check publication year for Byers (2015).

Appendix 4: Health Effects – Cardiovascular

- There are redundant entries in some tables. Table 4-3 has multiple redundant entries. In Table 4-30, the Martinez-Campos et al. (2012) study is entered twice.
- Some references are included in figures but missing in the References list (Larrieu 2007 in Figure 4-4; Weichenthal 2017 and Cakmak 2018 in Figure 4-7; Cakmak 2018 in Figure 4-8). These should be included in the References section.
- The entries in Table 4-1 are inconsistently presented, and some data are missing. Some references are individually listed, whereas in other instances readers are told what section to refer to obtain information on references. Ozone concentrations are also missing from several lines.
- For both Table 4-1 and Table 4-2, “No evidence...” should be worded differently because this suggests that no studies have been done. Perhaps instead the wording should be “Evidence of no effect...”
- In the References list, on page 4-160, the reference starting with “M, A” is missing the author names, and the article title is actually the same as that of Arjomandi et al. (2015) that is listed on page 4-154.
- Controlled human exposure studies can from one perspective can “provide the most certain evidence indicating the occurrence of health effects in human following specific O₃ exposures”, because “effects reported in controlled human exposure studies are due solely to O₃ exposures, and the interpretation of study results is not complicated by the presence of co-occurring pollutants or pollutant mixtures (as is the case in epidemiological studies).” However, from another perspective they are highly problematic. Controlled human exposure studies are focus on healthy subjects typically adults, are subject to uncertainties due to small sample size, have healthy subject bias, and restricted

exposure dose and duration, which limit the ability to capture the potential health effects of prolonged elevated exposure. This is especially of concern for ozone where effects on those with pre-existing conditions and the most vulnerable populations need to be considered. One example of a time limited study is that by Rich et al. 2018 (<https://www.sciencedirect.com/science/article/pii/S0160412018300448>) who exposed healthy elder subjects to different levels of ozone up to 3 hours. Though no significant association between ozone and subclinical biomarkers was observed, the short exposure duration didn't allow the researchers to conclude the possibility of health effects.

Appendix 6: Health Effects – Mortality

- 6.1.5 Effect Modification of the Ozone-Mortality Relationship (Page 6-9): Weather conditions here are more likely to be confounders (associated with both the potential risk factor and the outcome, and not in the causal pathway between exposure and disease) rather than effect modifiers.
- 6.1.6 Potential Confounding of the Ozone-Mortality Relationship (Page 6-16): For the co-pollutant models, the focus on PM2.5 and PM10 needs more rational explanation/justifications. Why not consider other criteria pollutants?
- 6.2.7 Summary and Causality Determination (Page 6-40): "There is coherence across support to the ozone-mortality relationship." This sentence contradicts the previous sentence and previous section (6.2.2 Biological Plausibility). The previous sentence suggested consistent positive associations between O₃ and cardiovascular mortality, and inconsistent associations between O₃ and respiratory mortality. However, in the 6.2.2 Biological Plausibility section, it suggested that the available evidence for respiratory morbidity supports potential biological pathways by which long-term ozone exposures could result in mortality; however, for cardiovascular morbidity, the evidence is more limited due to the few studies that provide generally inconsistent results.
- The biological plausibility evidence supports an association between O₃ and respiratory morbidity (and subsequent mortality), but the epidemiological studies support O₃ and cardiovascular mortality. More explanation/clarification is needed here.
- 6.2.7 Summary and Causality Determination (Page 6-41): "The strongest evidence due to long-term ozone exposures" These two sentences have been mentioned in the first two paragraphs in this section and many times in preceding sections. This repetition is unnecessary.
- We suggest this section be categorized by cause-specific mortality outcomes (e.g., cardiovascular, respiratory) in addition to total mortality.
- We were unable to verify several of the results. For example Table 6-3

- Goldberg et al. (2013) (P6-47) the first and last result could not find in article, and the acute CAD result does not match the article's Figure 4
- Buteau et al (2018) (P6-50)
- Madrigano et al (20150) (P6-51)
- Table 6-6 (starting page 6-56) and Table 6-7, missing explanation in footnote for the cross symbol (†) in red. Table 6-5 has Note at bottom of each page that defines this symbol as 'U.S. and Canadian studies published since the 2013 Ozone ISA.' In Table 6-6, some studies in other countries are given this symbol (e.g., Bentayeb et al (2015), Kim et al (2017), Sese et al (2017)).

Appendix 7: Health Effects – Other Health Outpoints

- Reproductive & Developmental Effects: Studies listed below that were missing from the review tables should be reviewed. Some of these studies are very recent, but we believe they warrant review for this current Integrated Science Assessment. The studies published in 2019 have been highlighted. We would like to point out that a few studies in our list covered multiple end-points in the developmental effects section, and while they were included in some of the categories, they were excluded from others. For instance, a study could have covered both fetal growth and preterm birth, but was only analyzed in the fetal growth portion only. In addition to setting separate conclusions for individual developmental outcomes, we also suggest adding a short-term ozone effects section in future Integrated Science Assessments.
- Central Nervous System (CNS) Effects: A few studies pertaining to suicide and other mental health outcomes have emerged very recently that provide more epidemiological evidence and should be considered in this Integrated Science Assessment. These and other studies that were not included in this Integrated Science Assessment can be found below. All studies that came out in 2019 have been highlighted. Furthermore, for future Integrated Science Assessments, we suggest that mental health (including depression and suicide) effects that are considered psychiatric outcomes should be separated from neurological outcomes like Alzheimer's disease and autism spectrum disorders as the underlying mechanisms could be quite different.

Appendix 8: Ecological Effects

- The effects of ozone exposure on photosynthesis are well known, and there is a very strong literature base on this topic. However, photosynthesis was mentioned only briefly, and generally only to provide background material. The Appendix would be strengthened by integrating the important role that

photosynthesis plays in influencing the diverse processes and relationships discussed throughout the Ecological Effects section.

- Since the last Ozone Integrated Science Assessment review, large ecosystem experiments, known as Free Air Carbon dioxide Enrichment, or FACE, studies, have contributed a great deal to the knowledge base. Although fewer FACE papers were examined in the current draft Ozone Integrated Science Assessment than in the draft Integrated Science Assessment for NO_x/SO_x Ecological Criteria, those selected for the current Appendix were relevant.

Appendix 9: The Role of Tropospheric Ozone in Climate Effects

- Overall, for this Appendix, there is certainly broader and more recent literature on this topic that was not examined or cited and is probably worthy of closer examination. EPA should consider updating their literature search and adding additional relevant articles (examples are provided below).
- For “Ozone Chemistry and Role in Climate”, methane (CH₄) was listed as one of the ozone precursors; and the report states that ozone can also affect the lifetime of CH₄. It was also stated that shifts in global tropospheric ozone concentrations may be driven most strongly by the spatial distribution of anthropogenic emissions.

Overall, the report very briefly states that U.S. background ozone continues to account for a large fraction of ambient ozone concentrations as a result of stratospheric exchange, international transport, wildfires, lightning, global methane emissions, and natural biogenic and geogenic precursor emissions. Regarding background ozone and methane, it would be useful to expand the discussion of background ozone. These background ozone levels have increased by about a factor of three over the last 50 years in the northern hemisphere and are currently close to levels that could damage human health and the environment (mainly vegetation). Ozone levels in the future will be governed largely by changes in both methane and nitrogen oxides (NO_x); according to a recent scientific paper (none cited in the EPA report), methane induces an increase in tropospheric ozone that is approximately one-third of that caused by NO_x. Hence, control of methane and NO_x emissions would reduce the formation of ozone considerably.

- With reference to global surface temperature, the report briefly talks about a causal relationship between tropospheric ozone and radiative forcing. The report also mentions a likely-to-be-causal relationship, via radiative forcing, between tropospheric ozone and temperature, precipitation, and related climate variables. However, the report lacks any discussion about ozone-climate penalty. Although the magnitude of the “ozone-climate penalty” has generally decreased, climate change is still expected to increase global mean temperatures leading to higher tropospheric ozone concentrations in already

polluted regions, potentially eroding the benefits of expensive emission controls.

- The widely accepted associations of high ozone events with stagnation and heat waves require re-examination. It should be noted that emission responses of natural precursors to climate warming may be significantly modulated by CO₂ levels and ecosystem feedbacks, such that the direction of emission changes should also be considered. Climate variability could drive fluctuations in surface ozone, which has implications for near-term air quality management. Several recent studies have generally projected a climate change penalty on ozone air quality, although the magnitudes are smaller than those projected by earlier studies.
- Use of acronyms should be consistent; e.g. don't go back and forth between "greenhouse gases" and "GHGs".
- Section 9.1.3.2. line 17, "...in the presence of nitrogen oxides (NO_x = NO + NO₂)": Add "and oxygen molecules" at the end of the sentence.
- Section 9.1.3.3. line 4: would be worth including a citation for NOAA ESRL GMD in addition to AR5, since essentially most of global GHG data are gathered by them.
- Section 9.1.3.3. line 8-9: With increasing halocarbon emissions globally, is tropospheric ozone still the third highest radiative forcing agent? Global R-134a levels have been increasing quickly. Check to make sure that the information is still accurate.
- Section 9.2.2. line 8-9: the language is slightly misleading. Zhang et al. 2016 stated that the overall magnitude of the emissions are only slightly smaller in contributing to the O₃ RF compared to the influences of the spatial distribution of anthropogenic emissions. This should be reflected appropriately.
- Section 9.4. References section: Has more citations listed than were cited in Appendix 9. This should be fixed if the assessment is current.
- Missing discussion of co-pollutants (confounding or effect modification).
- Although temperature is mentioned as an exposure along with other climatic factors, ozone and temperature correlations are high during the summer months, and a discussion regarding potential confounding or effect modification by temperature is missing. Some discussion is included in Section 3.10.1.2 for respiratory outcomes specifically, but other endpoints are not sufficiently addressed for confounding/effect modification by temperature in this Integrated Science Assessment.
- Grouped temperature, precipitation, and related climate variables together as "likely to be causal." Temperature should be separated from these other outcomes, as there is a lot of evidence for heat exposure specifically and several health outcomes.

Additional Publications to Review

We recommend U.S. EPA review the following publications, alphabetized by section, appearing to meet inclusion criteria but not discussed in this draft Integrated Science Assessment. Some of these publications are very recent and go beyond the cut-off period. Nevertheless, we believe they are worthy of examination during this draft process, particularly because some studies already included in this draft Integrated Science Assessment were published after the indicated cut-off date in 2018.

Appendix 3: Health Effects – Respiratory

Castner J, Guo L, Yin Y. Ambient air pollution and emergency department visits for asthma in Erie County, New York 2007-2012. *Int Arch Occup Environ Health*. 2018;91(2):205–214. doi:10.1007/s00420-017-1270-7

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