Comment on EPA’s Call for Information on the Integrated Science Assessment for Ozone and Related Photochemical Oxidants, Docket #: EPA-HQ-ORD-2023-0435¹

The undersigned health, medical, and nursing organizations offer the following comments to guide the review of science and causality determinations in EPA’s preparation of the Integrated Science Assessment (ISA) in its review of the national ambient air quality standard (NAAQS) for ozone and related photochemical oxidants. Our organizations strongly support strengthening the ozone NAAQS as warranted by current science, and we urge EPA to ensure a thorough and timely review that considers our suggestions and addresses our key concerns specified below.

To enable EPA to conduct a thorough and comprehensive review of the science and to complete the entire review process and set revised ozone NAAQS by the statutory deadline of December 2025, we offer the following comments.

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1. Introduction

In this Call for Information, the EPA is seeking information:

i. on "the design and scope of the review of the air quality criteria to ensure that it addresses key policy relevant issues and considers the new science that is relevant to informing our understanding of these issues. The Agency seeks new scientific information that may address key uncertainties identified in the last O₃ NAAQS review", and

ii. in “identifying relevant scientific information for the review by submitting research studies that were not part of the prior review, and that have been published or accepted for publication in a peer-reviewed journal including “toxicological studies of effects of controlled exposure to O₃ in laboratory animals, humans, and in vitro systems; epidemiologic (observational) studies of health effects associated with ambient O₃ exposures in human populations; studies examining populations and life stages that may be at increased risk of O₃-related health effects”.²

Before we provide our input on the design, scope, and content of the new ISA as it relates to the primary standard, we want to note two points at the outset. During the reconsideration process of the NAAQS for ozone and related photochemical oxidants (Ox) that EPA halted on Aug 18, 2023³:

i. the agency staff clarified that this process did not re-set the 5-year NAAQS review clock as explicitly laid out in the Clean Air Act. In compliance with this statutory requirement, EPA must complete the ozone NAAQS review by December 2025, given the previous review completed in December 2020. This review process must be thorough and efficient, allowing adequate - but not unduly extended - periods for document (Integrated Review Plan (IRP), ISA, Policy Assessment (PA), Risk/Exposure Assessment (REA)) preparation, for consultation with and input from the Clean Air Scientific Advisory Committee (CASAC), and for public comment. Although we strongly disagree with EPA’s decision to suspend the reconsideration process, thanks to CASAC’s comments and input during that process, EPA got a head start on the new review. The output from that process benefits the newly initiated review by allowing EPA to move more quickly than it might move in other reviews. Yet, in the August, 2023 press release⁴ announcing the new review, EPA has outlined a more-than year-long process just to develop the IRP (convening a public science and policy workshop in spring 2024, summarizing the proceedings of the workshop in summer 2024, releasing IRP in fall 2024). That schedule can and must be hastened.

ii. the experts on the ozone panel of the CASAC near-unanimously (17-1) concluded that the scientific evidence to-date unequivocally demonstrates that the current primary standard is entirely inadequate to protect public health. They further concluded that the scientific evidence supports their recommendations of alternative primary standard of 60-55 ppb. In doing so, they stated that that there was no need for a new ISA but a more robust analyses of data presented in the 2020 ISA was warranted.⁵ EPA could release its re-assessment of older studies and assessment of newer studies in an appendix or an addendum to the 2020 ISA and therein address the specific issues raised by the 2022 CASAC panel. Alternatively,

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² EPA. (08/25/2023). Call for Information on ISA for ozone and related photochemical oxidants, 88 FR 58264
⁴ EPA. (08/21/2023). EPA Initiates New Review of the Ozone National Ambient Air Quality Standards to Reflect the Latest Science
EPA could present this information in technical memos, as it did for the reconsideration process. The CASAC experts also disagreed with and raised concerns about several pivotal decisions and assumptions in EPA’s analyses based on which the agency concluded that the current primary standard of 70 ppb did not warrant revision in its 2020 review.

In this review process, we ask that EPA focus on addressing the concerns raised and recommendations made by the CASAC during the reconsideration process and also seriously consider the input from public comment to expedite the process without sacrificing scientific rigor in its assessments. Such a systematic approach is necessary to complete the ozone NAAQS review by December 2025 and for the public to experience the attendant benefits of stronger standards without additional delays.

In the following sections we offer our comments and recommendations for your consideration in drafting the ISA.

2. Determining causality
Pollutant exposure-related causality of health endpoints determined in the ISA underlies Policy Assessment (PA) which in turn informs the primary NAAQS. Since causality determinations essentially drive standard setting, a rigorous and unbiased review of scientific literature is essential to protect public health. At the outset, we draw EPA’s attention to the recent report from the National Academies on their assessment of the agency’s causality framework that underlies the NAAQS reviews’ and the CASAC letter to EPA. Both documents raised concerns about EPA’s science assessments and flag the significant limitations and the arbitrary application of the frameworks that the agency used in its 2020 ozone (PM) ISAs to base its conclusion to retain the standard.

The National Academies report notes that “(t)he ISA causal determination framework is not a procedure that can be tested objectively or evaluated against the ground truth” and thus needs to be interpreted and applied judiciously and with caution. The report also noted that EPA does not consider heterogeneity in exposure responses between healthy and vulnerable populations in determining causality. In the current framework, EPA explicitly considers only the overall average population effects for causality determination and considers heterogeneity in responses only after it has made a causal determination. “The current framework separates description of vulnerable groups…from causal determinations, potentially obscuring understanding of causal relationships for the more sensitive groups of subjects”. This heterogeneity in exposures and exposure responses between vulnerable subpopulations and the general population as a whole is fundamental to determining and applying “an adequate margin of

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safety” in standard setting (details in Sections 3 and 6). This point gains particular significance now as the number of sensitive and vulnerable groups that are more susceptible to pollution exposure is growing. At what level of the NAAQS the vulnerable groups would be protected follows from integrating ozone exposure and responses to such exposure from vulnerable groups into causal determinations. As such, we ask that EPA consider the heterogeneity in exposure responses in making causal determinations.

3. Applying adequate margin of safety
Section 109, Code 7409 of the Clean Air Act explicitly requires that the “National primary ambient air quality standards...shall be ambient air quality standards the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health.”

As the National Academies report pointed out that “the courts have repeatedly affirmed that the NAAQS must protect sensitive or at-risk people and have remanded NAAQS decisions to EPA for failure to adequately consider these groups or for failure to explain how the standards are adequate to protect their members.” As the 2021 PM CASAC panel also noted: “adequate margin of safety... corresponds to an adequate margin of safety for at-risk subpopulations, not the average person. This relates to multiple concepts of a margin of safety such as allowing for uncertainty in health effect estimates and protection of at-risk populations.” This panel recommended that EPA make clear that “the current scientific evidence indicates that some subpopulations face higher health burdens from PM₂.₅, including for higher levels of exposure and for increased risk of adverse health responses to a given level of exposure. This includes subpopulations based on race/ethnicity, socio-economic position, age (e.g., children), and others.”

The groups at increased risk of adverse health impacts from ozone exposure are multiple and diverse. They include people at vulnerable life stages (children, elderly, pregnant people), with health issues (pre-existing respiratory, cardiovascular, neurological, physiological and other morbidities), of specific socioeconomic/demographics (people of color, of specific races/ethnicities, of lower incomes, with lower education), at specific locations (living or working near major stationary sources, highways, ports), and of specific occupations (those working outdoors such as in construction, delivery services, mail carriers, etc.). Some groups have multiple vulnerabilities. Contribution of each of these vulnerability categories to ozone-caused or -associated adverse health effects should be integrated into causality determinations which inform NAAQS. Only then would the at-risk populations be protected to the same extent as the average population.

4. Weighting different types of research data
In making causal determinations, the ISA is expected to include data from different types of health studies: epidemiology studies (i.e. population- and panel-based observational designs), controlled human exposure (CHE) chamber studies, and animal toxicity studies. The ISA must adequately differentiate or differentially weight these different lines of evidence examining the health effects of ozone and related photochemical oxidants.

12 Clean Air Act. 42 U.S. Code § 7409 - National primary and secondary ambient air quality standards
13 National Academies’ Report on Causality Framework (10/2022), page 23
The 2022 CASAC panel recommended that in the ISA, EPA should “consider revising its approach to interpreting evidence from CHE and epidemiological studies. Relative weighting of study findings is scientifically more robust when based on individual study details, strengths, design, and infrastructural study planning and execution rather than a more generic up-scaling or weighting of one approach over another… (and) the various study designs on their own merit, to combine the relative strengths of the various design approaches to arrive at the most informed interpretation given study strengths and uncertainties. This approach is relevant when interpreting the evidence for causality determinations and also to help identify and establish exposure levels associated with no adverse health effects.”

Different studies have their own specific strengths and limitations that define their contributions to causality determinations. The ozone CASAC panel asked that in the ISA, EPA “directly address the differences in concentration-response relationships between CHE and epidemiology studies” and “more fully examine the strengths and weaknesses of CHE and epidemiology in understanding health effects at ambient concentrations.” The panel further recommended the “consideration of the various study designs on their own merit, and to combine the relative strengths of the various design approaches to arrive at the most informed interpretation given study strengths and uncertainties. This approach is relevant when interpreting the evidence for causality determinations and also to help identify and establish exposure levels associated with adverse health effects.”

An important inherent limitation of CHEs is that CHE study participants are usually young, healthy, and fit adults. “Important segments of the general population (such as infants and young children, pregnant women, senior adults, or those with pre-existing severe or unstable respiratory or cardiovascular disease) are typically excluded from (CHE) study participation for ethical or safety reasons” especially since “it is never possible to conclude that there is no risk” to these groups in such studies. CHEs also do not typically include the more vulnerable socioeconomic subpopulations such as historically marginalized racial/ethnic groups or individuals with disadvantaged socioeconomic status. CHE studies generally involve short durations of exposure with “few opportunities for follow-up of more delayed effects, are of small size limiting the ability to evaluate rare and especially serious clinical events and the form of the exposure (peak vs. chronic).” Another serious limitation is the difference between ambient air and laboratory-generated O₃ used in CHE studies. The latter involves exposure to a single pure pollutant (O₂) without other related photochemical oxidants (Oₓ) that are found in the former so that these studies may underestimate or miss Oₓ effects at low concentrations. CHE study findings are therefore “not conservative enough to protect at-risk populations” and “(t)his is relevant for considering whether a potential alternative standard has an adequate margin of safety to protect these potentially at-risk populations.”

Epidemiological studies also have limitations “in their ability to address and minimize confounding, for example by co-pollutant exposures, and by potential selection and information

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16 CASAC review of ozone ISA. (11/22/2022). page 2
17 CASAC review of ozone ISA. (11/22/2022). page 2
18 CASAC review of ozone ISA. (11/22/2022). page 2
21 CASAC review of ozone ISA. (Nov 22, 2022). page 13 (4)
22 CASAC review of ozone ISA. (Nov 22, 2022). pages 62 (A-33) and 21 (12)
bias,” but they often include a wider range of study participants, including vulnerable populations, “can evaluate longer-term exposure and exposure to the real-world ambient complex of mixtures as well as outcomes that are more delayed in nature.”\(^\text{23}\) As the 2022 ozone CASAC panel suggested, “when assessing evidence for a regulatory standard for ambient air pollution, the absence of evidence from the controlled human exposure studies should not negate evidence from the epidemiologic studies given the limitations of controlled human exposure studies.” and “(w)hen available, epidemiologic studies should be weighted more strongly than controlled human (and animal) exposure studies.”\(^\text{24}\)

Epidemiology studies are more numerous and consideration of such studies from across the world can add to the knowledge base and reduce uncertainties. Therefore, EPA must give more weight to the evidence from epidemiology studies even as it thoroughly evaluates evidence from multiple complementary study types. EPA should consider the findings from epidemiologic studies “just as, or even more, relevant than the CHE findings in determining an exposure level with no adverse effects”\(^\text{25}\) when evaluating O\(_3\)/O\(_x\) health effects at low concentrations and in vulnerable groups.

5. Reviewing Scientific literature

i. Revising PECOS

Causality determinations conducted in the ISA form the basis for determining the standard and its adequacy in protecting public health with an adequate margin of safety. To ensure scientifically robust and accurate determinations of causality of various health endpoints from short- and long-term Ox exposures, it is imperative that the EPA consider all relevant research studies irrespective of geographic location of study sites. In its 2020 ozone ISA\(^\text{26}\) EPA had introduced a new Population, Exposure, Comparison, Outcome, and Study Design (PECOS) framework, to refine the scope of ISAs by evaluating experimental and epidemiologic studies for their inclusion or exclusion from the ISAs in NAAQS reviews of criteria air pollutants. Both the 2022 ozone CASAC panel and the National Academies (in their causality framework assessment report) urged caution in applying the PECOS tool in ISAs. They recommended broadening PECOS study selection criteria to include studies conducted outside of the USA and North America and to apply them consistently, transparently, and only with an appropriate and strong rationale.

The 2022 ozone CASAC panel expressed “concerns about transparent and uniform application of (PECOS) eligibility criteria for study inclusion and about differential application of geographical location across health endpoints and exposure durations in determining study eligibility for consideration.”\(^\text{27}\) The panel cited specific examples in the 2020 ISA where the PECOS application was both inconsistent and lacked rationale: the ISA “limits the cardiovascular-relevant studies to North America, Europe, and Australia, which differs from the restriction to the U.S. and Canada for respiratory endpoints without a sufficient rationale for the difference. In addition, the PECOS structure excluded considerable research conducted in Asia that would be useful in addressing existing uncertainties without a sufficient rationale.”\(^\text{23}\) While “variations in local climate, concurrent exposures, lifestyle issues etc. exist and will persist,” the rationale for the current threshold in PECOS limiting epidemiological

\(^{23}\)-CASAC review of ozone ISA. (11/22/2022). page 13 (4)
\(^{24}\)-CASAC review of ozone ISA. (11/22/2022). pages 79 (A-50) and 64 (A-35)
\(^{25}\)-CASAC review of ozone ISA. (11/22/2022). page 2
\(^{27}\)-CASAC review of ozone ISA. (11/22/2022). page 14 (5)
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EPA justified its use of PECOS in restricting its consideration to only U.S. and Canada-based studies so as “to provide a focus on study populations and air quality characteristics that are most relevant to circumstances in the U.S.” Note that Canada’s air quality is controlled by more stringent ambient air quality standards (for all criteria pollutants) than those of the US. The Canadian Ambient Air Quality Standard for ozone was set at 63 ppb in 2015, is currently at 62 ppb, and will be reduced to 60 ppb in 2025 compared to the current US NAAQS of 70 ppb set in 2015. Further, as the panel pointed out that “(o)zone… is a pure chemical and its health effects should be the same throughout the world” and as such (dis)similarity of airsheds should not be a factor in considering studies from across the world. The CASAC members also pointed out “it is unclear…why the PECOS criteria for ‘study location’ differs between the short-term and long-term assessments in the 2020 ISA” and “(E)xclusion of well-designed and performed epidemiological research in non-North American populations limits the thoughtful application of scientific data that could be used to refine and improve understanding of primary and secondary health and material impacts.”

The National Academies’ report also cites the 2020 ozone ISA where EPA uses PECOS selectively to downweight its earlier causal determination of short-term ozone exposure on total (nonaccidental) mortality to “suggestive of, but insufficient to infer, a causal relationship.”

Regarding EPA’s reasoning in this conclusion, the report states how EPA is “still not explicit about the basis on which some studies are included, and others excluded, under these (PECOS) criteria”, and one study “which was included in the 2019 PM ISA (and so presumably passed study quality and relevance screening there)” was excluded from the 2020 ozone ISA. Clear and precise definitions of what evidence is considered relevant and what aspects of study quality are considered in the ISA along with their consistent application are essential to the NAAQS review process. Such definitions must be reviewed and revised by experts such as CASAC to make the process more robust and provide transparency. The process requiring iterative CASAC and public review followed by EPA response and revision provides an important mechanism for providing transparency and garnering consensus in the NAAQS process, including in determining causal relationships. In its 2020 ozone ISA, EPA used several tools including PECOS, Health Assessment Workspace Collaborative (HAWC), and Health and Environmental Research Online (HERO) to explain and document criteria for assessing study relevance and quality. The report stated that it inappropriate to “use the outputs of such tools (e.g. HAWC, PECOS, HERO) as decisive benchmarks for inclusion in causal determination,” but “their continued use and refinement would improve clarity regarding the study selection and evaluation process. The key aspects of study quality and relevance that are assessed in the weight of evidence approach for the causal question under consideration may then be documented. The exact criteria may be pollutant, study type, or endpoint specific, so any individual tool may not be applicable for every causal determination, and specific tools will evolve and new ones may be developed. Therefore, it may be inappropriate for the (causal determination) framework to prespecify use of any particular tool.

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28 CASAC review of ozone ISA. (11/22/2022), page 40 (A-11)
29 Canada Air Quality (ccme.ca)
30 CASAC review of ozone ISA. (11/22/2022), pages 65 (A-36), 40 (A-11)
34 EPA. Health and Environmental Research Online: a Database of Scientific Studies and References. (accessed 01/2023)
although the framework could include a set of core scientific principles regarding study inclusion and quality to increase transparency and replicability.” The “causal determination framework, (39) would benefit from formalization of criteria to assess study validity, and the individualized use of tools for each ISA (such as PECOS, study quality criteria tables, and narrative study quality reviews) to implement those criteria. (36)

We ask that the EPA implement these specific suggestions and recommendations from the CASAC panel and the National Academies in this ISA to ensure a thorough review of pertinent scientific literature in making robust causality determinations.

ii. Studies for consideration
In this ISA, we expect the agency to address the various scientific issues discussed by the members of the 2022 ozone CASAC panel during their reconsideration of the 2020 ozone NAAQS. During their multiple meetings from summer 2022 through summer 2023, the panel reviewed studies that EPA presented in the 2020 ISA and several others that were excluded. The panel also reviewed peer-reviewed studies published since the cut-off date for studies included the 2020 ISA. In addition to these studies cited in the panel’s Nov, 2022 report on its ISA review (37) and the June, 2023 report on its PA (Draft 2) review, (38) Here we highlight a few studies for consideration in the ISA:

Respiratory system effects: On the effects of ozone exposure on respiratory function, EPA distinguished between lung function impacts and symptoms in evaluating the CHE studies. Adams (2006) (39) conducted ozone dose–response chamber experiments on a cohort of 30 healthy young adults and found a 60 ppb exposure not to significantly affect lung function. But Brown et al. (2008) (40) conducted a reevaluation of the existing lung function data from Adams, and using standard statistical methods, showed that a 60 ppb exposure actually causes a highly statistically significant decrease in mean FEV(1) (41) responses. EPA’s own researchers, Kim et al. (2011), found that “exposure of healthy young adults to 0.06 ppm ozone for 6.6 hours causes a significant decrement of FEV1 and an increase in neutrophilic inflammation in the airways.” (42) More recent data from Hernandez et al. (2022) (43) shows similar results. Their randomized, double-blinded crossover study assessed “O3 exposure experienced during activities of daily living”. Healthy participants of 18–50 years of age were exposed to either filtered clean air or 60–80 ppb (average 70 ppb) ozone during a 6.6-hour day with minimal exercise (total of 5 minutes throughout the exposure day). The researchers found O3-induced decrements in lung function and neutrophilic airway inflammation similar to those

(39) Adams, W. C. (2006). Comparison of chamber 6.6-h exposures to 0.04–0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhalation Toxicology, 18(2), 127–136.
(41) Spirometry: Procedure, “Normal” Values, and Test Results. Forced expiratory volume (FEV1) is the amount of air a person can force from the lungs in one second. It is measured during a pulmonary function test (also called spirometry test) and used in the diagnosis of COPD.
(42) Kim, C. S. et al. (2011). Lung Function and Inflammatory Responses in Healthy Young Adults Exposed to 0.06 ppm Ozone for 6.6 Hours. American Journal of Respiratory and Critical Care Medicine, 183(9).
incorporating moderate intermittent exercise. These findings suggest that current \( O_3 \) NAAQS of “70 ppb causes deleterious effects on lung function and airway inflammation in periods of minimal exertion in healthy individuals.”

These and other studies which clearly show impaired lung function at 60 ppb used cohorts of healthy young subjects in the experiments. While EPA may not consider these lung function impacts as symptoms, these studies with pure ozone (compared to the ambient air mixture of multiple pollutants including Ox) only included healthy young adults. More severe respiratory symptoms at ozone levels down to 60 ppb are likely for the more sensitive populations our organizations serve such as children, elderly people, and people with existing pulmonary issues (e.g. asthma).

Since direct dose-response/exposure measurements of sensitive groups are not available, in inferring causality\(^44\) EPA must consider the above results as biological plausible of significant respiratory illness at 60 ppb exposure. One well-conducted robust study on respiratory impacts that could be useful in the context of interpreting CHE study effects on sensitive subgroups\(^45\) is the 1998 work from Korrick et al.\(^46\) This study which was in the 2013 ISA (2015 ozone NAAQS review) was inexplicably excluded from the 2020 ISA. In this large panel study of more than 500 subjects hiking up and back down Mt. Washington, NH, the scientists found a 4x larger decrement in FEV1 or FVC pre/post hike among a subset [\( n=40 \)] of participants with asthma or a history of wheeze compared to those without such diagnoses, even though exposures were mostly well below 70. These respiratory effects were observed below 50 ppb and the exposure for the top quintile was 53 ppb.

Multiple epidemiological studies provide evidence of harm to children at ozone levels below the current standard, including a recent Chinese study of a large cohort of children.\(^47\) This study analyzed the impacts of low level \( O_3 \) exposure on asthma-related hospitalizations among 3,475 children. Using air pollution and meteorological data, they employed a case-crossover design and conditional logistic regression analyses to evaluate the association between asthma attacks and outdoor air pollution with lag structures in both single and multi-pollutant models. They estimated the impacts of \( O_3 \) exposure on an asthma attack at three maximum daily 8-hour sliding average ozone concentrations of \( \geq 50 \) ppb, 40-50 ppb, and \(< 40 \) ppb. The study showed that \( O_3 \) concentration above 40 ppb contributed to an increased risk of acute asthma attacks on each day of lag, in both single- and multi-pollutant models.

Greek scientists recently conducted a panel study (Respiratory Effects of Ozone Exposure in children; RESPOZE)\(^48\) in two cities with ambient ozone concentrations higher than the EU standard of 61.2 ppb. Using fixed site measurements and modeling calibrated for personal exposures, they evaluated the respiratory health effects of long-term \( O_3 \) exposure in 10-11-year old schoolchildren. The study showed that a 5 ppb increase in ambient ozone is associated with reduced lung volumes (FVC and FEV1) and decreases in lung growth over

\(^{44}\) “An inference of causality is strengthened by results from experimental studies or other sources demonstrating biologically plausible mechanisms. A proposed mechanism, which is based on experimental evidence and which links exposure to an agent to a given effect, is an important source of support for causality.” \textit{Integrated Science Assessment for Oxides of Nitrogen – Health Criteria}

\(^{45}\) 06/2023. CASAC Review of EPA’s PA for the Reconsideration of the Ozone NAAQS (Draft Ver 2), page 55 (D-5).


the study period. American physicians also offer a clinical perspective on how the current ozone NAAQS of 70 ppb does not adequately protect children. In their review, they discussed the respiratory harms of ozone exposure on healthy children and those with underlying respiratory disease and the impacts of climate change on ozone levels. There is complementary evidence of causality of significant respiratory illness at exposures above 60 ppb from controlled human exposure studies assessed in the 2020 ISA.

**Cardiovascular system effects:** A recent European study offers insights into the mechanisms of the biological effects of ozone on cardiovascular mortality and cardiovascular morbidities, including hypertension, coronary ischemia, and impairment of autonomic control. A recent Chinese study suggests a potential biological mechanism between ambient ozone exposure and cardiometabolic abnormalities: acute short-term ozone exposure may trigger autonomic nervous system (ANS) imbalance and activate sympathetic-adrenomedullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes.

**Nervous system effects:** A new review of literature shows molecular and systemic biological mechanisms that strongly link ozone pollution to intestinal alterations and permeability which are implicated in several inflammatory and neurodegenerative diseases. Multiple lines of evidence show that long-term or repeated exposure to ambient ozone “induces a state of chronic oxidative stress with the loss of regulation of the inflammatory response, both in the intestine and in the brain, where the functionality of both structures is altered and plays a determining role in some neurodegenerative and chronic degenerative diseases” such as Parkinson’s and Alzheimer’s disease as well as bowel diseases as Inflammatory Bowel Disease, Crohn’s Disease, and Irritable Bowel Syndrome. A comprehensive and updated systematic review and meta-analysis of linkages between exposure to air pollution exposure and depression, showed that short-term exposure to O₃ was associated with an increased risk of depression (relative risk: 1.011, 95% confidence interval: 0.997–1.026).

An Indian study suggests that “prenatal and postnatal exposure to high levels of air pollution are linked to behavioral alterations in offspring. O₃ also enhances blood circulation. It has antibacterial action, which may have an impact on the gut microbiota. It also activates

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50 Adams, W. C. (2006). Comparison of chamber 6.6-h exposures to 0.04–0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. *Inhalation Toxicology*, 18(2), 127–136.


52 Kim, C. S. et al. (2011). Lung Function and Inflammatory Responses in Healthy Young Adults Exposed to 0.06 ppm Ozone for 6.6 Hours. *American Journal of Respiratory and Critical Care Medicine*, 183(9).


immunological, anti-inflammatory, proteasome, and growth factor signaling. Prolonged O₃ exposure causes oxidative damage to plasma proteins and lipids and damages the structural and functional integrity of the mitochondria.”

Reproductive System effects: Another recent systematic review of literature shows a strong link between prenatal exposure to ozone (and also fine particulate matter (PM₂.₅) and heat) and preterm birth, low birth weight, and stillbirth. “Positive associations were found across all US geographic regions. Exposure to PM₂.₅ or ozone was associated with increased risk of preterm birth in 19 of 24 studies (79%) and low birth weight in 25 of 29 studies (86%). The subpopulations at highest risk were persons with asthma and minority groups, especially black mothers.”

A large multicity Chinese study examined the climate penalty (increase in ambient temperature) on ozone exposure-associated neonatal impacts/birth outcomes such as small for gestational age (SGA), large for gestational age (LGA), preterm birth (PTB), and low birth weight (LBW). The researches estimated the modification effects of ambient temperature on associations of ambient O₃ exposure before and during pregnancy and found that with a 10 μg/m³ increase in ambient O₃ exposure at high temperature level (>75th percentile), the risk of LBW increased by 28% (HR: 1.28, 95% CI: 1.13-1.46) during the second trimester and the risk of LGA increased by 116% (HR: 2.16, 95%CI: 1.16-4.00) during the entire pregnancy.

Based on the data now available and the thorough review of studies by the CASAC panel, EPA should reassess and revise the causality determinations of short-term and long-term exposure particularly on nervous system effects, cardiovascular and mortality effects (especially the down-grading from likely causal to suggestive - relative to the 2015 ISA determination - of short-term exposure), and reproductive effects. In summary, new scientific evidence and re-evaluation of existing data presenting in the 2020 ISA implicate ozone exposure as a causal agent in metabolic, cardiovascular, and respiratory morbidities and related mortality. These data strongly support revising the current 70 ppb ozone NAAQS set in 2015 to no higher than 60 ppb to protect public health with an adequate margin of safety. Multiple international entities, which have assessed the same literature on ozone health impacts as the EPA, have set standards close to 60 ppb to protect public health, which was also the advice given to EPA by the 2015 CASAC.

6. Considering cumulative impacts
In this ISA, EPA needs to consider cumulative impacts, i.e. impacts from “totality of exposures to combinations of chemical and non-chemical stressors and their effects on health, well-being, and quality of life outcomes” in determining causality of health effects from ozone exposure. Ambient air has multiple pollutants including criteria air pollutants (CAPs) like ozone, NO₂, SO₂, PM₂.₅ and also hazardous air pollutants at varying concentrations. These pollutants do not exist

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60 Bekkar, B. et al. (2020). Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. JAMA Netw Open, 3(6), e208243
62 Ozone standards are 61.2 ppb in the European Union; 62 ppb in Australia; 63 ppb in Canada; and the World Health Organization recommends 51 ppb in its air quality guidelines.
63 EPA’s Guidelines for Cumulative Risk Assessment (05/2023). GLOSSARY OF KEY TERMS; page v
in isolation nor are they inhaled individually. Short-term and/or long-term exposures to these pollutants collectively cause or are associated with similar and sometimes overlapping adverse health endpoints. They might act in a concerted, additive, or coeffective fashion to amplify the observed health effect. If the co-pollutants are highly correlated with each other, and if each one has an effect on morbidity or mortality, then the statistical association of each individual pollutant with morbidity or mortality would also reflect the effects of other pollutants in the group. Qualitative and quantitative analyses of the morbidity/mortality burden attributable to specific pollutants in ambient air would always have some degree of uncertainty due to confounding from these co-pollutants.

Law professor Deborah Behles observed more than a decade ago in her analysis of what EPA considers in setting primary NAAQS: “EPA has designated six pollutants, which all have relationships with each other, as criteria pollutants…. Of these, particulate matter, ozone, nitrogen dioxide, and sulfur dioxide are closely related to each other due to their chemical and physical attributes, the similarity of their emission sources, and their association with similar adverse health impacts…. Inhaling air pollutants can lead to a variety of adverse respiratory and cardiovascular health effects. This potential risk for health impacts is likely greater when the mixture of pollutants that exists in ambient air, rather than isolated pollutants, are inhaled.

Despite the evidence of potential cumulative impacts, EPA has continued to focus its analysis of health impacts on isolated pollutants instead of the actual mixture we breathe…. EPA should evaluate and consider cumulative health impacts when it sets national ambient air quality standards under the Clean Air Act…. Consideration of cumulative health impacts is consistent with the Act’s requirement to set standards at a level requisite to protect public health, could translate into a more accurate way to estimate risks, and could provide a tool for prioritization of emission reductions in the most heavily impacted communities.”

EPA’s own research also attests to the importance of cumulative impacts in risk assessments of individual pollutants. “(T)o arrive at a realistic assessment of exposure risks, regulatory authorities arguably should consider cumulative stressors and exposure data derived from cumulative risk assessment.” Adoption of a multi-pollutant framework that includes “measurements of a rich array of air pollutants, and application and development of statistical methods that are suitable for a large and highly correlated number of variables and that can incorporate what is already known about their interrelationships” will result in “an air quality management program that protects public health through a better understanding of the features of a complex air pollution mixture that are most deleterious to health.”

In its May 2023 (draft) Cumulative Risk Assessment (CRA) Guidelines, EPA notes: “CRAs have been performed to inform decisions on some of the National Ambient Air Quality Standards (NAAQS). The NAAQS, as standards for ambient air, reflect consideration of the cumulative concentrations of various pollutants in ambient air, which result from emissions from many sources.” But this is true only for the secondary (human welfare-based) NAAQS for which EPA considers these CAPs together as co-pollutants: “Cumulative ecological risk assessment has also been performed to inform NAAQS decisions, e.g., in assessing ecological risk associated with the co-occurrence in ambient air of multiple oxides of sulfur and nitrogen.” But in setting

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64 Behles, D. N. (2010). 28 Pace Envtl. L. Rev. 200, page 2 (1)
65 Alves et al. (2012). EPA authority to use cumulative risk assessments in environmental decision-making, page 1
67 Environmental Protection Agency Risk Assessment Forum. (05/2023). Guidelines for Cumulative Risk Assessment Planning and Problem Formulation (Draft for Public Comment); Document #: 2023-12972
68 EPA’s Guidelines for Cumulative Risk Assessment (05/2023). Appendix A-6
primary (human health-based) NAAQS, EPA considers the cumulative risks (in Health Risk and Exposure Assessments) of CAPs only among chemically or physically related groups (for which individual NAAQS are set) but not across the different CAPs.\(^{69}\) The ozone NAAQS, for example, is for \(O_3\) as the indicator for ozone and other photochemical oxidants (collectively referred to as Ox), some of which are species with poorly defined properties and more difficult to quantitatively measure but may play a role in ambient health effects, co-occurring with ozone in ambient air.\(^{70}\) Similarly, \(NO_2\) and \(SO_2\) serve as indicators of multiple nitrogen oxides and sulfur oxides respectively. The PM\(_{2.5}\) and PM\(_{10}\) standards are set for groups of similar sized particulate aerosols: “In the case of risk assessments for fine particulate matter, the assessment is of the whole mixture of fine particulate matter and reflects cumulative health risk associated with all particulate substances in ambient air that fall into the particle size class of interest.”\(^{71}\)

EPA’s current risk assessment strategy for primary NAAQS is not responsive to cumulative risk factors such as other pollutants that co-occur with the specific CAPs under consideration. For example, ozone and PM\(_{2.5}\) co-occur in ambient air and would be expected to have additive effects on specific health endpoints which they share. “A recent Canadian study…states that "Associations between Ox and mortality were consistently stronger in regions with elevated PM\(_{2.5}\) transition metal/sulfur content and oxidative potential."”\(^{72}\)

Ed Avol, a 2022 ozone CASAC member, summarized thus: “A recurring shortfall of virtually all NAAQS reviews has been the lack of acceptance and strategy to address multi-pollutant co-exposures. Rarely do real-world ambient exposures occur one pollutant at a time. Based on both clinical and epidemiological research, other co-pollutants can serve to increase the impact or intensity of response. Acknowledgement of this more realistic exposure scenario would seem appropriate. In the regulatory context of reviewing individual criteria pollutants under the Clean Air Act, one approach to address multi-pollutant exposures might be to consider other contaminants as potential risk factors that could elevate or decrease exposure risk, much as SES, occupation, life stage, race, pre-existing disease, et cetera are considered in assorted reviews.”\(^{73}\) Mr. Avol also asked EPA to consider health endpoints (from a CAP exposure) cumulatively, i.e. focus on “the combined strength of identified negative health outcomes across several organ system indices (respiratory, cardiovascular, neurologic, reproductive, metabolic)” instead of on “individual organ system uncertainties”\(^{74}\)

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\(^{69}\) EPA. (2014). Health Risk and Exposure Assessment for Ozone - Final Report; EPA-452/R-14-004a; This REA for ozone NAAQS is an example of EPA’s REA that does not include cumulative risks.

\(^{70}\) Clean Air Scientific Advisory Committee (CASAC). (11/22/2022). Review of the EPA’s Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report); EPA-CASAC-23-001; George A. Allen comment, pages 31-33

\(^{71}\) EPA’s Guidelines for Cumulative Risk Assessment (05/2023). Appendix A-6

\(^{72}\) CASAC. (11/22/2022). Review of the EPA’s ISA for Ozone; George A. Allen comment, pages 31-33

\(^{73}\) CASAC. (6/9/2023). Review of the EPA’s PA Draft Version 2 for Ozone NAAQS Reconsideration; page 60

\(^{74}\) CASAC. (6/9/2023). Review of the EPA’s PA Draft Ver2 for Ozone NAAQS Reconsideration; Ed Avol, page 59
Comment on EPA’s Call for Information on ISA for ozone NAAQS, Docket #: EPA-HQ-ORD-2023-0435 – 10/24/2023

Figure 1. Summary of the major risk factors influencing the health impacts associated with ozone exposure. These factors (in red boxes) should be considered cumulatively in determining causality of ozone impacts as this drives NAAQS determination. The individual health effects (boxed in black) also need to be combined to assess the magnitude of impact on total human health caused by ozone exposure.

In summary, EPA should consider cumulative impacts of multipollutant exposure and of the socioeconomic factors (described in Section 3) on the human body as a whole, in determining causality of health effects of ozone exposure in the ISA. Such a holistic cumulative approach would better capture the adverse impacts of the ozone rather than under-estimate them as the current approach does and afford better protection through tougher standards.

7. Considering climate change

Climate change is an effect modifier of ambient air pollutants. It is also a threat multiplier and injustice amplifier. Climate change has “health and welfare consequences beyond air quality and other effects from combinations of climate and air quality.” Climate change imposes measurable impacts (i.e. climate change penalty) on air quality even if current conventional pollution from anthropogenic sources remains the same or even goes down.

As a conventional air pollutant due to its powerful photochemical oxidative property, ozone contributes to climate change indirectly by damaging plants - the only and largest natural carbon sequestering agents. Plants inhale ozone during respiration through their leaf stomata which causes oxidation of plant tissue, resulting in compromised photosynthesis and premature plant death. As seen with human health, the health of plants exposed to ozone is further affected by many factors including the presence of other air pollutants which exacerbate ozone injury.

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76 National Parks Service. Effects of Air Pollution: Ozone Effects on Plants

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Figure 2. Direct (in shaded box) and indirect climate change impacts of ambient tropospheric ozone.
More frequent and intense heatwaves, increased solar radiation, and higher summertime temperatures accelerate the chemical process of ozone formation and likely increase ground-level ozone concentration peaks. Ozone exposure also exacerbates the adverse health effects caused by other climate change impacts such as heat stress, poor air quality leading to poor life quality and premature death.77,78

Ozone also contributes to climate change directly – it is the third most important anthropogenic greenhouse gas after carbon dioxide and methane.79 Short-lived climate pollutants including ozone are the largest contributors to global warming after carbon dioxide, are responsible for up to 45% of current global warming, contribute to ~7 million annual premature deaths worldwide from air pollution, and cause 110 million metric tons/y of crop losses globally.80

In recognizing the changing atmospheric environment (climate change induced modifications in “weather patterns, and large-scale emissions changes (that) alter the chemical environment that governs atmospheric transformations”), the National Academies’ report on assessing the causality determinations framework notes that “The framework does not address how the current causal determinations would capture the ways changing climate likely will impact causal linkages between criteria pollutants and long-term ecological effects.”81 The report suggested that EPA update the ISA Preamble82 “to seek and emphasize new information on the effects of climate change on air quality, as well as the expected long-term effects of changing air quality and climate on large-scale ecological processes and human vulnerability.”83 In the ozone ISA, the EPA needs to evaluate if the causality framework adequately capture how climate change will impact causal linkages between criteria pollutants and associated health effects and also update the Preamble, per NAS suggestion.

To protect public health “from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air,” EPA should therefore consider both the direct and indirect climate change contributions of ambient ozone to the associated adverse health impacts. This climate penalty is another factor that needs to be integrated into the cumulative risk assessment approach.

8. Considering environmental justice

To ensure environmental justice and equitable benefits of clean air, the disproportionately higher health burden from ozone exposures borne by vulnerable subpopulations needs to be assessed in the ISA. The American Lung Association previously provided detailed comment to EPA on this issue during the recently concluded particulate matter NAAQS reconsideration, the rescinded ozone NAAQS reconsideration. This was specifically noted in the National Academies report on EPA’s causality assessment framework: “The need for greater attention to at-risk populations and environmental justice is also a major theme in comments on later stages of the NAAQS review process (American Lung Association, 2021). However, the concern is also

80 Climate and Clean Air Coalition (CCAC). (2019). Why act on short-lived climate pollutants (infosheet)
evident in EPA’s ISA causal determinations.” The report stated that “environmental justice requires enhanced consideration of heterogeneity in health responses linked to socioeconomic status, race and ethnicity, and community- and individual-level social determinants of health.”

This heterogeneity in response to ambient air pollutant exposure could be due to numerous factors. “Heightened response in humans can be due to age, comorbidities, or other environmental, socioeconomic, behavioral, epigenetic, or genetic factors.” As the ozone CASAC panel noted, “exposure to social and environmental stressors are often co-located” which “influences disparate health impacts (i.e., effect modification) and perpetuates health disparities.” The panel recommended that “it would be useful to frame the EJ features and EJ-related literature in a future ISA” and EPA should include “studies with an adequate number of participants and data from racial/ethnic minority groups and from a range of income and wealth categories” in the ISA. The PM CASAC panel also recommended that EPA pay more attention to both disparities and consideration in setting the standards to narrow the persistent proportional exposure gap.

The purpose of setting primary NAAQS being to “…protect the health of any [sensitive] group of the population,” the ozone CASAC panel made specific suggestions related to at-risk communities for consideration in the ISAs:

- that the analysis of at-risk populations “be spread over the entirety of the ISA as relevant outcomes are discussed” and not relegated to a single section as they are not “separate from, and secondary to, the main conclusions of the ISA,”
- to include discussion of all available data on at-risk communities and “bring forward analyses and references from previous ISAs that are relevant for the current ISA; especially for those at-risk populations for which there is adequate or suggestive evidence for increased risk,”
- to “consider including “insufficient quantity” to the classification of suggestive evidence” in causality determination “to allow for adequate analysis for growing literature addressing potential adverse effects for the identified at-risk communities,”
- the “research exploring adverse effects of ozone on at-risk populations” being limited, “(b)etter characterization requires an increased number of studies specifically designed to explore associations between ozone and at-risk populations. Therefore, increased research in this area is encouraged to enable better evaluation in the future.

The EPA should therefore ensure that the ISA includes studies that satisfy the environmental justice recommendations and suggestions of the CASAC panels and the National Academies, and ensure that environmental justice is “an area of focus for future research to fully inform and characterize concentration-response functions,” especially where there is paucity of scientific data.

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84 National Academies’ Report on Causality Framework (10/2022), page 55
85 National Academies’ Report on Causality Framework (10/2022), page 114
86 National Academies’ Report on Causality Framework (10/2022), page 114
87 CASAC review of ozone ISA. (11/22/2022), page 22 (13)
88 CASAC review of ozone ISA. (11/22/2022), page 22 (13)
89 CASAC. (03/18/2022). CASAC Review of the EPA’s Policy Assessment for the Reconsideration of the National Ambient Air Quality Standards for Particulate Matter (External Review Draft); EPA-CASAC-22-002, page 2
90 CASAC review of ozone ISA. (11/22/2022), pages 21-22 (12-13)
91 CASAC review of ozone ISA. (11/22/2022), page 22 (13)
9. Concluding remarks

Current scientific data and above considerations in assessing the data warrant revising the current primary O₃ NAAQS of 70 ppb, set nearly a decade ago, to 60 - 55 ppb. In these comments, we highlight several points some of which were also raised by the 2022 ozone CASAC panel and the National Academies report, for EPA’s consideration in reviewing the scientific literature and making causality determinations in the ozone ISA. In this ISA, we expect EPA to:

• not exclude any relevant study that contributes to causality determinations,
• give more weight to epidemiological studies (which better capture real-life exposure scenarios),
• apply the precautionary principle to protect vulnerable populations (especially in case of scientific uncertainties) - by integrating the heterogeneity of their responses and impacts (relative to general population) to ozone exposure,
• consider the cumulative health impacts of co-pollutants (which would resolve the issue of confounding by co-pollutants in epidemiology studies) and impacts of socioeconomic factors on ozone exposure-related health endpoints,
• integrate the effects of climate change on O₃ levels and exposure responses, and
• consider environmental justice in O₃ exposure and impact disparities.

In addition to conducting a comprehensive and expeditious review of the science, we also expect EPA to conclude the ozone NAAQS review process by the end of 2025 to meet the statutory deadline imposed by the Clean Air Act.

Thank you,

Allergy & Asthma Network
Alliance of Nurses for Healthy Environments
American Lung Association
American Thoracic Society
Asthma and Allergy Foundation of America
Climate Psychiatry Alliance
International Society for Environmental Epidemiology - North America Chapter (ISEE-NA)
Medical Society Consortium on Climate and Health
National Association of Pediatric Nurse Practitioners
Physicians for Social Responsibility