American Lung Association.

June 1, 2022

Dr. Elizabeth A. (Lianne) Sheppard, Chair
And Members, Ozone Review Panel
Clean Air Scientific Advisory Committee

C/O Aaron Yeow
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RE: Comments on the Draft Policy Assessment for the Reconsideration of Ozone National Ambient Air Quality Standards

Dear Dr. Sheppard and panel members:

The American Lung Association appreciates the opportunity to comment to CASAC on EPA's draft Policy Assessment for the reconsideration of the National Ambient Air Quality Standards for Ozone (NAAQS). To protect public health from the impacts of ozone pollution, especially for people with lung disease and other at-risk populations, the Lung Association calls for the primary ozone standard to be set at no higher than 60 parts per billion (ppb).

National health and medical organizations have called for a standard no higher than 60 ppb throughout EPA's past two reviews, in 2015 and 2020. We wrote to CASAC in 2015, "Unfortunately, the recommendation for the 8-hour standard in the second draft *Policy Assessment* is weak. That range of 70 to 60 ppb…should not be the recommendation of this CASAC, because the post-2006 epidemiologic research documenting evidence of adverse health effects at 60 ppb and below, as well as new chamber study evidence."[1]

In reviewing the evidence since that 2015 review, the Lung Association continues to find that setting the standard at no higher than 60 ppb is necessary to protect the public health with an adequate margin of safety. As we outline below, the existing evidence showing cardiovascular impacts; the studies showing reduced lung function in healthy adults at 60 ppb; the fact that effects on other individuals at higher risk can't be measured in controlled human exposure studies; and the presence of copollutants that interact with ozone all mean that a more protective of no higher than 60 ppb is necessary to protect health.

Below please find our comments on specific sections of the draft Policy Assessment (PA).

Specific comments related to CASAC Charge Questions[2] for Review of the Draft PA

Chapter 1 (Intro), bullet 2: In its decision to reconsider the 2020 O_3 NAAQS decision, the EPA stated that the reconsideration would be based on the existing scientific record. What are the Panel's views on EPA's evaluation of newer studies and its conclusion that they do not materially change the findings of the 2020 ISA or warrant reopening the air quality criteria?

[1] American Lung Association (2014, May 19): Health and Medical Partners Comments to EPA CASAC on Ozone Standard
[2] EPA (2022, Apr 28): Agency Charge for Policy-Relevant Science for the Ozone NAAQS Reconsideration

We strongly disagree with EPA's evaluation of scientific data and EPA's conclusion that they do not materially change the findings of the 2020 ISA or warrant reopening the air quality criteria.

Per the draft Policy Assessment (PA)[3], EPA "considered differences in the health effects evidence since 2015 for effects other than respiratory effects. Specifically, the newly available evidence supported updated conclusions regarding metabolic effects, cardiovascular effects, and mortality" to determine that the 2015 NAAQS are adequate in being protective of human health with an adequate margin of safety. In doing so, EPA seems to arbitrarily favor some studies and reject others to support its pre-conceived conclusion that the 2020 O_3 NAAQS do not warrant revision.

1. *Metabolic effects of short-term O_3 exposure: Strongest evidence from animal toxicology that support a new causal determination of "likely to be causal" from "suggestive of, but not sufficient to infer" in the last review.*

We agree with this determination.

2. *Cardiovascular effects & mortality effects of short-term O_3 exposure: evidence from CHE and epidemiological studies that support a significant backward shift in a new causal determination to "suggestive of, but not sufficient to infer" from "likely to be causal" in the previous review.*

We strongly disagree with EPA's science assessments and this determination.

EPA's rationale for this change: "The number of controlled human exposure studies showing little evidence of ozone induced cardiovascular effects has grown substantially" and "the plausibility for a relationship between short-term ozone exposure to cardiovascular health effects is weaker than it was in the previous review, leading to the revised causality determination."

EPA rejects the existence of "consistent or generally consistent evidence for a limited number of O_3-induced cardiovascular endpoints in animal toxicological studies and cardiovascular mortality in epidemiologic studies" because of "a general lack of coherence between these results and findings in controlled human exposure and epidemiologic studies of cardiovascular health outcomes." EPA's expectation of coherence and convergence of data from animal toxicology studies, controlled human exposure (CHE)/chamber studies, and epidemiological studies to enable it to make a direct cause and effect determination with absolute certainty is highly idealistic.

Regarding controlled human exposure studies, some of them do show cardiovascular effects. The lack of consistency across all CHE studies could be due to differences in the design of the experiments or the analyses of the data. The latter was fundamental in completely reversing a finding on the respiratory effects of O_3 exposure at 60 ppb when existing CHE data was reanalyzed by different researchers (See below).

The Agency emphasizes the persistence of the "remaining uncertainties and limitations recognized in the 2013 ISA (e.g., lack of control for potential confounding by copollutants in epidemiologic studies)". Epidemiologic studies, especially those that use single pollutant exposure models for ozone impacts analyses, when it exists within a mixture of pollutants, will

[3] EPA (2022, Apr): Policy Assessment for the Reconsideration of the Ozone National Ambient Air Quality Standards (External Review Draft)

always be subject to uncertainties. It is precisely for situations such as these that the Clean Air Act requires EPA to include an adequate "margin of safety" in setting the NAAQS, which the Agency interprets thus: "(t)he requirement that primary standards provide an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting."[4]

Because the CHE evidence does not clearly rule out any cardiovascular effect, because (by EPA's own admission) there is "consistent or generally consistent evidence for a limited number of O_3-induced cardiovascular endpoints in animal toxicological studies and cardiovascular mortality in epidemiologic studies," and because the Clean Air Act explicitly requires EPA to include an adequate margin of safety to account for data uncertainties/lack of consistency, the Agency must, at the very least, retain the current determination of ozone impacts on cardiovascular health and mortality to be "likely to be causal". The weight of evidence from the multiple sources demands this, as does the precautionary principle[5].

3. *Respiratory effects of short-term O_3 exposure: Evidence from CHE studies: "Findings from controlled human exposure studies of healthy subjects at the benchmark 60 ppb concentration which showed statistically significant decrements in lung function but not respiratory symptoms, including one study which showed a statistically significant increase in a biomarker of airway inflammatory response relative to filtered air exposures."*

We disagree with EPA's assessment. EPA discounts the CHE studies that showed decreased lung function at ozone concentrations lower than current standard because they did not also show symptoms.

Adams (2006)[6] 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)[7] conducted a reevaluation of the existing lung function data from Adams, and using standard statistical methods, they showed that a 60 ppb exposure actually causes a highly statistically significant decrease in mean FEV(1)[8] 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."[9]

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[4] EPA. (2020, Apr). Integrated Science Assessment for Ozone and Related Photochemical Oxidants – Final Report. EPA/600/R-20/012

[5] European Parliament (2015, Sep 12). Think Tank: The precautionary principle: Definitions, applications and governance - In-Depth Analysis

[6] 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.

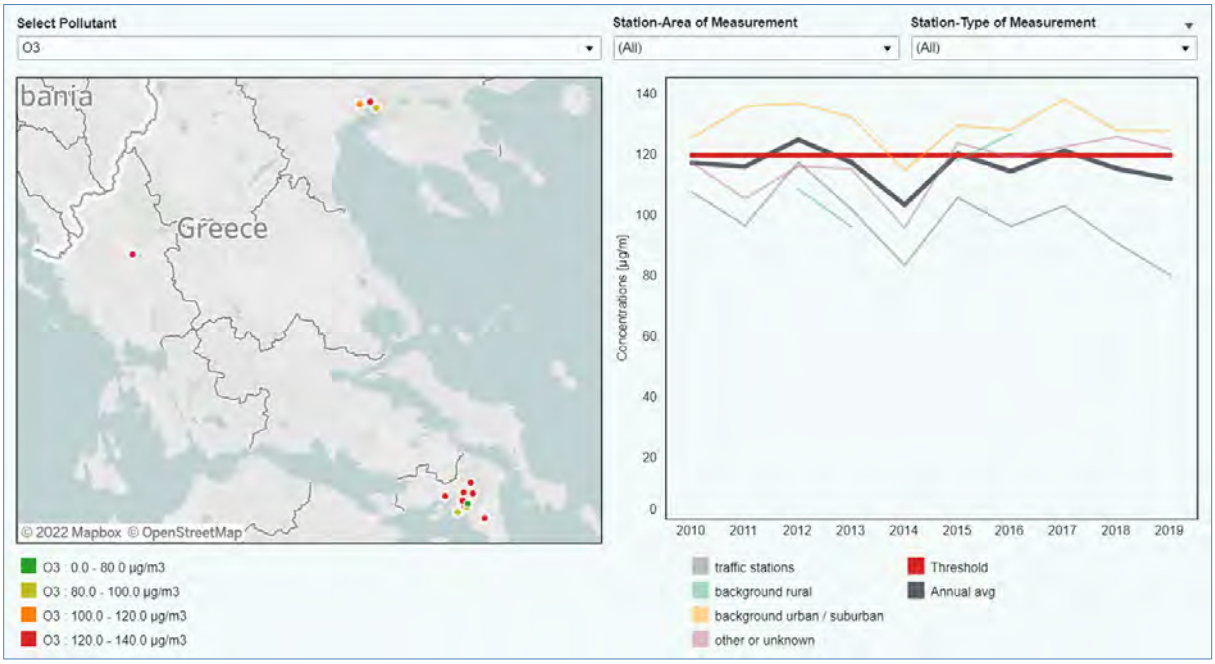
[7] Brown, J. S., Bateson, T. F., & McDonnell, W. F. (2008). Effects of exposure to 0.06 ppm ozone on FEV1 in humans: a secondary analysis of existing data. *Environmental health perspectives*, *116*(8), 1023–1026.

[8] 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.

[9] Kim, C. S., Alexis, N. E., Rappold, A. G., Kehrl, H., Hazucha, M. J., Lay, J. C., Schmitt, M. T., Case M., Devlin R. B., Peden, D. B., & Diaz-Sanchez, D. (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).

These and other studies which clearly show impaired lung function at 60 ppb used cohorts of healthy young subjects in the experiments. It is highly biologically plausible that among at-risk populations such as children, elderly people, and people with existing pulmonary issues (e.g. asthma), these exposures could lead to more severe respiratory illnesses with symptoms. Since direct dose-response/exposure measurements of sensitive groups are not obtainable, EPA must consider the above results as biological plausible in inferring causality[10] of significant respiratory illness at 60 ppb exposure.

Greek scientists recently conducted a panel study (Respiratory Effects of Ozone Exposure in children; RESPOZE)[11] in two cities with ambient ozone concentrations higher than the EU standard of 49.1 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 the study period.



[12]

Another recent study from China[13] analyzed the impacts of low level O_3 exposure on asthma-related hospitalizations in a cohort of 3,475 children. Using air pollution and meteorological data, they employed a case-crossover design and conditional logistic regression analyses to evaluate

[10] "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." Integrated Science Assessment for Oxides of Nitrogen –Health Criteria

[11] Dimakopoulou, K., *et al*. (2020). Long-term exposure to ozone and children's respiratory health: Results from the RESPOZE study. *Environmental research*, *182*, 109002

[12] https://www.eea.europa.eu/themes/air/country-fact-sheets/2021-country-fact-sheets/greece

[13] Huang, W., Wu, J., & Lin, X. (2022). Ozone Exposure and Asthma Attack in Children. *Frontiers in pediatrics*, *10*, 830897

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 ≥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.

In summary, new evidence and re-evaluation of existing evidence, since 2015, 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.

Chapter 3 (Review of the Primary Standard), bullet 1: EPA's approach to considering the health effects evidence and the risk assessment to inform preliminary conclusions on the primary standard: To what extent is the evaluation of the available information, including the key considerations as well as associated limitations and uncertainties, technically sound and clearly communicated?

In the PA, EPA makes repeated references to the "uncertainties and limitations recognized in the 2013 ISA (e.g., lack of control for potential confounding by copollutants in epidemiologic studies) (which) still remain" (ISA, section IS.1.3.1). Ozone occurs in a mixture of air pollutants which are all hazardous to human health, either directly or indirectly. Some of these co-pollutants are highly correlated and associated with each other and could also have additive effects on health. Qualitative and quantitative analyses of the morbidity/mortality burden attributable to specific pollutants using a single pollutant exposure model would therefore always have some degree of uncertainty due to confounding copollutants, as epidemiological studies over the past two decades have shown. If several 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.

Instead of looking for isolated pollutant impacts in what is an unrealistic scenario, EPA should consider the cumulative impacts of the entire pollutant mixture in determining ozone NAAQS. In an article in Pace Environmental Law Review, Prof. Deborah Behles observed more than a decade ago that "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."[14]

"EPA should evaluate and consider cumulative health impacts when it reviews and revises ozone NAAQS 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."[15]

[14] Behles, D. N. (2010). Examining the Air We Breathe: EPA Should Evaluate Cumulative Impacts When It Promulgates National Ambient Air Quality Standards. *28 Pace Envtl. L. Rev. 200*.
[15] Behles, D. N. (2010). *28 Pace Envtl. L. Rev. 200*.

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".[16] This study also finds that because the two grants of authority from the Clean Air Act in setting NAAQS, i.e. "requisite to protect the public health" while "allowing an adequate margin of safety" are distinguishable, the courts upheld "EPA's interpretation of its authority to consider any information or analyses the Agency reasonably determines is necessary to decide the level at which standards are protective of the public health."[17]

Therefore, EPA should consider cumulative impacts of copollutants in revising the 2015 ozone NAAQS to no higher than 60ppb. [18]

Conclusion

The American Lung Association works on behalf of everyone's lung health, but particularly serves populations with lung diseases such as lung cancer, asthma and COPD. We also place a heavy emphasis on the lung health of children and of seniors, because people under 18 and over 65 are at greater risk of harm to the lungs from a variety of sources. All of these populations are at greater risk of health harm from ozone pollution exposure – and are therefore unable to participate in CHE studies to further pinpoint those health harms.

The Clean Air Act directs EPA ensure that these populations are protected from ozone pollution. EPA's heavy reliance on CHE studies in the draft Policy Assessment falls far short of this requirement, as does its effort to discount existing epidemiological evidence on cardiovascular impacts and its failure to consider the impacts of cumulative exposure from ozone as part of a mix of air pollutants.

We urge you to follow the science and the law and conclude that a standard of no higher than 60 ppb is requisite to protect public health with an adequate margin of safety in the final Policy Assessment.

Signed,

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[16] Alves, S., Tilghman, J., Rosenbaum, A., & Payne-Sturges, D. C. (2012). U.S. EPA authority to use cumulative risk assessments in environmental decision-making. *International journal of environmental research and public health*, *9*(6), 1997–2019.
[17] Alves *et al*. U.S. EPA authority to use cumulative risk assessments in environmental decision-making.
[18] Alves *et al*. U.S. EPA authority to use cumulative risk assessments in environmental decision-making.