Comment on U.S. Environmental Protection Agency's Call for Information in preparing an Integrated Science Assessment in the review of Nitrogen Dioxide National Ambient Air Quality Standards, Docket # - EPA-HQ-ORD-2022-0831[1]

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 ISA for the nitrogen dioxide NAAQS. Our organizations strongly support strengthening the NO_2 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.

Submitted by

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[1] Environmental Protection Agency (Dec 9, 2022). Call for Information on the Integrated Science Assessment for Oxides of Nitrogen—Health Criteria [ORD–2022–0831; FRL–10465–01–ORD]; Federal Register Vol. 87, No. 236

Contents

1. Include all elements of NAAQS in assessing science and determining causality of nitrogen oxides' exposure

In its evaluation of scientific literature, EPA needs to consider all four elements of nitrogen dioxide (NO_2) NAAQS in the integrated science assessment (ISA): indicator species, averaging times (informed by exposure times), concentrations, and the form of the standard. Such a comprehensive assessment of all components of NAAQS will better inform causality determinations of specific health endpoints and ensure public health protection.

Since the publication of the last NO_2 ISA in 2016,[2] numerous peer-reviewed research articles have been published on the health impacts of NO_2 and NO_x (nitric oxide (NO) + NO_2) which implicate these pollutants in various morbidities and mortality. Our literature search of PubMed for articles published between 2015 and 2023 using query terms of "NO_2 and pollution and health" and "NO_x and pollution and health" yielded nearly 4,000 and over 1,000 entries respectively from diverse international institutions and organizations. Among these were several literature reviews, systematic reviews, and metadata analyses of air pollution which included the impacts of NO_2/NO_x on specific health endpoints. Some reviews also shed light on the mechanism/pathogenesis[3] and biomarkers[4] of specific health effects.

Findings from a few of these recent reviews implicate short-term and/or long-term exposures to NO_2/NO_x in the causation, increased risk of development, or exacerbation of existing conditions, or in the statistically significant associations with specific adverse health endpoints,

[2] Environmental Protection Agency (EPA). (Jan, 2016). Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria, Final Report - EPA/600/R-15/068.
[3] Bontinck, A., Maes, T., & Joos, G. (2020). Asthma and air pollution: recent insights in pathogenesis and clinical implications. *Current opinion in pulmonary medicine*, *26*(1), 10–19.
[4] Desai, G., Chu, L., Guo, Y., Myneni, A. A., & Mu, L. (2017). Biomarkers used in studying air pollution exposure during pregnancy and perinatal outcomes: a review. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals*, *22*(6), 489–501.

including: increased risks of hypertension and triggering of myocardial infarction, and stroke (fatal and nonfatal),[5] myocardial infarction, cardiovascular mortality, hypertension and heart rate variability,[6] diastolic blood pressure and hypertension,[7] increased arterial stiffness and reflected waves,[8] cardiovascular and respiratory mortality,[9] stroke,[10] developing hypertensive disorders of pregnancy,[11] childhood asthma development,[12] Type 2 diabetes,[13] increased risk of dementia,[14] increased risk of depression,[15] increased risk of Parkinson's disease,[16] recurrence or prevalence of multiple sclerosis,[17] positive association with all-cause mortality,[18] increased risk of cardiorespiratory, kidney, autoimmune, neurodegenerative, cancer or pregnancy/birth-related outcomes,[19] adverse central nervous system effects in children and adults,[20] and prevalence of allergic rhinitis.[21]

Two projects from the multicenter ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE)) showed long-term exposure to low-level ambient air pollution (which included NO_2)

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[5] de Bont, J., *et al*. (2022). Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses. *Journal of internal medicine, 291*(6), 779–800.

[6] Gandhi, T. J., *et al*. (2022). Outdoor Physical Activity in an Air Polluted Environment and Its Effect on the Cardiovascular System-A Systematic Review. *International journal of environmental research and public health*, *19*(17), 10547.

[7] Yang, B. Y., *et al*. (2018). Global association between ambient air pollution and blood pressure: A systematic review and meta-analysis. *Environmental pollution (Barking, Essex: 1987)*, *235*, 576–588.

[8] Zanoli, L., *et al*. (2017). A systematic review of arterial stiffness, wave reflection and air pollution. *Molecular medicine reports*, *15*(5), 3425–3429.

[9] Newell, K., Kartsonaki, C., Lam, K. B. H., & Kurmi, O. (2018). Cardiorespiratory health effects of gaseous ambient air pollution exposure in low and middle income countries: a systematic review and meta-analysis. *Environmental health : a global access science source*, *17*(1), 41.

[10] Haddad, P., *et al*. (2023). Long-term exposure to traffic-related air pollution and stroke: A systematic review and meta-analysis. *International journal of hygiene and environmental health*, *247*, 114079.

[11] National Toxicology Program (2019). NTP monograph on the systematic review of traffic-related air pollution and hypertensive disorders of pregnancy. *NTP monograph*, (7), NTP-MGRAPH-7.

[12] Khreis, H., *et al*. (2017). Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. *Environment international*, *100*, 1–31.

[13] Yang, B. Y., *et al*. (2020). Ambient air pollution and diabetes: A systematic review and meta-analysis. *Environmental research*, *180*, 108817.

[14] Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., & Anstey, K. J. (2019). Air Pollution and Dementia: A Systematic Review. *Journal of Alzheimer's Disease*, *70*(s1), S145–S163.

[15] Borroni, E., Pesatori, A. C., Bollati, V., Buoli, M., & Carugno, M. (2022). Air pollution exposure and depression: A comprehensive updated systematic review and meta-analysis. *Environmental pollution*, *292*(Pt A), 118245.

[16] Kasdagli, M. I., *et al*. (2019). Air pollution and Parkinson's disease: A systematic review and meta-analysis up to 2018. *International journal of hygiene and environmental health*, *222*(3), 402–409.

[17] Farahmandfard, M. A., Naghibzadeh-Tahami, A., & Khanjani, N. (2021). Ambient air pollution and multiple sclerosis: a systematic review. *Reviews on environmental health*, *36*(4), 535–544.

[18] Orellano, P., Reynoso, J., Quaranta, N., Bardach, A., & Ciapponi, A. (2020). Short-term exposure to particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) and all-cause and cause-specific mortality: Systematic review and meta-analysis. *Environment international*, *142*, 105876.

[19] Markozannes, G., *et al*. (2022). Outdoor air quality and human health: An overview of reviews of observational studies. *Environmental pollution (Barking, Essex: 1987)*, *306*, 119309.

[20] Sram, R. J., Veleminsky, M., Jr, Veleminsky, M., Sr, & Stejskalová, J. (2017). The impact of air pollution to central nervous system in children and adults. *Neuro endocrinology letters*, *38*(6), 389–396.

[21] Li, S., *et al* (2022). Association between exposure to air pollution and risk of allergic rhinitis: A systematic review and meta-analysis. *Environmental research*, *205*, 112472.

to increase the incidence of stroke and coronary heart disease[22] and "long-term exposure to concentrations of $PM_{2.5}$ and NO_2 lower than current annual limit values was associated with non-accidental, cardiovascular, non-malignant respiratory, and lung cancer mortality in seven large European cohorts."[23]

In the ISA, EPA must ensure that the query terms used to mine the science databases include individual oxides of nitrogen that are together represented by NO_2 in setting NO_2 NAAQS. It is critical to the NAAQS process and consequent public health protection that the literature survey adequately captures the health effects of all nitrogen oxides, as stated in Section 108(c) of the Clean Air Act (CAA). In the following sections we offer comment in the application of tools that EPA employs for data analyses, and in implementing CAA statutory requirements[24] for NAAQS reviews.

2. Include all relevant studies in causality determinations – review and revise the PECOS framework

In preparing the ISA for the NO_2 NAAQS, we urge EPA to improve its Population, Exposure, Comparison, Outcome, and Study Design (PECOS) framework and apply it consistently. To ensure scientifically robust and accurate determinations of causality of various health endpoints from short- and long-term NOx exposures, it is imperative that the EPA consider **all** relevant research studies in pertinent literature as it prepares this ISA. In its 2020 ozone ISA,[25] EPA introduced a new framework, PECOS, for refining the scope of ISAs in NAAQS reviews of criteria air pollutants. This discipline-specific framework developed for experimental and epidemiologic studies, among others, employs the five parameters to evaluate studies leading to their inclusion in or exclusion from initial ISA reviews. At the outset, EPA should (i) resolve the concerns raised by scientists from both the Clean Air Scientific Advisory Committee (CASAC)[26] and the National Academies (NAS)[27] in the design and application of PECOS framework, and (ii) incorporate the recommendations made by the experts, in preparing the NO_2 ISA. Both bodies have expressed concerns on EPA's inconsistent and seemingly arbitrary application of the PECOS in deciding the inclusion/exclusion of ISA-relevant studies. "Because

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[22] Wolf, K., *et al*. (2021). Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project. *The Lancet. Planetary health*, *5*(9), e620–e632.

[23] Stafoggia, M., *et al*. (2022). Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. *The Lancet. Planetary health*, *6*(1), e9–e18.

[24] Clean Air Act, 42 U.S. Code § 7408 Section 108(c) - Air quality criteria and control techniques: Review, modification, and reissuance of criteria or information; 42 U.S. Code § 7409 Section 109(c) - National primary ambient air quality standard for nitrogen dioxide

[25] EPA. (Apr, 2020). Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants - Final Report.

[26] Clean Air Scientific Advisory Committee (CASAC). (Nov 22, 2022). Review of the EPA's Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants, Final Report - EPA-CASAC-23-001

[27] National Academies of Sciences, Engineering, and Medicine (Oct, 2022) Advancing the Framework for Assessing Causality of Health and Welfare Effects to Inform National Ambient Air Quality Standard Reviews. ISBN: 978-0-309-69011-9; Sponsor: EPA

the PECOS structure limits (inconsistently) the studies to North America and Canada, the research conducted in Europe and Asia is lost to addressing uncertainties."[28]

The ozone CASAC panel expressed "concerns about transparent and uniform application of eligibility criteria for study inclusion and about differential application of geographical location across health endpoints and exposure durations in determining study eligibility for consideration."[29] The panel cited specific examples in the 2020 ISA where EPA's PECOS application was both inconsistent and lacked rationale, e.g. limiting cardiovascular-relevant studies to North America, Europe, and Australia, which differs from the restriction of respiratory-relevant studies to US and Canada and exclusion of considerable research conducted in Asia, which in turn differs from the inclusion of studies on developmental effects from Brazil and China. Also, as CASAC members 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."[30] Inclusion of poorly conducted or flawed studies from North America and Europe and exclusion of well-designed studies from Asia and other parts of the world should be avoided in the NO_2 ISA.

The NAS report also notes EPA's inconsistent use of PECOS tools in determining study relevance for inclusion in the ISA. "EPA notes… that the use of PECOS tools is consistent with prior reviews …. However, the authors are still not explicit about the basis on which some studies are included, and others excluded, under these criteria."[31] As examples, the report cites a study which was referenced in the 2013 ozone ISA but excluded in the 2020 ozone ISA, and another study which "was included in the 2019 PM ISA (and so presumably passed study quality and relevance screening there) and was "considered" for the 2020 ozone ISA, but was excluded from that ISA during the full text screening process."[32]

Both CASAC and NAS recommend improvements to the current PECOS framework. In its final report, the ozone CASAC panel recommended that "the EPA not restrict the geographic regions considered for health studies in its PECOS statements without an appropriate and strong rationale." While "variations in local climate, concurrent exposures, lifestyle issues etc. exist and will persist," the rationale for the current threshold in PECOS limiting epidemiological studies to US or Canadian populations "seems unduly restrictive and should be revisited."[33] The panel also stated that "(m)ore transparent and consistent eligibility criteria are preferable for future application."[34]

[28] CASAC review of ozone ISA. (Nov 22, 2022), page 64 (A-35)
[29] CASAC review of ozone ISA. (Nov 22, 2022), page 14 (5)
[30] CASAC review of ozone ISA. (Nov 22, 2022). pages 65 (A-36), 40 (A-11)
[31] National Academies' Report on Causality Framework (Oct, 2022). Pages 48, 43
[32] National Academies' Report on Causality Framework (Oct, 2022). page 44
[33] CASAC review of ozone ISA. (Nov 22, 2022). page 40 (A-11)
[34] CASAC review of ozone ISA. (Nov 22, 2022). page 3

The NAS report states that "Precise definition (such as provided by PECOS) of what evidence is considered relevant, and what aspects of studies are considered to enhance their quality, clarify the process and provide transparency" and "(s)uch definitions require review and revision by experts *(e.g., for ISAs by CASAC-EPA interaction)*… (e)xternal critical review and achieving consensus with reviewers enhances the robustness of the process, and the current ISA Preamble frameworks explicitly require such review. This is particularly critical for the definitions used (e.g., the PECOS), for the application of quality criteria, and the synthesis of the evidence. 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."[35]

In its 2020 Ozone ISA, EPA used several tools including PECOS, Health Assessment Workspace Collaborative (HAWC),[36] and Health and Environmental Research Online (HERO),[37] to explain and document criteria for assessing study relevance and quality. The NAS considers 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, 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*[38]* 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."[39]

In its application of PECOS, EPA excluded studies from Asia and Latin America from both PM and ozone ISAs citing differences of their airsheds from that of the US. But members of the ozone CASAC panel pointed out that "(o)zone, unlike PM, 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. This argument would apply to NO_2 also since this too is a pure chemical, exposure to which could be predicted to have similar health impacts on all populations. In this context, we want to alert EPA to the fact that Canada, whose airshed very closely resembles that of the US has adopted much stronger NO_2 Canadian Ambient Air Quality Standards (CAAQS)[40] which will get more stringent with time:

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[35] National Academies' Report on Causality Framework (Oct, 2022). page 88

[36] Shapiro, A. J., *et al*. (2018). Software Tools to Facilitate Systematic Review Used for Cancer Hazard Identification. *Environ Health Perspect*.,126(10),104501; About | HAWC (hawcproject.org)

[37] EPA. Health and Environmental Research Online: a Database of Scientific Studies and References. (accessed Jan, 2023)

[38] EPA. (Nov, 2015). Preamble to the Integrated Science Assessments. EPA/600/R-15/067

[39] National Academies' Report on Causality Framework (Oct, 2022). page 115

[40] Canadian Council of Ministers of the Environment. (Jan, 2023). Canadian Ambient Air Quality Standards (CAAQS).

NO_2* CAAQS	**Level**		**Statistical Form & Averaging Time**
	2020	2025	
Short-term - 1 h	60 ppb**	42 ppb	average over a single calendar year of all 1-hour average concentrations
Long-term – annual	17 ppb	12 ppb	3-year average of annual 98th percentile of daily maximum 1-hour average concentrations

* NO_2 is generally not measured directly, but by subtraction following a separate measurement of the total of NO + NO_2 and of NO itself monitored via chemiluminescence technique; [41] ** ppb - parts per billion by volume;

3. Weight epidemiological studies appropriately in making causality determinations

In making causal determinations, the ISA is expected to include data from different types of health studies: epidemiology (epi) studies (i.e. population- and panel-based observational designs), controlled human exposure (CHE) chamber studies, and animal toxicology studies. The ISA must adequately differentiate or differentially weight these different lines of evidence examining health effects of nitrogen oxides. Different studies have their own specific strengths and limitations that define their contributions to causality determinations.

CHE study participants are usually young, healthy, and fit adults and do not include vulnerable subpopulations such as children, senior adults, pregnant people, individuals with pre-existing morbidities, historically marginalized groups, or individuals with disadvantaged socioeconomic status. CHE study findings are "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."[42] 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)."[43] Another serious limitation is the difference between ambient air and laboratory-generated NO_2 used in CHE studies – the latter involves exposure to a single pure pollutant without the other nitrogen oxides (NO_y) that are found in the former, so that these studies may underestimate or miss NO_y effects at low concentrations.

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 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."[44] The concentrations and health impacts of other nitrogen oxides, relative to NO_2 alone, are relevant to the interpretation of findings from CHE and epidemiology studies. Members of the ozone CASAC panel suggested that "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

[41] Health Canada. (May 2016). Human Health Risk Assessment for Ambient Nitrogen Dioxide. ISBN: 978-0-660-05365-3, page 36 (21)

[42] CASAC review of ozone ISA. (Nov 22, 2022), pages 62 (A-33) and 21 (12)

[43] CASAC review of ozone ISA. (Nov 22, 2022), page 13 (4)

[44] CASAC review of ozone ISA. (Nov 22, 2022), page 13 (4)

exposure studies." and "(w)hen available, epidemiologic studies should be weighted more strongly than controlled human (and animal) exposure studies."[45] As with ozone, findings from epidemiologic studies "should be considered just as, or even more, relevant than the CHE findings in determining an exposure level with no adverse effects"[46] when evaluating NO_2/NO_y health effects at low concentrations and in vulnerable groups. Epidemiology studies are more numerous and consideration of such studies from across the world can add to the knowledge base and reduce uncertainties.

The ozone CASAC panel suggested that in the ISAs, 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."[47]

The ozone CASAC panel recommended that ISA reviews "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."[48] 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."[49]

In its report on causality determination framework, the National Academies' made several recommendations to the EPA: "Providing explicit guidance - such as what aspects of a study will be considered in assessing its relevance and quality - in a framework for causal determination can help increase the transparency and replicability of the study selection, evaluation, and weighting process… Study strengths and limitations, and the relevance (or lack thereof) of the study for the causal question under consideration could be systematically documented."[50] The report noted that a "(g)uidance for such articulation is not currently provided in the causal determination framework. Whereas no single study selection or evaluation tool should prescriptively include or exclude eligibility for inclusion of a study in the ISA and it may be inappropriate for the framework to prespecify use of a specific tool for making causal determinations, the framework could include a set of core scientific principles regarding study inclusion and quality to increase transparency and replicability… The framework recognizes that

[45] CASAC review of ozone ISA. (Nov 22, 2022), pages 79 (A-50) and 64 (A-35)
[46] CASAC review of ozone ISA. (Nov 22, 2022), page 2
[47] CASAC review of ozone ISA. (Nov 22, 2022), page 2
[48] CASAC review of ozone ISA. (Nov 22, 2022), page 2
[49] CASAC review of ozone ISA. (Nov 22, 2022), page 2
[50] National Academies' Report on Causality Framework (Oct, 2022), page 5

co-pollutants may be confounding factors when assessing the potential effects of a criteria pollutant, but it is not explicit about other types of confounding, such as confounding by weather effects, other environmental factors, or socio-economic or demographic differences within populations... In particular, when evaluating individual studies, the weight of evidence approach could take into account:

1) how well a study articulates concerns about confounding and what the relevant confounding factors are…

2) whether the relevant confounders are observed and adjusted for in the study design and analysis using scientifically reasonable statistical methods… and

3) whether analyses of the robustness of study results to an unobserved confounder have been conducted, and how such an unobserved confounder might change study conclusions."[51]

We ask that the EPA implement these specific suggestions and recommendations from the CASAC panels and the National Academies in the NO_2 ISA to ensure a systematic and thorough review of pertinent scientific literature to make robust causality determinations.

4. Evaluate the adequacy of NO_2 as the indicator species in setting NAAQS that cover diverse gaseous and air-borne nitrogen oxides.

In setting NO_2 NAAQS, CAA Sec 108(c) specifies that criteria for NO_2 include consideration of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other derivatives of oxides of nitrogen.[52] Accordingly, "EPA considers the term oxides of nitrogen to refer to all forms of oxidized nitrogen" including the directly emitted NO_x (NO and NO_2) and those species, NO_z, formed from atmospheric reactions of NO_x (e.g. nitrate radicals (NO_3), nitrous acid (HONO), nitric acid (HNO_3), dinitrogen pentoxide (N_2O_5), nitryl chloride ($ClNO_2$), peroxynitric acid (HNO_4), PAN and its homologues (PANs), other organic nitrates like alkyl nitrates (e.g. isoprene nitrates - IN), and pNO_3).[53] These nitrogen oxides ($NO_y = NO_x + NO_z$), which vary in their reactivity, atmospheric residence times, and spatial and temporal distributions, are not all quantitatively measured. Instead, EPA uses NO_2 as the regulatory indicator of all the NO_y in setting NAAQS. Using just NO_2 as the indicator to assess health effects of all ambient nitrogen oxides may underestimate and possibly miss cumulative impacts of the whole suite of nitrogen oxides. A similar concern was raised by a member of the ozone CASAC panel about O_3 (which is the indicator of related photochemical oxidants in ambient air), particularly in capturing the health impacts of this "photochemical soup" in controlled human exposure/chamber studies.[54] In preparing the ISA, EPA should review the scientific literature on the health effects of these gaseous and air-borne nitrogen oxides, and evaluate if NO_2 is the most appropriate indicator of NO_y that effectively captures their various health effects.

[51] National Academies' Report on Causality Framework (Oct, 2022), page 5

[52] Clean Air Act, Section 108(c): 42 U.S. Code § 7408 - Review, modification, and reissuance of criteria or information

[53] EPA (Jan, 2016). Integrated Science Assessment for Oxides of Nitrogen - Health Criteria. EPA/600/R-15/068, page 140

[54] CASAC review of ozone ISA. (Nov 22, 2022), page 32 (A-3)

5. Apply adequate margin of safety to protect vulnerable populations, as required by the Clean Air Act

Section 109, Code 7409 of the Clean Air Act[55] explicitly states 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 on assessing causality determination points out, "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."[56] The PM CASAC panel also noted that the "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."[57]

The PM CASAC panel recommended that EPA make clear that "the current scientific evidence indicates that some subpopulations face higher health burdens from $PM_{2.5}$, 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."[58] We ask that such an assessment be applied to NO_2/NO_y in causality determinations in the ISA, to ensure that all vulnerable groups are protected to the same extent as the average population.

6. Consider the health impacts of nitrogen oxides and their co-pollutants cumulatively

Cumulative impacts mean both the aggregation of impacts from exposure to a single pollutant over time (longitudinal analysis) and also the aggregation of impacts of multiple pollutants at a given time. EPA needs to consider both in its consideration of NO_2/NO_x NAAQS. Here we focus on the cumulative impacts of NOx and its co-pollutants that exist together in the ambient air.

In her analysis of what EPA considers in setting primary NAAQS, law professor Deborah Behles observed more than a decade ago: "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."[59] Extending this observation to the NAAQS review/revision process, she noted: "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

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[55] Clean Air Act. 42 U.S. Code § 7409 - National primary and secondary ambient air quality standards

[56] National Academies' Report on Causality Framework (Oct, 2022), page 20

[57] Clean Air Scientific Advisory Committee (CASAC). (Mar, 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 – October 2021). EPA-CASAC-22-002, page 21 (12).

[58] CASAC review of PM PA. (Nov 22, 2022), page 11.

[59] 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,* pages 8-9 (7-8)

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."[60]

The $PM_{2.5}$ CASAC panel also recommended the consideration of cumulative impacts of the mixture of pollutants in ambient air, when reviewing NAAQS: "Consider the estimation of cumulative risk and impacts on health morbidity and mortality. There is increasing evidence that risk is cumulative and methods to estimate this risk are improving. In addition, the relationships between multiple exposures or co-pollutants, modifiers and outcomes (e.g., demographic, socioeconomic, built environment factors) should also be incorporated or acknowledged as sources of uncertainty."[61]

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."[62] 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."[63]

NO_2/NO_y are air pollutants that are not produced in isolation nor are they inhaled in isolation. They occur within a mixture of air pollutants which are highly correlated and associated with each other and are all hazardous to human health, either directly or indirectly. Effects of co-pollutant mixtures in which NO_2/NO_x generally occur, sensitivity of vulnerable groups to such mixtures, multiple pathways of exposures of some of these chemical co-pollutants, as well as non-chemical stressors such as life stages, socioeconomic factors, and community vulnerability all together have a cumulative impact that could significantly modify the effects of NO_2/NO_y exposure on human health. 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 co-pollutants. 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.

[60] *Ibid*. Behles, D. N. (2010). *28 Pace Envtl. L. Rev. 200*, page 2 (1)
[61] CASAC review of PM PA. (Nov 22, 2022), page 11.
[62] Alves *et al*. (2012). EPA authority to use cumulative risk assessments in environmental decision-making. page 1
[63] Vedal, S. & Kaufman, J. D. (2011). What Does Multi-Pollutant Air Pollution Research Mean? *American Journal of Respiratory and Critical Care Medicine*, *183*(1), 4-6.

In its ISA, EPA should therefore consider cumulative impacts of exposure to NO_2/NO_y and its co-pollutants and include multipollutant studies instead of limiting consideration to studies on isolated NO_2 impacts. Broadening the current approach to a comprehensive and holistic scenario that assesses the combined health impacts of pollutants that are co-emitted with NO_2, or impact health in a concerted, additive, or coeffective fashion with NO_2, would be more effective in protecting public health. This would also resolve the issue of co-pollutant confounding of exposure impacts on specific health endpoints which underlie causal determinations.

7. Consider climate change penalty on the health impacts of nitrogen oxides

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."[64] 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. Nitrogen oxides in ambient air produced from fuel-bound nitrogen are emitted primarily from fossil fuel combustion in diverse mobile and stationary combustion sources. "While anthropogenic sources dominate, NO_x is also formed by lightning strikes and wildland fires and is also emitted by soil… Nitrogen oxides, ozone (O_3) and fine particulate matter ($PM_{2.5}$) pollution related to atmospheric emissions of nitrogen (N) and other pollutants can cause premature death and a variety of serious health effects. Climate change is expected to impact how N-related pollutants affect human health… Other climate-related changes may increase the atmospheric release of N compounds through impacts on wildfire regimes, soil emissions, and biogenic emissions from terrestrial ecosystems."[65]

Extending the advice of the CASAC panel to EPA on ozone NAAQS to NO_2 NAAQS, the penalty of climate change (e.g., from dramatic increases in the duration, frequency, and intensity of wildfires,[66] drought/dust storms/erosion, lightning,[67]) on ambient NO_2/NO_y levels needs to be addressed in the ISA for causal determination.[68]

The PM CASAC panel noted "weather-associated changes in $PM_{2.5}$ composition, termed as "weather penalty." Increased temperature in the industrial Midwest and Northwest during the warm and cold seasons, and in the upper Midwest and West during the cold season, along with increased relative humidity and decreased wind speeds, resulted in large changes in $PM_{2.5}$ chemical composition."[69] In its causal determinations, EPA needs to ascertain if such a regional weather penalty might also be applicable to NO_2 emissions and NO_y composition in ambient air.

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[64] National Academies' Report on Causality Framework (Oct, 2022), page 105.

[65] Peel, J. L., Haeuber, R., Garcia, V., Russell, A. G., & Neas, L. (2013) Impact of nitrogen and climate change interactions on ambient air pollution and human health. *Biogeochemistry*, 114:121–134.

[66] EPA. Climate Change Indicators: Wildfires (Accessed Jan, 2023)

[67] Romps, D. M., Seeley, J. T., Vollaro, D., & Molinari, J. (2014). Projected increase in lightning strikes in the United States due to global warming. *Science* 346(6211), 851-854

[68] CASAC review of ozone ISA. (Nov 22, 2022), page 50 (A-21)

[69] CASAC review of PM PA. (Nov 22, 2022), page 71 (A-35)

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."[70] The report suggested that EPA update the ISA Preamble[71] "to seek and emphasize new information on the effects of climate change on air quality, as well as the expected long-term coeffects of changing air quality and climate on large-scale ecological processes and human vulnerability."[72] In the NO_2/NO_y ISA, the EPA needs to evaluate if the causality framework does adequately capture how climate change will impact causal linkages between criteria pollutants and associated health effects and also update the Preamble, per NAS suggestion.

In protecting public health "from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air," EPA should therefore also consider the penalty imposed by climate change and by locally extreme weather changes on ambient NO_2/NO_y pollution.

8. Improve NO_2 emissions monitoring to better inform NAAQS process

The subject of regulatory monitors is important not only in the context of NAAQS compliance but also in scientific studies that use data from such monitors to track health impacts. Gaseous and air-borne nitrogen oxides are reactive species with temporal and spatial heterogeneity in their generation and distribution, and potentially impact communities near their emission sources in a disproportionate manner. Stationary sources make up more than a third of NO_2 emissions (Fig. 1) and yet very few active regulatory monitors are found near the large number powerplants that use combustible fuels (Fig. 2) or near industrial clusters.

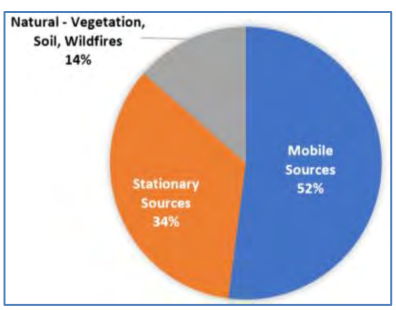

Figure 1. NO_2 emission sources. Data Source: 2017 National Emissions Inventory (NEI), EPA

[70] National Academies' Report on Causality Framework (Oct, 2022), pages 32, 105
[71] EPA. (2015). Preamble to the Integrated Science Assessments
[72] National Academies' Report on Causality Framework (Oct, 2022), page 110

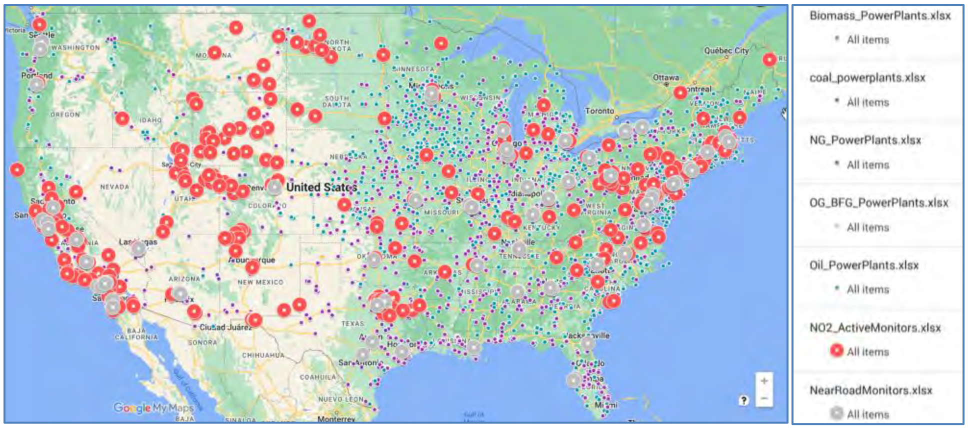

Figure 2. Google map displaying location of currently active NO_2 monitors & combustion-driven power plants. Data source: EPA

Some of the active NO_2 monitors are near-road monitors to track emissions from mobile sources and even there, they are absent from large sections of major roadways, from marine ports, and airports. These observations lead to several questions:

(i) are the current monitors adequate to measure emissions from all major sources? Lack of monitors ≠ no emissions;

(ii) are the locations of existing monitors optimal for recording prevalent NO_2 emissions in the area? Given the hazardous nature and reactive chemistry of this gas (and other oxides of nitrogen that it represents) coupled with its relatively short residence time, the current source-to-monitor design to evaluate NO_2 emissions may need revisiting. NO_2 (and other nitrogen oxides) should be treated as a fenceline pollutant and actively monitored at the emission source to provide an accurate measurement of its emission levels and patterns. Communities living close to the source might be disproportionately exposed to short-term high concentrations of NO_2 and the other oxides it represents;

(iii) are all monitors truly active and reporting emissions as they should? Transparent QA/QC review of the data from these monitors might be needed;

(iv) is NO_2 the best indicator of nitrogen oxides in ambient air to inform their collective health impacts?

On January 17, 2023, one of the commenters, the American Lung Association, provided detailed comment to EPA on monitors (IRA Air Pollution Funding Comment ID: EPA-HQ-OAR-2022-0876-0021, Tracking #: ld1-3jh4-vihx) in which the organization referred EPA to S.4510 - Public Health Air Quality Act of 2022[73] and S.2476 - Environmental Justice Air Quality Monitoring Act of 2021.[74] These bills describe expanding NAAQS monitoring network with specifics on the number, location, and types of monitors to be used for NAAQS, and also address environmental justice. In its comments, the Lung Association highlighted fenceline monitoring, and exposure assessment using a hybrid approach that integrates data from regulatory monitors, low-cost sensor technologies, and satellite measurements to fill in data gaps in providing an accurate

[73] Sen. Tammy Duckworth (IL) *et al*. sponsors. (07/12/2022). S. 4510 - Public Health Air Quality Act of 2022

[74] Sen. Ed Markey (MA) *et al*. sponsors. (07/27/2021). S. 2476 - Environmental Justice Air Quality Monitoring Act of 2021

accounting of NO_2 emissions to inform NAAQS. We suggest that EPA review the information in these and other resources to improve both NO_2 NAAQS review and its implementation.

9. Consider environmental justice in nitrogen oxides exposure and impact disparities

To ensure environmental justice and equitable benefits of clean air, the disproportionately higher health burden from NO_2 and other nitrogen oxides' 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 NAAQS reviews of both particulate matter and ozone, which was noted in the National Academies report: "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 evident in EPA's ISA causal determinations."[75] 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."[76] 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."[77] 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."[78] 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.[79] 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.[80]

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[81] 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,"

[75] National Academies' Report on Causality Framework (Oct, 2022), page 55
[76] National Academies' Report on Causality Framework (Oct, 2022), page 114
[77] National Academies' Report on Causality Framework (Oct, 2022), page 114
[78] CASAC review of ozone ISA. (Nov 22, 2022), page 22 (13)
[79] CASAC review of ozone ISA. (Nov 22, 2022), page 22 (13)
[80] CASAC review of PM PA. (Nov 22, 2022), page 2
[81] CASAC review of ozone ISA. (Nov 22, 2022), pages 21-22 (12-13)

- 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." This limitation is likely true of NO_2 and the broader group of nitrogen oxides and needs to addressed in the ISA.

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,"[82] especially where there is paucity of scientific data.

10. Concluding remarks

The goal of primary NO_2 NAAQS review is to evaluate current scientific knowledge on exposure-health impacts and then to assess if current standards still align with this knowledge or if it warrants their revision. In these comments, we highlight several points some of which were also raised by the CASAC panels and the National Academies report, for EPA consideration in reviewing the scientific literature and making causality determinations in the ISA:

- assessing current science to inform all components of NAAQS,
- not excluding any relevant study that contributes to causality determinations,
- giving due weight to epidemiological studies (which better capture real-life exposure scenarios),
- applying the precautionary principle to protect vulnerable populations (especially in case of scientific uncertainties),
- considering the cumulative health impacts of co-pollutants (which would resolve the issue of confounding by co-pollutants in epidemiology studies),
- integrating the effects of climate change on ambient levels of NO_2, and
- considering environmental justice in NO_2 exposure disparities.

We also ask if NO_2 is an appropriate indicator for the broader group of nitrogen oxides and whether there are enough number of regulatory NO_2 monitors and at optimal locations to accurately measure the reactive gas and effectively inform the NAAQS process.

Current science data and some of the above considerations together strongly warrant strengthening the current NO_2 NAAQS of 100 ppb 1-hour standard (revised more than a decade ago) based on the 98^{th} percentile averaged over 3 years and the annual standard of 53 ppb (which was never revised since establishment) based on annual average concentrations. We expect the ISA to derive similar conclusions.

We urge EPA to conduct a comprehensive and expedient review of the science, taking into consideration the suggestions and recommendations that we and others have submitted, to

[82] CASAC review of ozone ISA. (Nov 22, 2022), page 22 (13)

ensure all potential health impacts of short-term and long-term exposure to NO_2 are accounted for in making causality determinations.