

Cumulative Health Impacts Assessment and the National Ambient Air Quality Standards

American Lung Association

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Summary

The numerous adverse health effects of ambient air pollutant exposures are now well documented in scientific literature. The air pollutants in outdoor air do not exist in isolation nor are they inhaled individually. Ambient air is a mixture of multiple pollutants including the commonly present criteria pollutants, which have the potential to interact with one another and influence their individual impacts on human health.

The criteria air pollutant exposome, i.e. the totality of environmental exposures and their health impacts, includes multiple risk factors that potentially add to the health effects resulting from exposure to a specific pollutant. Non-chemical stressors, such as socioeconomic status and sociodemographic factors and preexisting health issues, add to the health impacts of criteria air pollutant exposures. Climate change is another major risk factor that impacts public health on its own and also imposes a penalty on conventional air pollutant exposure.

Assessing the cumulative health impacts of all these stressors requires establishing the risk posed by each, quantifying that risk, and weighting the risk in regulating specific air pollutants. The problem with the current paradigm of criteria air pollutant control, i.e. setting health-based primary National Ambient Air Quality Standards (NAAQS) for the six individual pollutants without considering the health effects of co-pollutants, is that there can be adverse health impacts from co-exposures to these pollutants even if no individual pollutant exceeds its current standard. Cumulative impacts assessment also plays a role in the framing and use of the Air Quality Index (AQI) which is based on short-term primary NAAQS.

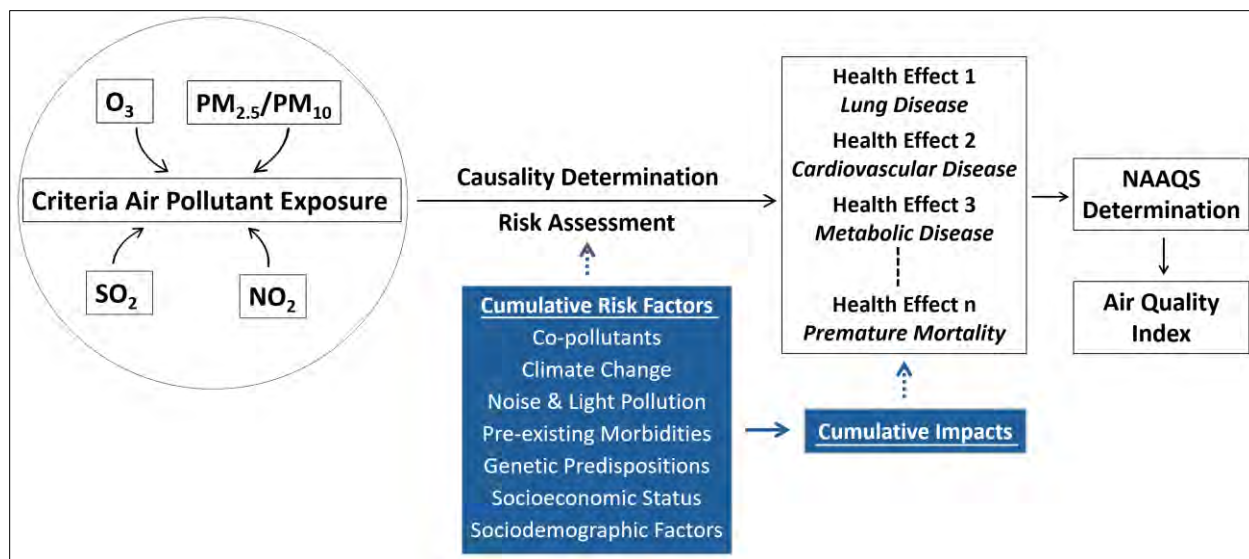
In this paper we briefly discuss the state of scientific research in the assessment of cumulative health impacts of co-pollutant exposures as one of the multiple risk factors and the application of such assessments in regulatory policy and risk communication related to criteria air pollutants and their NAAQS determinations to better protect public health.

Ambient air is a complex mixture of multiple chemical pollutants which are not produced in isolation, nor are they inhaled in isolation. Among this mixture are criteria air pollutants (CAPs) such as nitrogen oxides (NO_x), sulfur oxides (SO_x), particulate matter (PM), and ozone and related photochemical oxidants (Ox) which are closely associated with each other due to the similarity of their emission sources (or those of their precursors) and of their adverse health impacts from both short-term and long-term exposures.^{i,ii} It is now clear that non-chemical stressors such as preexisting morbidities, life stages, noise pollution, light pollution, economic status, education level, race and climate change are some additional risk factors that may amplify the health impacts of chemical air pollutant exposures.ⁱⁱⁱ

The criteria air pollutant exposome, i.e. the totality of environmental co-exposures and multiple risk factors that potentially add to the adverse health impacts of criteria air pollutant exposures, includes a large array of stressors. Cumulative impacts assessment is the consideration of the “totality of exposures to combinations of chemical and non-chemical stressors and their effects on health, well-being, and quality of life outcomes.”^{iv} Such an assessment requires an “analysis, characterization, and possible quantification of the combined risks to health and/or the environment from multiple agents and/or stressors”^v, i.e. *cumulative risk assessment* (CRA).^{vi}

The Clean Air Act requires EPA to review and revise (as warranted by current science), at least once every five years, the National Ambient Air Quality Standards (NAAQS) for criteria air pollutants based on their health and welfare effects. Even though the “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,”^{vii} EPA has historically focused on assessing the scientific evidence of the health effects of only one criteria pollutant at a time in determining its NAAQS without assessing the impacts of any other co-occurring risk factor. Cumulative impact assessment is also needed to ensure that the NAAQS meet the Act’s “margin of safety” requirement to protect vulnerable at-risk subpopulations^{viii} which the courts have repeatedly affirmed 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.”^{ix}

Lack of consideration of cumulative impacts of multiple risk factors could likely result in weaker standards of criteria pollutants and run counter to the public health protection metric of primary NAAQS as laid out in the Clean Air Act. (Figure 1)



Partial exposome of a criteria air pollutant. *In the current framework of criteria air pollutants (e.g. O₃ – ozone, PM_{2.5} – fine particulate matter, PM₁₀ – coarse particulate matter, SO₂ – sulfur dioxide, NO₂ – nitrogen dioxide) regulation, EPA determines their primary National Ambient Air Quality Standards (NAAQS) based on the health impacts attributable solely to the single pollutant under consideration. However, multiple risk factors including the simultaneous co-exposure to multiple air pollutants could add to the health burden of criteria air pollutant exposures. Consideration of the cumulative health impacts of various chemical and non-chemical stressors is needed to accurately determine NAAQS that are truly protective of public health. The Air Quality Index (AQI), a public health risk communication tool based on short-term NAAQS of the CAPs could be made more effective if cumulative impact assessment were included in its framework as well.*

Qualitative and quantitative assessment of cumulative impacts is complex because of the many categories of different stressors and the paucity of policy-relevant data on most of them.^x In 2012, EPA staff noted that there is no agency-wide policy for considering the various “chemical, biologic, radiologic, physical, and psychologic stressors” that affect human health in decision-making.^{xi} This continues to be true today.

Members of multiple scientific bodies have recommended additional research into and consideration of cumulative health impacts of multiple risk factors in EPA’s decision-making.^{xii} In its 2022 consultation with EPA on cumulative impact assessments, the Science Advisory Board (SAB) recommended that the agency: a. “as a first step, determine geographic “hot spots” and narrow the initial scope to stressors present in those regions. Hot spots representing different parts of the country and different scales could be considered”, b. “identify the “lowest hanging fruit” (combinations of stressors for which we have the most information), the “greatest potential impact” (combinations of stressors for which we may not have enough information, but the evidence points to serious health impacts), and “of greatest concern” [combinations of stressors of greatest concern to community groups, experts (including environmental, health, and social scientists), and other stakeholders]. Peer-reviewed methods that have been previously used to assess multiple stressors are a good starting point.”^{xiii} As the SAB recommended, EPA could turn to existing literature on mixed methods strategies that integrate quantitative and qualitative data in the holistic consideration of multiple risk factors and the assessment of cumulative impacts in environmental decision-making.^{xiv} EPA could also

review the different components of cumulative impacts assessments, including the various risk factors, that are already considered individually in major environmental laws as well as in regulatory decisions at most levels of government.^{xv}

Among the chemical stressors, multipollutant co-exposures are important universal health risk factors whose cumulative health impacts need serious consideration in regulating ambient air pollution, such as in determining the NAAQS of criteria pollutants. “The parameters of the Clean Air Act, which govern the review of each NAAQS separately, have contributed to researchers often examining the health effects of exposure to individual criteria pollutants, rather than simultaneous exposure to multiple pollutants.”^{xvi} Thus, the assessment of cumulative health impacts of multipollutant exposures in determining health-based primary NAAQS has been constrained by a limited availability of policy-applicable scientific data.^{xvii} More than a decade ago, EPA staff scientists proposed transitioning to a multipollutant paradigm in the regulation of criteria air pollutants through the “adoption of a framework for multipollutant science and risk assessment that encompasses well-studied and ubiquitous air pollutants.”^{xviii} This proposal was made to enable “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.”^{xix}

In early 2023, EPA drafted a set of principles for evaluating cumulative risks in the regulation of toxic pollutants under the Toxic Substances Control Act (TSCA) “to examine risk to people from exposure to multiple chemicals with similar effects.”^{xx,xxi} However, an equivalent is still wanting in the determination of health-based primary NAAQS for criteria pollutants. There is now increasing data on the impacts of co-pollutant mixtures on specific health endpoints associated with the exposure to a single criteria pollutant.^{xxii,xxiii,xxiv,xxv}

In 2023, EPA released draft guidelines for cumulative risks analysis (CRA) planning and a problem formulation approach to support risk management in the agency’s decision-making: “CRAs have been performed to inform decisions on some of the...NAAQS, (which) as standards for ambient air, reflect consideration of the cumulative concentrations of various pollutants in ambient air, which result from emissions from many sources.”^{xxvi} However, this is true only for the *human welfare-based* secondary NAAQS, for which EPA considers the impacts of some of the criteria air pollutants cumulatively: “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.”^{xxvii}

By contrast, in the “Health Risk and Exposure” assessments for *human health-based* primary NAAQS, EPA considers the exposure risk and cumulative health impacts of *only* those groups of pollutants that are chemically- or physically-related to the individual criteria pollutants whose NAAQS are being reviewed, but not those of other groups.^{xxviii} For example, the ozone NAAQS is set for ozone and related photochemical oxidants (collectively referred to as Ox) that co-occur with ozone in ambient air.^{xxix} Ozone serves as the indicator species for the group, members of which share similar chemical profiles and are also likely to have similar health effects. Similarly, NO₂ and SO₂ serve as indicators of multiple oxides of nitrogen (NO_y = NO_x (reactive nitrogen oxides: NO + NO₂) + NO_z (other nitrogen oxides))^{xxx} and sulfur (SO_x) respectively for which these NAAQS are set. The NAAQS for particulate matter are set for groups of particulate

aerosols that are of similar physical size (fine particles - PM_{2.5} and coarse particles - PM₁₀). “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.”^{xxxix} The primary NAAQS reviews do not consider the cumulative impacts of any of these groups in the context of exposure to other chemical stressors, such as the other groups of pollutants regulated by the NAAQS.

The importance of assessing cumulative impacts of co-pollutants was also underscored in the recommendations of recent CASAC panels: “A recurring shortfall of virtually all NAAQS reviews has been the lack of acceptance and strategy to address multi-pollutant co-exposures... Based on both clinical and epidemiological research, other co-pollutants can serve to increase the impact or intensity of response... 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”;^{xxxix} “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”;^{xxxix} “ozone never exists in isolation; co-pollutant effects must be considered with different exposure models.”^{xxxix} An additional important recommendation was for EPA’s consideration of health endpoints cumulatively by focusing 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.”^{xxxix}

In recent NAAQS reviews, the issue of multipollutant exposure was also raised in the context of weighting different types of health research data in making causal determinations. In arguing to weight epidemiological data more than data from experimental dose-response/controlled human exposure (CHE) chamber studies because the latter are “not conservative enough to protect at-risk populations,” CASAC panels and also public health advocates noted one inherent limitation of CHE studies: that they involve exposure to a single pure pollutant, which may underestimate or miss the effects of other pollutants realistically present in ambient air. “This is relevant for considering whether a potential alternative standard has an adequate margin of safety to protect these potentially at-risk populations.”^{xxxix} Application of an “adequate margin of safety” in protecting the multiple and diverse vulnerable groups requires a comprehensive assessment of the cumulative impacts of multiple risk factors that such groups experience that could increase the adverse health impacts of their CAP exposures. It also involves applying the precautionary principle^{xxxix} to protect these subpopulations, especially in cases of scientific uncertainties, by integrating the heterogeneity of their responses (relative to general population) to CAP exposures so they are protected to the same extent as the average population.

The first systematic analysis of existing epidemiologic and experimental literature on multipollutant effects (as joint effects, effect measure modification, or interactions) on an array of cardiovascular outcomes was published in 2018 by EPA scientists.^{xxxix} Comparing the effects

of pairwise combinations of criteria pollutants (PM_{2.5} & O₃, PM₁₀ & NO₂, NO₂ & O₃, PM & CO, CO & O₃) relative to single pollutant exposures, they found evidence of O₃ concentration modifying the effect of PM, with the PM and O₃ combination providing “evidence for additivity, synergism, and/or antagonism depending on the specific health endpoint.” For other pollutant pairs, they found heterogeneous results and noted that “the limited number of studies inhibited making a conclusion about the nature of the relationship between pollutant combinations and cardiovascular disease.”

In March 2024, EPA published a case study that seems to incorporate some of the SAB recommendations, a comparative analyses of quantified cumulative impacts of multiple criteria air pollutants on a specific health effect associated with changes in pollutant levels over time.^{xxxix} Using a developmental multipollutant version of the Environmental Benefits Mapping and Analysis Program - Community Edition (BenMAP-CE),^{xi} the study estimated the change in the number of pediatric asthma emergency department (ED) visits as a function of modeled changes in air pollution between 2011 and 2025 in Atlanta, Georgia, applying risk estimates from the 2014 study. The authors analyzed short-term exposures to both individual and combinations of criteria pollutants (O₃, PM_{2.5}, NO₂, SO₂, CO) that represent “shared properties or predefined sources” such as oxidant gases, power plant emissions, secondary pollutants, traffic emissions. The study found the estimated number of avoided asthma ED visits to be higher among multipollutant groups in which pollutant interaction terms were included, compared to that from single-pollutant models. This robust study underscores the importance of a multipollutant paradigm and the consideration of co-pollutant interactions for a more comprehensive assessment of health impacts in regulating individual criteria pollutants, compared to single-pollutant models. It also demonstrates that performing multipollutant health impact assessments in air quality regulation is appropriate, needed, and technically feasible.

Comparative analyses of the impacts of single pollutant exposures and cumulative effects of copolluting criteria pollutants are needed to inform regulatory actions such as primary NAAQS determinations of the six individual criteria pollutants, in the implementation of these standards, and also in air quality risk communication, which is based on the primary NAAQS of the individual criteria pollutants.

EPA’s Air Quality Index (AQI) is a public health risk communication tool used by state and local air agencies to inform their residents on daily air quality, generally accompanied with action alerts and air quality forecast information.^{xli} In its current framework, the AQI covers the group of six criteria air pollutants, using the same scale for each of the individual pollutants to set levels of outdoor air quality and associated exposure risks. This scale is based on the pollutants’ respective short-term NAAQS, i.e. AQI value of 100 of any pollutant - which indicates moderate air quality - corresponds to the level of the short-term NAAQS of that pollutant.

The AQI communicates health risks of exposure to only that single pollutant which is present at the highest level in ambient air on any given day, relative to the other pollutants in the group. Elevated levels of the other pollutants in the group do not prompt additional warnings. This maximum value single-pollutant AQI paradigm does not capture the cumulative health impacts of co-pollutants or other non-chemical stressors and may not convey the true public health risk

of exposures to “more complex air mixtures,” which are realistic representations of ambient air. Modifying the current AQI framework or adopting an aggregate air quality index that integrates cumulative risk factors and their cumulative health impacts could help gain efficiencies in protecting public health. EPA’s recent multipollutant study on co-polluting criteria pollutants that show “joint effects with interactions” to be similar to “sum of (the effects of) single pollutants”^{xlii} warrant a review of the AQI structure so that the current AQI values are better aligned with multipollutant exposures.

EPA recently announced that it is prioritizing cumulative impacts assessment in decision-making by funding research studies focusing on the Exposome or the Total Environment Framework: “build from the traditional risk assessment approach to include combinations of chemical and non-chemical stressors, changing climate, multiple health endpoints, community engagement, and mixed methods analytical approaches that incorporate both quantitative and qualitative data to inform decisions in the best interest of the community.”^{xliii} Some nonprofit research organizations are also funding similar studies on cumulative impacts of multiple stressors and its translation into implementable strategies.^{xliiv} These research projects/programs focus on a broad and diverse group of stressors with the goal of addressing disproportionate environmental burden on specific communities in various agency actions related to air, water, and land.

Focusing on one specific set of stressors in one specific regulatory domain could yield results that could be used in multiple policies. Air pollution, such as criteria air pollutant exposure, is a universal health hazard that affects everyone. Cumulative impacts of contemporaneous exposure to multiple criteria air pollutants can be assessed more easily than some of the non-chemical stressors because of the relative ease of quantification of the health impacts of multipollutant exposures in the regulation of individual criteria air pollutants. Integrating impacts of contemporaneous exposure to multiple pollutants would be helpful in designing more effective air pollution policy interventions than the current single pollutant approach. To better understand the interactions between copollutants and accurately capture their cumulative health impacts, a more robust scientific evidence base is needed. Conducting policy-applicable (“fit-for-purpose”) multipollutant research studies across different study types (epidemiological studies, animal toxicological studies, human exposure chamber studies, exposure modeling, etc.), refining existing multipollutant models, exploring new methodologies, conducting more case studies in different geographic and demographic contexts, etc. will fill the current data gaps and best inform the NAAQS process in ensuring public health protection from multipollutant exposures.

In conclusion, consideration of cumulative health impacts of copollutant exposures is needed – in NAAQS determinations and in their implementation such as the Air Quality Index to communicate public health risk – to better protect human health from criteria air pollutants. Multipollutant exposures in which individual criteria pollutants are present at levels lower than their respective NAAQS could still be harmful to health because of their combined impacts. Data from policy-applicable scientific studies on cumulative impacts criteria air pollutant co-exposures would help align primary NAAQS determination more accurately with exposure risks and afford better public health protection under the Clean Air Act.

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- ⁱ Behles, D. N. (2010). [Examining the Air We Breathe: EPA Should Evaluate Cumulative Impacts When It Promulgates National Ambient Air Quality Standards](#). *Pace Environmental Law Review*, 28(1), 200.
- ⁱⁱ EPA. [Integrated Science Assessments \(ISAs\)](#); Tables ES-1 (Summary of causality determinations) in: ISA for Ozone and Related Photochemical Oxidants, April 2020, EPA/600/R-20/012; ISA for Particulate Matter, December 2019, EPA/600/R-19/188; ISA for Oxides of Nitrogen – Health Criteria, January 2016, EPA/600/R-15/068.
- ⁱⁱⁱ Humphrey, J. L. *et al.* (2024). [Disentangling impacts of multiple pollutants on acute cardiovascular events in New York city: A case-crossover analysis](#). *Environmental Research*, 242, 117758; Study found significant same-day associations of both with risk of overall cardiovascular disease and sub-diagnosis of heart failure events and “chronic life stress among African-Americans may lead to hastened aging and cardiovascular susceptibility”; Fann, N. L., *et al.* (2021). [Associations Between Simulated Future Changes in Climate, Air Quality, and Human Health](#). *JAMA Netw Open*, 4(1):e2032064; “reducing air pollutant emissions could attenuate but not eliminate the climate change-induced increase in mortality associated with air pollution”; Sun, Y., *et al.* (2022). [Exposure to air pollutant mixture and gestational diabetes mellitus in Southern California: Results from electronic health record data of a large pregnancy cohort](#). *Environment international*, 158, 106888. “This study found that exposure to a mixture of ambient PM_{2.5}, PM₁₀, NO₂, and PM_{2.5} chemical constituents was associated with an increased risk of GDM” & “NO₂ and black carbon PM_{2.5} contributed most to GDM risk.”; Canterbury, A. *et al.* (2020). [Association between cumulative social risk, particulate matter environmental pollutant exposure, and cardiovascular disease risk](#). *BMC cardiovascular disorders*, 20(1),76; This community-based cohort study found that the association of increasing cumulative social risk with higher cardiovascular disease and mortality risks is partially accounted for by exposure to PM_{2.5} environmental pollutants; Li, Y., *et al.* (2019). [Association between air pollution and type 2 diabetes: an updated review of the literature](#). *Therapeutic advances in endocrinology and metabolism*, 10, 2042018819897046.; “Current cumulative evidence appears to suggest that T2DM-related biomarkers increase with increasing exposure duration and concentration of air pollutants. The chemical constituents of the air pollutant mixture may affect T2DM to varying degrees. The suggested mechanisms whereby air pollutants induce T2DM include increased inflammation, oxidative stress, and endoplasmic reticulum stress”; Shaw, G. M., *et al.* (2024). [Ambient Environment and the Epidemiology of Preterm Birth](#). *Clinics in perinatology*, 51(2), 361–377; Khraishah, H. *et al.* (25 Apr, 2024). [Understanding the Cardiovascular and Metabolic Health Effects of Air Pollution in the Context of Cumulative Exposomic Impacts](#). *Circulation Research*, 134, 1083–1097; This review summarizes “the current state of epidemiologic and mechanistic evidence underpinning the association of air pollution with cardiometabolic disease and how complex interactions with other exposures and individual characteristics may modify these associations” and identifies “gaps in the current literature and suggest emerging approaches for policy makers to holistically approach cardiometabolic health risk and impact assessment.”
- ^{iv} EPA. (9/16/2023). [Guidelines for Cumulative Risk Assessment: Planning and Problem Formulation](#) (Public Comment Draft). GLOSSARY OF KEY TERMS; page v
- ^v EPA. (9/16/2023). [Guidelines for Cumulative Risk Assessment](#). GLOSSARY OF KEY TERMS; page v
- ^{vi} Chiger & Nachman (2024). [Invited Perspective: Advancing Cumulative Approaches in Regulatory Decision Making](#). *Environmental Health Perspectives*, 132(3).
- ^{vii} Behles, D. N. (2010). *28 Pace Env'tl. L. Rev.* 200, page 2 (1)
- ^{viii} Clean Air Act. 42 U.S. Code § 7409 - [National primary and secondary ambient air quality standards](#); Section 109: “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.”
- ^{ix} [National Academies’ Report on Causality Framework](#) (Oct, 2022). page 23
- ^x EPA’s Science Advisory Board (4/25/2022). [Consultation on Cumulative Impact Assessments](#), EPA-SAB-22-003; Dr. Susan Anenberg, page 12 (B-4)
- ^{xi} Alves, S. *et al.* (2012). [EPA authority to use cumulative risk assessments in environmental decision-making](#). *Int. J. Environ. Res. Public Health*, 9(6), 1997-2019
- ^{xii} [NRC, 2012](#); [NASEM, ongoing](#); [SAB, 2022](#); Clean Air Scientific Advisory Committee (CASAC) 2022-2023
- ^{xiii} Science Advisory Board (4/25/2022). [Consultation on Cumulative Impact Assessments](#)
- ^{xiv} Ellickson, K. M., Pauli B. J. &Whitehead, S. (July 8, 2024). [Mixed Methods Approaches: Structures and](#)

[Methodologies for Cumulative Impact Assessment Development](#). Environmental Justice - Ahead of Print

^{xv} K. Ellickson, Union of Concerned Scientists. (Sept 30, 2024). [Protecting Public Health Is Complicated. But Science Can Help, and the Time Is Now.](#)

^{xvi} Coffman, E. et al. (3/6/2024). [Quantifying Multipollutant Health Impacts Using the Environmental Benefits Mapping and Analysis Program—Community Edition \(BenMAP-CE\): A Case Study in Atlanta, Georgia](#). *Environmental Health Perspectives*, 132(3). Invited Perspective: Advancing Cumulative Approaches In Regulatory Decision Making

^{xvii} Science Advisory Board (4/25/2022). [Consultation on Cumulative Impact Assessments](#), page 41 (B-33), Dr. A. Childress: “Given that the EPA expected to start moving beyond single chemical risk assessments to multi-chemical and cumulative risk assessments in 2003, it is surprising that studies have not been done.”

^{xviii} Johns, D. O. et al. (9/2012). [Practical Advancement of Multipollutant Scientific and Risk Assessment Approaches for Ambient Air Pollution](#). *Environmental Health Perspectives*, 120(9), 1238-1242.

^{xix} 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.

^{xx} February 24, 2023. [EPA Releases Proposed Approach for Considering Cumulative Risks under TSCA | US EPA](#)

^{xxi} EPA. (2/24/2023). [EPA Releases Proposed Approach for Considering Cumulative Risks under TSCA.](#)

^{xxii} Gogna, P. et al. (5/6/2024). [A cohort study of the multipollutant effects of PM_{2.5}, NO₂, and O₃ on C-reactive protein levels during pregnancy](#). *Environ. Epidemiol.*, 8(3):e308; *Pollutant mixtures showed stronger relationships with maternal systemic C-reactive protein (CRP) levels compared with individual pollutants and illustrate the importance of conducting multipollutant analyses.*

^{xxiii} Mainka, A. & Žak, M. (10/2022). [Synergistic or Antagonistic Health Effects of Long- and Short-Term Exposure to Ambient NO₂ and PM_{2.5}: A Review](#). *Int J Environ Res Public Health*, 19(21):14079. “Both short- and long-term exposure to PM_{2.5} or NO₂ adjusted for NO₂ and PM_{2.5}, respectively, revealed a synergistic effect appearing as higher mortality from respiratory diseases.”

^{xxiv} Sun, Y., et al. (2022). [Exposure to air pollutant mixture and gestational diabetes mellitus in Southern California: Results from electronic health record data of a large pregnancy cohort](#). *Environment international*, 158, 106888. “This study found that exposure to a mixture of ambient PM_{2.5}, PM₁₀, NO₂, and PM_{2.5} chemical constituents was associated with an increased risk of gestational diabetes mellitus.”

^{xxv} Adebayo-Ojo, T. C. et al. (1/2022). [Short-Term Joint Effects of PM₁₀, NO₂ and SO₂ on Cardio-Respiratory Disease Hospital Admissions in Cape Town, South Africa](#). *Int J Environ Res Public Health*, 19(1), 495; *This study found “robust associations of daily respiratory disease hospital admissions with daily PM₁₀ and NO₂ concentrations” and “overall cumulative risks for RD per IQR increase in PM₁₀ and NO₂ for children at 2% and 3.1% respectively.”*

^{xxvi} Environmental Protection Agency Risk Assessment Forum. (9/16/2023). [Guidelines for Cumulative Risk Assessment Planning and Problem Formulation \(Draft for Public Comment\)](#); Document #: 2023-12972

^{xxvii} EPA. (9/16/2023). [Guidelines for Cumulative Risk Assessment. Appendix A-6](#)

^{xxviii} EPA. (8/2014). [Health Risk and Exposure Assessment for Ozone - Final Report](#); EPA-452/R-14-004a; This REA for ozone NAAQS is an example of an REA where EPA does not include cumulative risks.

^{xxix} 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

^{xxx} EPA. [FACT SHEET FOR NO_y MONITORING](#)

^{xxxi} EPA. (9/16/2023). [Guidelines for Cumulative Risk Assessment. Appendix A-6](#)

^{xxxii} CASAC. (6/9/2023). [Review of the EPA’s PA Draft Ver 2 for Ozone NAAQS Reconsideration](#); page 60

^{xxxiii} [CASAC review of PM PA](#). (11/22/2022), page 11.

^{xxxiv} CASAC. (2/19/2020). [Review of the EPA’s Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards \(External Review Draft\)](#); EPA-CASAC-20-003; page 101

^{xxxv} CASAC. (6/9/2023). [Review of the EPA’s PA Draft Ver2 for Ozone NAAQS Reconsideration](#); Ed Avol, page 59

^{xxxvi} [CASAC review of ozone ISA](#). (Nov 22, 2022). pages 62 (A-33) and 21 (12)

^{xxxvii} [Precautionary principle - EUR-Lex \(europa.eu\)](#)

^{xxxviii} Luben, T. J. et al. (2/2018). [A cross-disciplinary evaluation of evidence for multipollutant effects on cardiovascular disease](#). *Environmental Research*, 161, 144-152.

^{xxxix} Coffman, E. *et al.* (3/6/2024). [BenMAP-CE Case Study in Atlanta, Georgia](#). *Env. Health Pers.* 132(3).

^{xi} EPA. [Environmental Benefits Mapping and Analysis Program – Community Edition \(BenMAP-CE\)](#). “BenMAP-CE is a US EPA tool that estimates the number and economic value of air pollution–related deaths and illnesses relying on preloaded or user-inputted datasets of air quality data, demographic data (i.e., baseline incidence and population data), concentration–response relationships for multiple individual air pollutants and numerous health outcomes, and economic values.”

^{xlii} [Air Quality Index \(AQI\) - AirNow](#); AirNow website & app report daily air quality using the AQI. AirNow is a federal, state, tribal, local government partnership platform that provides local air quality for numerous urban and rural areas across the country as well as an overview of air quality at the state, national, and international levels.

^{xliii} Coffman, E. *et al.* (3/6/2024). [BenMAP-CE Case Study in Atlanta, Georgia](#). *Env. Health Pers.* 132(3).

^{xliiii} Tulve, N. S. *et al.* (Feb, 2024). [Challenges and opportunities for research supporting cumulative impact assessments at the United States environmental protection agency's office of research and development](#). *Lancet Reg Health Am.*,30, 100666.

^{xliiv} [RFA 24-1 Cumulative Impact Assessment For Decision-Making: A Community-Academic Partnership Approach](#) | Health Effects Institute