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A cross-disciplinary evaluation of evidence for multipollutant effects on cardiovascular disease

Thomas J. Luben[a,*,1], Barbara J. Buckley[a], Molini M. Patel[a], Tina Stevens[b], Evan Coffman[b,c], Kristen M. Rappazzo[a,b], Elizabeth O. Owens[a], Erin P. Hines[a], Danielle Moore[b], Kyle Painter[b], Ryan Jones[a], Laura Datko-Williams[b,d], Adrien A. Wilkie[b,e], Meagan Madden[b,f], Jennifer Richmond-Bryant[a]

[a] Office of Research and Development, US EPA, RTP, NC, USA
[b] Oak Ridge Institute of Science and Education (ORISE) Research participant at the US EPA, RTP, NC, USA
[c] Office of Air and Radiation, US EPA, RTP, NC, USA
[d] CROS NT, LLC, Chapel Hill, NC, USA
[e] Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC, USA
[f] Development Research Group, The World Bank, Washington, DC, USA

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ABSTRACT

Background: The current single-pollutant approach to regulating ambient air pollutants is effective at protecting public health, but efficiencies may be gained by addressing issues in a multipollutant context since multiple pollutants often have common sources and individuals are exposed to more than one pollutant at a time.
Objective: We performed a cross-disciplinary review of the effects of multipollutant exposures on cardiovascular effects.
Methods: A broad literature search for references including at least two criteria air pollutants (particulate matter [PM], ozone [O_3], oxides of nitrogen, sulfur oxides, carbon monoxide) was conducted. References were culled based on scientific discipline then searched for terms related to cardiovascular disease. Most multipollutant epidemiologic and experimental (i.e., controlled human exposure, animal toxicology) studies examined PM and O_3 together.
Discussion: Epidemiologic and experimental studies provide some evidence for O_3 concentration modifying the effect of PM, although PM did not modify O_3 risk estimates. Experimental studies of combined exposure to PM and O_3 provided evidence for additivity, synergism, and/or antagonism depending on the specific health endpoint. Evidence for other pollutant pairs was more limited.
Conclusions: Overall, the evidence for multipollutant effects was often heterogeneous, and the limited number of studies inhibited making a conclusion about the nature of the relationship between pollutant combinations and cardiovascular disease.

1. Introduction

Under the Clean Air Act, EPA regulates six criteria pollutants [particulate matter (PM), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and lead (Pb)] individually. Implementation of the National Ambient Air Quality Standards (NAAQS) has reduced annual average concentrations of criteria air pollutants by 28–87% from 1980 to 2013 (U.S. EPA, 2016b, 2017). However, several research groups have commented that single-pollutant regulation is inefficient because multiple pollutants often have common sources and individuals are not exposed to only one pollutant at a time (Dominici et al., 2010; Greenbaum and Shaikh, 2010; Hidy and Pennell, 2010; Johns et al., 2012; Mauderly et al., 2010; NRC, 2004). Generally speaking, a multipollutant regulatory approach might focus on how different air pollutant mixtures contribute to population-level exposures and identify which mixtures are most closely associated with particular health outcomes. Once relevant mixtures are identified, regulators could focus on the sources of those mixtures, transport and transformation of emissions from those sources, and relevant population exposures to those mixtures. While this approach is certainly

* Correspondence to: USPS Address: U.S. EPA, MD B243-01, RTP, NC 27711.
E-mail address: luben.tom@epa.gov (T.J. Luben).
[1] UPS, FEDEX & Other Delivery Address: U.S. EPA, MD B243-01, 4930 Old Page Rd, Durham, NC 27703.

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complex, it will be more efficient by allowing for regulatory assessments to be conducted for a subset of relevant mixtures. For example, a case study that modeled scenarios to quantify health impacts of air pollution management strategies found larger reductions in both pollutant concentrations and cases of premature mortality attributable to PM with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) or O_3 exposure for multipollutant emission control strategies than for single-pollutant control strategies (i.e., reductions were greater than additive) (Wesson et al., 2010).

There are also uncertainties related to evaluating one air pollutant at a time, which may be one reason for the growing interest in health effects of multipollutant exposures in both epidemiologic and experimental (i.e., controlled human exposure, animal toxicological) studies. Epidemiologic studies may statistically adjust for the association of another air pollutant in multivariable copollutant models to discern a potential independent association for a single pollutant. However, inferences from such analyses may be uncertain as effect estimates can be inflated for pollutants measured with less error or can be unreliable if copollutants are highly correlated (Zeger et al., 2000). Single-pollutant analyses do not account for the possibility that exposure to multiple pollutants may have effects that are other than additive, (i.e., the combined influence of multiple pollutants represented by the sum of their independent effects). While multipollutant analyses do not reduce or eliminate residual confounding or the impacts of measurement error commonly attributed to single-pollutant models, they allow for examination of the combined influence of multiple pollutants.

Several statistical methods have been applied or are being developed to examine the relationship between multipollutant exposures and health effects (Billionnet et al., 2012; Davalos et al., 2016). To date, experimental studies have evaluated *interactions*, effects of simultaneous exposure to two or more pollutants that differ from the summed effect of each exposure occurring alone (Vanderweele, 2009). These interaction effects may be antagonistic, an effect of simultaneous exposure to two or more pollutants that is lower in magnitude than the sum of the effect of the individual pollutants, or synergistic, an effect of simultaneous exposure to two or more pollutants that is greater than the sum of the effect of the individual pollutants (Mauderly, 1993; Mauderly and Samet, 2009). In epidemiologic studies, various multipollutant regression techniques are available to estimate *joint effects* by including additive or multiplicative interaction terms in the regression model. For example, Winquist et al. (2014) assessed the joint effect of combinations of air pollutants for asthma emergency department visits by calculating the effect of a specified change in each pollutant in the combination. Epidemiologic and experimental studies have also examined *effect measure modification*, where the effect of one pollutant varies by level of another (Howe et al., 2012; Vanderweele, 2009).

The objective of this review was to perform a cross-disciplinary evaluation of the multipollutant effects on health endpoints related to cardiovascular disease (CVD). In other words, the review entails integration of results from observational epidemiologic studies with experimental controlled human exposure and animal toxicological studies. The cross-disciplinary nature of this review allows us to integrate across the continuum of CVD endpoints, from biomarkers of inflammation and coagulation, sub-clinical markers of CVD, clinical endpoints including hospital admission and emergency department visits, and mortality, and aids in reducing uncertainties related to potential confounding, exposure misclassification, and differences across animal species that would be present if the review were limited to one scientific discipline. In this review, *multipollutant effects* were specified to include at least two criteria air pollutants evaluated for *interactions* (in experimental studies), *joint effects* (in epidemiologic studies), or *effect measure modification* (in experimental or epidemiologic studies). We identified studies reporting interactions, joint effects, and effect measure modification (which include data on concentrations of individual criteria air pollutants) which are more informative of multipollutant effects than studies of clusters, indices and whole atmosphere exposures, where information on concentrations of individual criteria pollutants are often not available. To be complete, we discuss studies of cluster, indices and whole atmosphere exposures in Section 3.7. We assessed the coherence of results from epidemiologic and experimental studies to strengthen inference about health effects due to multipollutant exposures.

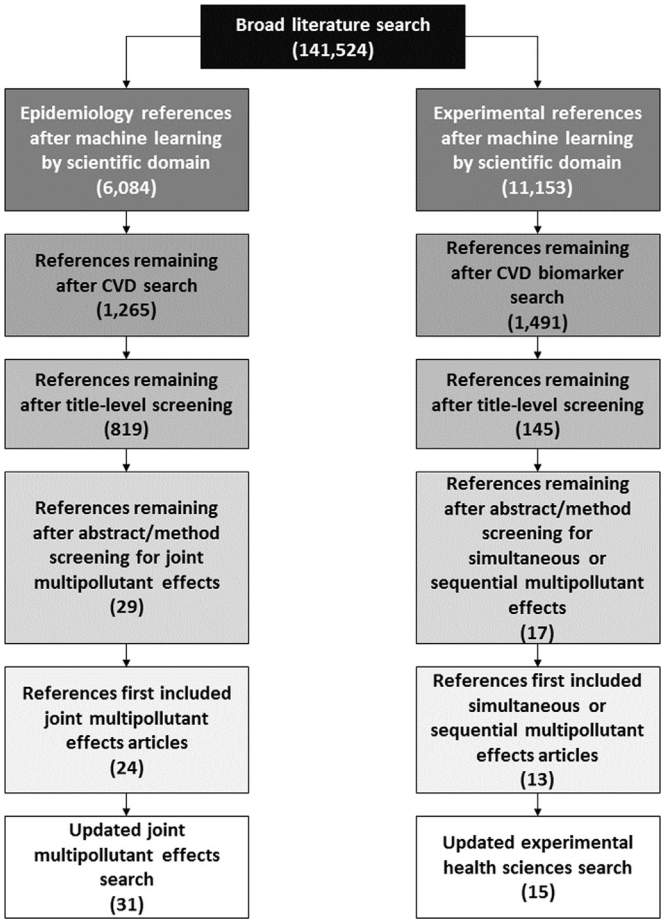

Fig. 1. Schematic of the literature search and screening processes.

2. Methods

We identified studies on multipollutant exposures and CVD-related effects published through December 31, 2015 using a stepwise systematic literature search that employed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as illustrated in Fig. 1 and described in detail in the Supplemental Materials. The literature review began with a broad literature search for references including at least two criteria air pollutants among PM, O_3, oxides of nitrogen (NO_X), sulfur oxides (SO_X), and CO using an array of search terms (Supplemental Tables S1 and S2). The retrieved references were refined by applying an automatic topic classification algorithm to segregate references into epidemiologic or experimental study domains. The algorithm, trained by a set of known relevant seed references, had recall greater than 90% but lower precision (Supplemental Tables S3 and S4), meaning the bins captured most of the relevant references for the intended domain but also captured many references from other domains. Next, specific terms related to CVD (identified from (Gill et al., 2011)) were applied to the domain-specific bins (Supplemental Table S5). From those results, irrelevant references (i.e., non-criteria pollutants and non-CVD-related health effects) were excluded based on manually screening the title and, if necessary, reviewing the abstract. If we could not conclusively determine whether inclusion criteria were