Providing perspective for interpreting cardiovascular mortality risks associated with ozone exposures

Catherine Petito Boyce [a], Julie E. Goodman [b,*], Sonja N. Sax [b], Christine T. Loftus [a]

[a] Gradient, 600 Stewart Street, Ste 1900, Seattle, WA 98101, USA
[b] Gradient, 20 University Road, Ste 5, Cambridge, MA 02138, USA

A B S T R A C T

When identifying standards for air pollutants based on uncertain evidence, both science and policy judgments play critical roles. Consequently, critical contextual factors are important for understanding the strengths, limitations, and appropriate interpretation of available science, and potential benefits of risk mitigation alternatives. These factors include the relative magnitude and certainty of the risks posed by various factors and the impacts of other risk factors on air pollutant epidemiology study findings. This commentary explores ozone's status as a risk factor for cardiovascular mortality in contrast with decades of strong and consistent evidence for other established risk factors. By comparison, the ozone evidence is less conclusive, more heterogeneous, and subject to substantial uncertainty; ozone's potential effects, if any, are small and challenging to discern. Moreover, the absence of a demonstrated causal relationship calls into question efforts to quantify cardiovascular mortality risks attributed to ozone exposures on a population level and highlights the need to explicitly acknowledge this uncertainty if such calculations are performed. These concerns are relevant for other similar policy contexts – where multiple established risk factors contribute to the health impact of interest; exposure-effect associations are relatively small, weak, and uncertain; and a causal relationship has not been clearly established.
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1. Introduction

When identifying health-protective standards for air pollutants based on uncertain evidence, both science and policy judgments play critical roles. For example, while the process of setting National Ambient Air Quality Standards (NAAQS) for criteria air pollutants includes developing "a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation" for determining the NAAQS, the decision regarding the level and form of the NAAQS "is a policy choice left specifically to the Administrator's judgment" (U.S. EPA, 2013). As detailed in McClellan (2012), it is particularly important to distinguish among those aspects of the standard setting process that reflect scientific determinations and those that are policy judgments. Moreover, it is important to ensure that the standard setting process compiles contextual information relevant for the necessary policy choices (McClellan, 2012).

Consequently, critical contextual factors can and should play an important role in understanding both the strengths and limitations of the available science and the implications of policy choices. For example, to fully evaluate whether proposed changes to air quality standards will improve health, it is useful to consider not only how air pollutant exposures might contribute to specific health effects, but also to compare these potential impacts with those of other known risk factors. In making this comparison, policy decision makers should consider both the relative magnitude of the risks and the relative strength of the evidence supporting associations. Placing potential health risk estimates from air pollution exposures in a more complete context for policy decisions becomes increasingly important as air quality standards are reduced to levels that are near background levels and difficult to meet, and are based on scientific evidence reflecting greater degrees of uncertainty regarding the nature and magnitude of potential health impacts. Comparing the estimated magnitude and certainty of ozone health impacts to that of other known risk factors provides a useful perspective on the potential benefits of risk mitigation alternatives. Similarly, insights regarding appropriate uses of available evidence can result from reviewing the relative strength of the evidence for a causal relationship between the health effect of interest and ozone *versus* that for other risk factors. As a case study of these

* Corresponding author. Fax: +1 617 395 5001.
E-mail addresses: cpetitoboyce@gradientcorp.com (C. Petito Boyce), jgoodman@gradientcorp.com (J.E. Goodman), ssax@gradientcorp.com (S.N. Sax), cloftus@gradientcorp.com (C.T. Loftus).

issues, this commentary explores the status of ozone as a risk factor for cardiovascular mortality and reviews the information available for ozone in the context of that for other well-established risk factors.

The US Environmental Protection Agency (US EPA) is mandated by the Clean Air Act to develop NAAQS for six air pollutants (including ozone), using a process that integrates numerous types of scientific evidence. In a recent re-evaluation of the NAAQS for ozone, US EPA reviewed studies addressing a broad range of potential health effects, reflecting a variety of study types and both short- and long-term exposures (defining short-term exposures as those occurring over a period of hours, days, or weeks, and long-term exposures as those occurring over periods of months to years; US EPA, 2013). Of the six categories of health effects explored, US EPA determined that the evidence for only one is reflective of a "causal" relationship – *i.e.*, respiratory morbidity following short-term ozone exposures – and focused primarily on respiratory effects and overall mortality in its discussion of health effects of concern for ozone. For all of the other health effects categories, US EPA assigned categories indicating greater uncertainty in the underlying evidence. For example, based in part on data limitations and the lack of coherence between results observed in epidemiology and animal toxicology studies (which US EPA identified as "an important uncertainty" p.2–29), US EPA characterized the evidence of cardiovascular or mortality effects following short-term exposures as "likely" to reflect a causal relationship. Indicating an even greater degree of uncertainty in the limited available data, US EPA characterized the evidence of cardiovascular or mortality effects following long-term exposures as only "suggestive" of a causal relationship.

Cardiovascular disease is the leading cause of morbidity and mortality in the US, and health organizations such as the American Heart Association (AHA) have led large nationwide initiatives to reduce the overall burden of this disease in the US population (Lloyd-Jones et al., 2010). Strong temporal and geographic variations in cardiovascular disease mortality have been observed. For example, Fig. 1 illustrates how the US death rate for cardiovascular disease has steadily declined since 1979, while Fig. 2 shows how recent (2005–2007) US death rates for cardiovascular disease vary by geographic region (NIH, 2012). Temporal and geographic differences in the death rates are attributed to changes in population levels of various established risk factors for cardiovascular disease and mortality (discussed further below), as well as increasing use of more effective treatments and changing population demographics (*e.g.*, the growth in the proportion of older individuals in the US population) (Lloyd-Jones et al., 2010).

A number of factors have been identified as risk factors for mortality related to cardiovascular health. These factors include modifiable factors (*i.e.*, factors that potentially can be changed by individuals) such as body mass, and certain disease states, dietary habits, activity patterns, and other behaviors (*e.g.*, smoking). The scientific support for the role of these recognized factors in cardiovascular disease mortality is considered sufficiently strong that public health practitioners, policy makers, clinicians, and individuals routinely make or recommend making changes to these factors to reduce risks of cardiovascular system-related disease and mortality. Non-modifiable factors such as family history, age, race, socioeconomic status, and exposures to extreme temperatures are also well-recognized as playing an important role in cardiovascular mortality. Although these factors either cannot be changed or are less amenable to change, they also are considered important in understanding cardiovascular mortality risks.

In contrast, a causal role for ozone in cardiovascular mortality has not been established. As noted above, in its review of the scientific literature for ozone health effects, US EPA recognized a number of fundamental limitations and inconsistencies in the available information regarding cardiovascular and mortality effects. Moreover, two recent comprehensive weight-of-evidence evaluations concluded that the strength of the evidence was not sufficient to conclude that short- or long-term ozone exposures play a causal role in cardiovascular morbidity and mortality (Goodman et al., 2014; Prueitt et al., 2014). Using an approach based on one developed by the Institute of Medicine (IOM, 2008), these evaluations instead categorized the evidence as "below equipoise," indicating that "[t]he evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically formed judgment." Other studies have also called into question the causal role of ozone in mortality (including cardiovascular mortality) and other cardiovascular health impacts such as myocardial infarction (*e.g.*, Smith et al., 2009; Mustafic et al., 2012).

Below, we review the strength of evidence and magnitude of risk for factors traditionally recognized as contributors to cardiovascular mortality risk. This information is then compared to the evidence available regarding the role of ozone in cardiovascular mortality. We then discuss the role that established risk factors may play in studies of ozone cardiovascular risks (*e.g.*, as residual confounders) and approaches for exploring the implications of individual-level risk estimates for populations.

2. Available evidence regarding cardiovascular mortality risk factors

2.1. Established risk factors

Many decades of biomedical research have contributed to the current state of knowledge regarding cardiovascular disease and mortality. A number of established risk factors for cardiovascular mortality have been well-described in the literature, including modifiable risk factors (*e.g.*, diet and smoking) as well as non-modifiable personal characteristics (*e.g.*, family history of cardiovascular disease) (Berry et al., 2012; Danaei et al., 2009; Mittleman and Mostofsky, 2011). Fig. 3 displays relative risk (RR) estimates for cardiovascular mortality associated with two broad categories of risk factors: those analyzed as long-term/chronic risk factors that occur over long periods of time, and short-term risk factors (*i.e.*, triggers), evaluated in epidemiology studies as events that may precipitate an acute cardiovascular event immediately following exposure. Additional information regarding the studies in this figure is summarized in Table 1.

This case study focuses on mortality rather than morbidity because cardiovascular disease often results in death, and mortality as a health endpoint can be measured in a relatively straightforward manner (van der Maas, 2003). Epidemiology studies of cardiovascular disease mortality commonly use coding systems such as the International Classification of Diseases (ICD) to characterize the causes of death reflected in their study datasets (NIH, 2012).[1] As a consequence, the various categories and subcategories of mortality considered in such studies are well-defined and consistent across studies.

In selecting a RR estimate for each risk factor included in this figure and table, we conducted a literature search to identify the most recent and comprehensive perspectives on the evidence. When available, we included results from recent pooled or meta-analyses that present an integrated summary of results from multiple high-quality research investigations. Preference was given to

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[1] Cardiovascular disease is typically defined by ICD-9 codes 390-405, 410-449, 451-459, and 745-747; and ICD-10 codes of I00-I99 and Q20-Q28 (NIH, 2012 being catalogued).