

March 13, 2014

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Dr. H. Christopher Frey
Chair, Clean Air Scientific Advisory Committee
Science Advisory Board
US Environmental Protection Agency
1200 Pennsylvania Avenue NW
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Re: Comments on EPA's Health Risk and Exposure Assessment and Policy
Assessment for Ozone

Dear Dr. Frey:

In its 2013 Integrated Science Assessment (ISA) for ozone, EPA concluded that the available evidence supports a likely causal relationship between long-term ozone exposure and respiratory effects, including respiratory mortality. EPA also concluded that the evidence supports a likely causal relationship between short-term exposure and mortality (US EPA, 2013). EPA evaluated these endpoints in the ozone Health Risk and Exposure Assessment (REA). Based on this evaluation, EPA made recommendations in the ozone Policy Assessment (PA) regarding proposed alternative standards (US EPA, 2014a,b).

At the request of the trade associations listed below, Gradient has performed independent reviews of the studies that EPA cited in support of its conclusions (see attached). Gradient has found that the epidemiology evidence, in conjunction with other relevant data, does not support a causal link between ozone exposure and mortality or morbidity. We present a summary of Gradient's findings below.

Long-term Exposure and Respiratory Effects

In 2006, EPA concluded that the evidence indicated a suggestive but inconclusive relationship between long-term ozone exposure and respiratory effects (US EPA, 2006). In 2013, EPA concluded that the evidence was likely causal (US EPA, 2013), citing stronger evidence than was available in 2006. However, evidence available since 2006 is not stronger, nor does it support a causal link.

EPA based its 2013 conclusion primarily on epidemiology studies, particularly those evaluating asthma incidence (new-onset asthma), asthma prevalence and symptoms, asthma hospital admissions and emergency department (ED) visits, pulmonary structure and function, and pulmonary inflammation, injury, and oxidative stress. The majority of the analyses that focus on the impacts of long-term air pollution exposure on new-onset asthma in children demonstrate a lack of respiratory effects (including asthma) associated with long-term ozone exposure, even in areas with high levels of

ozone (e.g., Peters *et al.*, 1999; Gauderman *et al.*, 2000, 2002, 2004; McConnell *et al.*, 2002, 2010; Berhane *et al.*, 2004). One analysis reported a positive association between playing three or more sports in a high-ozone exposure community and an increased risk of developing asthma (McConnell *et al.*, 2002), while other studies indicated children that may be more genetically susceptible to respiratory inflammation also have an increased risk of asthma (Li *et al.*, 2006; Islam *et al.*, 2008, 2009). It is unclear, however, whether ozone actually played a role in any of these associations.

Long-term studies evaluating the association between ozone and asthma prevalence or asthma symptoms at a single time point (e.g., in a given year), as well as those evaluating long-term exposure to ozone and asthma hospital admissions and ED visits, have shown largely mixed results, with most showing no effects on these outcomes. Many of these studies did not account for co-pollutant exposure, other factors that could have led to asthma hospital admissions and ED visits, or the fact that, generally, people spend most of their time indoors. Similarly, when considered together, the three studies EPA cited that reported a possible link between long-term ozone exposure and allergies or respiratory-related illness are likely unreliable, both because of study limitations (such as not accounting for potential allergens (Parker *et al.*, 2009; Rage *et al.*, 2009)) and the lack of observed statistical differences for children living in high- vs. low-exposure communities (Wenten *et al.*, 2009).

Epidemiology studies have also evaluated effects of long-term ozone exposure on pulmonary structure and lung function. As with those evaluating the association with asthma incidence or symptoms, the majority of these studies found no association between long-term ozone exposure and lung function (Peters *et al.*, 1999; Mortimer *et al.*, 2008a,b; Latzin *et al.*, 2009; Forbes *et al.*, 2009). In fact, Gauderman *et al.* (2000, 2002) reported that, in following children as they grew, there was no evidence that ozone affected lung function in any way to compromise children's respiratory health later in life. Only one study, conducted in Mexico City, reported ozone exposures that correlated with a decline in lung function in children (Rojas-Martinez *et al.*, 2007). However, this study relied on crude measures of ozone exposure and did not account for confounding factors.

EPA also noted that new epidemiology evidence of other pulmonary effects from long-term exposure to ozone, such as inflammation, injury, and oxidative stress, is too limited to draw conclusions. Considering this conclusion and the lack of support for causation demonstrated above, the new evidence does not support a likely causal association between long-term ozone exposure and respiratory effects.

Long-term Exposure and Mortality

In 2013, EPA also strengthened its 2006 conclusion that evidence was suggestive of a causal link between long-term exposure and premature mortality (US EPA, 2013). However, as with respiratory effects, the evidence is not stronger now than it was in 2006. Much of the newly available studies that evaluate this relationship were re-analyses of existing data rather than new data. For example, three of the five newly available studies since 2006 used different statistical analyses to reanalyze previously

analyzed data. Importantly, the previous studies of these data reported no links between ozone and mortality. While small risks were observed for all-cause and cause-specific mortality in some of the re-analyses, results were not consistent within or across the studies, which does not support causality. Of the other two new studies EPA identified, one reported a link between ozone exposure and mortality in populations with specific health conditions (Zanobetti and Schwartz, 2011). The other reported no link between ozone and mortality at ozone concentrations typically seen in the US today (Wang *et al.*, 2009).

Of these five new studies, EPA relied most heavily on Jerrett *et al.* (2009), which reported a link between ozone exposure and respiratory mortality. However, these findings are not consistent with other risk estimates reported in this study, such as the lack of association between ozone and all-cause or cardiovascular (CV) related mortality, which would be expected if ozone truly impacted respiratory mortality. The positive findings are also not supported by other studies that did not show statistically significant associations between ozone and respiratory deaths (Abbey *et al.*, 1999; Lipsett *et al.*, 2011).

Short-term Exposure and Mortality

In 2013, EPA modified its 2006 conclusion from a suggestive to likely causal relationship between short-term exposure and premature all-cause and CV mortality (US EPA, 2013). It also maintained its conclusion that short-term ozone exposure causes respiratory effects, including mortality. Numerous multi-city studies have evaluated all-cause and cause-specific mortality from air pollution in specific cities around the world. Many of these studies are re-analyses of data evaluated in prior studies. These studies generally reported small average mortality risks across cities that ranged from about a 1-6% increase in all-cause mortality with an increase in ozone concentration. However, these estimates varied greatly between cities and depended on the choice of statistical model and model assumptions, sometimes showing a link and sometimes not. For a large number of cities, in any given study there was no association between increased ozone and mortality or associations showed a significant deficit (indicating a benefit of ozone); this casts doubt on the overall average risk estimates. Associations between respiratory or CV mortality and short-term ozone exposure are even more variable; the majority of available analyses, including the large study, Air Pollution and Health: A European Approach (APHENA), by Katsouyanni *et al.* (2009) on which EPA relied heavily, does not demonstrate statistically significant associations.

Finally, the assessment of both short- and long-term ozone exposure and mortality suffer from many of the same uncertainties and shortcomings. These include not fully considering factors that may account for statistical links between ozone and mortality (*e.g.*, meteorological factors such as temperature, lifestyle factors such as smoking) and the use of crude exposure measurements utilized in epidemiology studies (*e.g.*, from a few outdoor monitors located in populated areas) that do not accurately reflect people's exposure to ozone. In addition, the link between ozone exposure and mortality is not supported by animal toxicity or mechanistic studies. In fact, a biologically plausible

mechanism has yet to be discovered by which ozone exposure at levels typically found in the US today can cause death.

Short- and Long-term Exposure and Cardiovascular Effects

Gradient recently conducted a weight-of-evidence (WoE) analysis to determine whether evidence supports an association between short- and long-term ozone exposures and CV effects using a novel WoE framework adapted from the US EPA's National Ambient Air Quality Standards causality framework (Goodman *et al.*, 2014; Prueitt *et al.*, 2014). Specifically, Gradient synthesized and critically evaluated the relevant epidemiology, controlled human exposure, experimental animal, and mechanistic data and made a causal determination using the same categories proposed by the Institute of Medicine report *Improving the Presumptive Disability Decision-making Process for Veterans* (IOM, 2008). Gradient found that the totality of the data indicates that the results for CV effects are largely null across human, experimental animal, and mechanistic studies. The few statistically significant associations reported in epidemiology studies of CV morbidity and mortality are very small in magnitude and likely attributable to confounding, bias, or chance. In experimental animal studies, the reported statistically significant effects at high exposures are not observed at lower exposures and are, thus, not likely relevant to humans exposed to current ambient ozone exposures. Mode-of-action data also do not support a biologically plausible mechanism for CV effects of ozone. Overall, the limitations of the available studies preclude definitive conclusions regarding causation or a lack thereof. Still, taken together, the WoE indicates that a causal relationship between short-term exposure to ambient ozone levels and adverse effects on the CV system is not likely in humans.

Conclusions

Overall, EPA's conclusions regarding long-term ozone-related respiratory effects (including mortality), short-term ozone-related all-cause mortality, and short- and long-term ozone-related cardiovascular morbidity and mortality are not supported by the available evidence. For all of these endpoints, there is a lack of definitive evidence supporting an effect of ozone (as opposed to other factors). In addition, there is a lack of consistency and coherence within and across studies that calls into question a causal link. Furthermore, the evidence of causality for these endpoints is no stronger today than it was in 2006, with epidemiology studies mostly indicating a lack of association and other evidence (*e.g.*, animal and mechanistic studies) providing little, if any, additional support. Therefore, EPA's causal determinations for these endpoints should not be stronger than in its 2006 review.

Based on Gradient's assessments, the evidence does not support a causal or even likely causal association at ozone levels at or below the current National Ambient Air Quality Standards. In particular, short-term ozone-related all-cause mortality and long-term ozone-related respiratory mortality endpoints should not be considered in the REA, and none of these endpoints should be used to inform policy decisions in the PA.

If you have any questions about these comments, please contact Timothy Hunt, Senior Director for Air Quality Programs at the American Forest & Paper Association and American Wood Council at 202-463-2588 or by email at tim_hunt@afandpa.org or thunt@awc.org. Thank you in advance for your consideration of these comments.

Submitted on Behalf of,

American Chemistry Council
American Forest & Paper Association
American Iron and Steel Institute
American Petroleum Institute
American Wood Council
Corn Refiners Association
Council of Industrial Boiler Owners
National Oilseed Processors Association
Portland Cement Association
Rubber Manufacturers Association
Treated Wood Council
U.S. Chamber of Commerce
Utility Air Regulatory Group

Attachments:

Gradient report on Long-Term Ozone Exposure and Mortality – April 26, 2013
Gradient report on Short-term Ozone Exposure and Mortality – December 20, 2013
Gradient report on Long-Term Ozone Exposure and Respiratory Morbidity – December 20, 2013

References

Abbey, DE; Nishino, N; McDonnell, WF; Burchette, RJ; Knutsen, SF; Lawrence Beeson, W; Yang, JX. 1999. "Long-term inhalable particles and other air pollutants related to mortality in nonsmokers." *Am. J. Respir. Crit. Care Med.* 159(2):373-382.

Berhane, K; Gauderman, WJ; Stram, DO; Thomas, DC. 2004. "Statistical issues in studies of the long-term effects of air pollution: The Southern California Children's Health Study." *Stat. Sci.*19(3):414-449.

Forbes, LJ; Patel, MD; Rudnicka, AR; Cook, DG; Bush, T; Stedman, JR; Whincup, PH; Strachan, DP; Anderson, RH. 2009. "Chronic exposure to outdoor air pollution and markers of systemic inflammation." *Epidemiology* 20:245-253.

Gauderman, WJ; McConnell, R; Gilliland, F; London, S; Thomas, D; Avol, E; Vora, H; Berhane, K; Rappaport, EB; Lurmann, F; Margolis, HG; Peters, J. 2000. "Association between air pollution and lung function growth in Southern California children." *Am. J. Respir. Crit. Care Med.* 162:1383-1390.

Gauderman, WJ; Gilliland, GF; Vora, H; Avol, E; Stram, D; McConnell, R; Thomas, D; Lurmann, F; Margolis, HG; Rappaport, EB; Berhane, K; Peters, JM. 2002. "Association between air pollution and lung function growth in Southern California children: Results from a second cohort." *Am. J. Respir. Crit. Care Med.* 166:76-84.

Gauderman, WJ; Avol, E; Gilliland, F; Vora, H; Thomas, D; Berhane, K; McConnell, R; Kuenzli, N; Lurmann, F; Rappaport, E; Margolis, H; Bates, D; Peters, J. 2004. "The effect of air pollution on lung development from 10 to 18 years of age." *N. Engl. J. Med.* 351(11):1057-1067.

Goodman, JE; Prueitt, RL; Sax, SN; Lynch, HN; Zu, K; Lemay, JC; King, JM; Venditti, FJ. 2014. "Weight-of-evidence evaluation of short-term cardiovascular effects of ozone." *Crit. Rev. Toxicol.* Submitted.

Institute of Medicine (IOM). 2008. *Improving the Presumptive Disability Decision-Making Process for Veterans.* (Eds: Samet, JM; Bodurow, CC), Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans, Board on Military and Veterans Health, National Academies Press, Washington, DC.

Islam, T; McConnell, R; Gauderman, WJ; Avol, E; Peters, JM; Gilliland, FD. 2008. "Ozone, oxidant defense genes, and risk of asthma during adolescence." *Am. J. Respir. Crit. Care Med.*177(4):388-395.

Islam, T; Berhane, K; McConnell, R; Gauderman, WJ; Avol, E; Peters, JM; Gilliland, FD. 2009. "Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children." *Thorax* 64(3):197-202.

Jerrett, M; Burnett, RT; Pope, CA; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. 2009. "Long-term ozone exposure and mortality." *N. Engl. J. Med.* 360(11):1085-1095.

Katsouyanni, K; Samet, JM; Anderson, HR; Atkinson, R; Le Tertre, A; Medina, S; Samoli, E; Touloumi, G; Burnett, RT; Krewski, D; Ramsay, T; Dominici, F; Peng, RD; Schwartz, J; Zanobetti, A. 2009. "Air Pollution and Health: A European and North American Approach (APHENA)." HEI Research Report 142, 132p., October 29.

Latzin, P; Roosli, M; Huss, A; Kuehni, CE; Frey, U. 2009. "Air pollution during pregnancy and lung function in newborns: A birth cohort study." *Eur. Respir. J.* 33(3):594-603.

Li, YF; Gauderman, WJ; Avol, E; Dubeau, L; Gilliland, FD. 2006. "Associations of tumor necrosis factor G-308A with childhood asthma and wheezing." *Am. J. Respir. Crit. Care Med.* 173(9):970-976.

Lipsett, MJ; Ostro, BD; Reynolds, P; Goldberg, D; Hertz, A; Jerrett, M; Smith, DF; Garcia, C; Chang, ET; Bernstein, L. 2011. "Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort." *Am. J. Respir. Crit. Care Med.* 184(7):828-835.

McConnell, R; Berhane, K; Gilliland, F; London, SJ; Islam, T; Gauderman, WJ; Avol, E; Margolis, HG; Peters, JM. 2002. "Asthma in exercising children exposed to ozone: A cohort study." *Lancet*359(9304):386-391.

McConnell, R; Islam, T; Shankardass, K; Jerrett, M; Lurmann, F; Gilliland, F; Gauderman, J; Avol, E; Kunzli, N; Yao, L; Peters, J; Berhane, K. 2010. "Childhood incident asthma and traffic-related air pollution at home and school." *Environ. Health Perspect.* 118(7):1021-1026.

Mortimer, K; Neugebauer, R; Lurmann, F; Alcorn, S; Balmes, J; Tager, I. 2008a. "Early-lifetime exposure to air pollution and allergic sensitization in children with asthma." *J. Asthma* 45(10):874-881.

Mortimer, K; Neugebauer, R; Lurmann, F; Alcorn, S; Balmes, J; Tager, I. 2008b. "Air pollution and pulmonary function in asthmatic children: Effects of prenatal and lifetime exposures." *Epidemiology* 19(4):550-557.

Parker, JD; Akinbami, LJ; Woodruff, TJ. 2009. "Air pollution and childhood respiratory allergies in the United States." *Environ. Health Perspect.* 117(1):140-147.

Peters, JM; Avol, E; Gauderman, WJ; Linn, WS; Navidi, W; London, SJ; Margolis, H; Rappaport, E; Vora, H; Gong, H Jr.; Thomas, DC. 1999. "A study of twelve Southern California communities with differing levels and types of air pollution: II. Effects on pulmonary function." *Am. J. Respir. Crit. Care Med.* 159:768-775

Prueitt, RL; Lynch, HN; Zu, K; Sax, SN; Venditti, FJ; Goodman, JE;. 2014. "Weight-of-evidence evaluation of long-term cardiovascular effects of ozone." *Crit. Rev. Toxicol.* Submitted

Rage, E; Jacquemin, B; Nadif, R; Oryszczyn, MP; Siroux, V; Aguilera, I; Kauffmann, F; Kunzli, N. 2009. "Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults." *Allergy* 64(1):40-46.

Rojas-Martinez, R; Perez-Padilla, R; Olais-Fernandez, G; Mendoza-Alvarado, L; Moreno-Macias, H; Fortoul, T; McDonnell, W; Loomis, D; Romieu, I. 2007. "Lung function growth in children with long-term exposure to air pollutants in Mexico City." *Am. J. Respir. Crit. Care Med.* 176(4):377-384.

US EPA. 2006. "Air Quality Criteria for Ozone and Related Photochemical Oxidants (Volumes I-III)." National Center for Environmental Assessment-RTP Division, EPA 600/R-05/004aF. Accessed at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923>.

US EPA. 2013. "Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Final)." National Center for Environmental Assessment (NCEA), EPA/600/R-10/076F. 1251p., February.

US EPA. 2014a. "Health Risk and Exposure Assessment for Ozone (Second External Review Draft)." EPA-452/P-14-004a; EPA-452/P-14-004b; EPA-452/P-14-004c; EPA-452/P-14-004d; EPA-452/P-14-004e; EPA-452/P-14-004f. Accessed on February 03, 2014 at http://www.epa.gov/ttn/naags/standards/ozone/s_o3_2008_rea.html, January.

US EPA. 2014b. "Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards (Second External Review Draft)." EPA-452/P-14-002. 510p., January.

Wang, XY; Hu, W; Tong, S. 2009. "Long-term exposure to gaseous air pollutants and cardio-respiratory mortality in Brisbane, Australia." *Geospat. Health* 3(2):257-263.

Wenten, M; Gauderman, WJ; Berhane, K; Lin, PC; Peters, J; Gilliland, FD. 2009. "Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: An example of epistasis in gene-environment interactions." *Am. J. Epidemiol.* 170(12):1494-1501.

Zanobetti, A; Schwartz, J. 2011. "Ozone and survival in four cohorts with potentially predisposing diseases." *Am. J. Respir. Crit. Care Med.* 184(7):836-841.

Short-term Ozone Exposure and Mortality

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Abbreviations

APHEA2	Air Pollution and Health: A European Approach 2
APHENA	Air Pollution and Health: A European and North American Approach
AQCD	Air Quality Criteria Document
CI	Confidence Interval
CO	Carbon Monoxide
CRF	Concentration-response Function
CV	Cardiovascular
df	Degree of Freedom
EPA	Environmental Protection Agency
ESCALA	Estudio de Salud y Contaminación del Air en Latonamérica
GLM	Generalized Linear Model
ISA	Integrated Science Assessment
NAAQS	National Ambient Air Quality Standard
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO ₂	Nitrogen Dioxide
NS	Natural Spline
OC	Organic Carbon
PACF	Partial Autocorrelation Function
PAPA	Public Health and Air Pollution in Asia Study
PM	Particulate Matter
ppb	Parts Per Billion
PS	Penalized Spline
SO ₂	Sulfur Dioxide

Executive Summary

In the 2013 *Integrated Science Assessment for Ozone and Related Photochemical Oxidants – Final Report* (ISA) (US EPA, 2013), EPA upgraded its conclusion that evidence regarding short-term ozone exposure and all-cause and cardiovascular (CV) mortality from "highly suggestive" to a "likely to be a causal" association. With regard to respiratory mortality, EPA maintained that there is a causal relationship between short-term ozone exposure and respiratory effects, including respiratory mortality. EPA highlighted epidemiology studies published since the 2006 *Air Quality Criteria Document* (AQCD) for ozone (US EPA, 2006) to support these causal determinations. Many of these studies were expanded or additional analyses of cohorts evaluated in previous National Ambient Air Quality Standards reviews.

We summarize the evidence regarding short-term ozone exposure and all-cause and cause-specific (*i.e.*, respiratory and CV) mortality from studies that EPA evaluated in the AQCD and ISA, as well as more recent studies that were not included in the ISA. In addition, we discuss the uncertainties that are inherent in these epidemiology studies that EPA should consider more fully when drawing causality conclusions.

Most of the multi-city studies highlighted in the ISA reported small, statistically significant all-cause mortality associations with short-term ozone exposures but less consistent effects for respiratory and CV mortality. Comparisons across different studies are complicated by the different model specifications (*e.g.*, lag times), different ozone averaging times (1-hour *vs.* daily 8-hour maximum *vs.* 24-hour average), and by ozone increments used to report mortality effect estimates. EPA implemented a standardization approach to facilitate comparisons, but it did not fully address many of the differences among studies. This approach itself may introduce further uncertainty.

Although pooled estimates from multi-city studies generally report statistically significant effects, study authors report substantial and unexplained heterogeneity in the mortality effect estimates for individual cities, calling into question whether it is appropriate to pool these estimates. Differences have also been reported in seasonal analyses, and these differences are not always consistent across different regions of the world. Additional uncertainty in the reported results relates to important sources of confounding, including co-pollutants and meteorology, especially temperature. Studies have reported conflicting evidence for confounding effects, and the proper control for confounding effects from temperature is not well established. A remaining challenge is how to interpret results considering exposure measurement error. This source of bias results from the use of central-site monitors to represent personal exposures, which tend to be poorly correlated, especially for ozone exposures.

Several new studies, mostly international, that evaluated the association between all-cause and cause-specific mortality and short-term ozone exposures have been published since the ISA cutoff. Although these studies also report small, statistically significant associations, similar uncertainties and inconsistencies are apparent in these studies that merit additional consideration before a causality determination can be established. In particular, issues of confounding and unexplained heterogeneity across regions and seasons remain a concern. In addition, the effects of model specification with regard to biologically relevant lag times and the appropriate control for meteorological factors that impact effect estimates results have not been resolved in recent studies.

Overall, current evidence is not sufficiently robust to support a causal or even a likely causal relationship between short-term ozone exposure and either all-cause, respiratory, or CV mortality.

1 Introduction

In the 2006 ozone *Air Quality Criteria Document* (AQCD) (US EPA, 2006), EPA concluded that evidence was "highly suggestive that [short-term ozone exposure] directly or indirectly contributes to nonaccidental and cardiopulmonary-related mortality." In the *Integrated Science Assessment for Ozone and Related Photochemical Oxidants – Final Report* (ISA) (US EPA, 2013), EPA upgraded its causality determination, concluding that evidence indicated that there was a "likely to be a causal relationship." With regard to respiratory mortality, EPA maintained that evidence indicates a causal relationship. EPA relied primarily on evidence from epidemiology studies published since the AQCD to support its conclusions. Some of these studies are new, multi-city analyses, but many are extensions or re-analyses of previous studies; still others focus on addressing uncertainty *via* extensive sensitivity analyses rather than providing new findings.

The key studies EPA highlighted in the AQCD and discussed in the ISA include the analysis of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) by Bell *et al.* (2004), a study of 14 cities by Schwartz (2005), a study of 21 European cities by Gryparis *et al.* (2004) (Air Pollution and Health: A European Approach 2, APHEA2), and three meta-analyses that included both US and non-US studies (Bell *et al.*, 2005; Ito *et al.*, 2005; Levy *et al.*, 2005). In the ISA, several new US multi-city analyses were evaluated: four studies that were re-analyses of the NMMAPS or other US cities; a re-analysis of the APHEA2 cities; and a new multi-city European study. In addition, EPA discussed the results of the Air Pollution and Health: A European and North American Approach (APHENA) project, a multi-continent study of US, European, and Canadian datasets that were analyzed in a systematic fashion using the same methodology for all datasets (Katsouyanni *et al.*, 2009). The ISA also discussed a similar analysis of four large Asian cities, the Public Health and Air Pollution in Asia (PAPA) study (Wong, 2010). Several additional relevant studies were not included in the ISA; these are largely international single- and multi-city studies conducted in Asia, Europe, or Latin America, as well as one US study.

We summarized the evidence regarding all-cause and cause-specific mortality [respiratory and cardiovascular (CV) mortality] from studies that EPA included in the ISA, as well as more recent studies that were not included in the ISA. In addition, we discuss the uncertainties that are inherent in these epidemiology studies, which EPA needs to consider more fully when drawing causality conclusions. More specifically, in Section 2, we provide a brief overview of key all-cause mortality studies evaluated in the AQCD and the ISA, as well as additional studies that were not included in the ISA. In Section 3, we review the evidence for a relationship between cause-specific mortality and short-term ozone exposure, focusing on results for respiratory and CV mortality that were evaluated in studies presented in the ISA and more recent studies not in the ISA. In Section 4, we highlight specific sources of uncertainty and other issues that call into question the results of these epidemiology studies, providing examples from multi-city studies that specifically address these uncertainties.

2 All-cause Mortality

EPA highlighted results from what it considered to be key epidemiology studies in the ISA, and a few studies evaluated in the 2006 AQCD, and concluded they provided evidence of a "likely to be causal" relationship between short-term ozone exposure and all-cause mortality. Many of these studies were expanded or additional analyses of cohorts evaluated in previous National Ambient Air Quality Standards (NAAQS) reviews, and they do not provide additional evidence that warrants upgrading the causality classification. In fact, many of the new studies provide sensitivity analyses that demonstrate that significant uncertainty remains in the risk estimates, calling into question causality.

2.1 Key Studies Included in the Ozone ISA

The key studies EPA highlighted in the AQCD and discussed in the ISA include an NMMAPS evaluation by Bell *et al.* (2004), a study of 14 cities by Schwartz (2005), a study of 21 European cities by Gryparis *et al.* (2004) (APHEA2), and three meta-analyses that included both US and non-US studies (Bell *et al.*, 2005; Ito *et al.*, 2005; Levy *et al.*, 2005). In the ISA, several new US multi-city analyses were evaluated: four re-analyses of the NMMAPS cities (Bell *et al.*, 2007; Bell and Dominici, 2008; Smith *et al.*, 2009; Stylianou and Nicholich, 2009); four studies with summer-only analyses of US Cities (Zanobetti and Schwartz, 2008a,b; Medina-Ramon and Schwartz, 2008; Franklin and Schwartz, 2008); two smaller European studies, one a re-analyses of the APHEA2 cities and another of 10 Italian cities, both restricted to summer-only evaluations (Samoli *et al.*, 2009; Stafoggia *et al.*, 2010); and a study of four urban centers in Santiago Province, Chile (Cakmak *et al.*, 2011).

In addition, EPA discussed the results of the APHENA project. This is a multi-continent study designed specifically to address the challenges in comparing data across multi-city studies that use different statistical methods, model assumptions, and/or averaging times. The researchers analyzed data from the US, Europe, and Canada in a systematic fashion using the same methodology for all datasets (Katsouyanni *et al.*, 2009). In the ISA, EPA also discussed a similar analysis of four large Asian evaluations, the PAPA study (Wong, 2010).

EPA placed more weight on the findings in the multi-city studies because of the increased power from the expanded dataset. However, as we discuss below and in more detail in Section 4, it is unclear whether pooling estimates across cities with divergent mortality effect estimates is appropriate. Also, while these studies have the advantage of being large, multi-city studies, there are a number of limitations that were not fully considered by EPA in its evaluation, such as the unexplained variability in mortality estimates across cities, confounding by co-pollutants, and unaccounted for measurement error.

2.1.1 Multi-city Studies

The results from key multi-city studies are summarized in Table A.1. Comparisons across studies is complicated, however, because results across studies because methodologies and model assumptions differ (*e.g.*, lag times, ozone data averaging times, and control of potential confounding factors, such as temperature, humidity, co-pollutants). In the ISA, EPA standardized mortality risk estimates *post hoc* to facilitate comparisons across studies. EPA defined mortality effect estimates per 40-parts per billion (ppb) increase in ozone for estimates based on a 1-hour maximum, per 30-ppb increase in ozone for

estimates based on an 8-hour maximum, and per 20-ppb increase in ozone based on 24-hour average concentrations.¹ The basis for these ozone increments is discussed in the ozone ISA (US EPA, 2013). The ozone increments for different ozone averaging times was based on an analysis of the relationship between measured ozone concentrations across the country for different ozone averaging times (Langstaff, 2003). Based on these relationships, EPA derived a ratio for the different ozone metrics: 2:1.5:1 for 1-hour maximum: 8-hour maximum: 24-hour average. While this helps make results across studies comparable, it does not account for several methodological differences that further complicate comparisons (*e.g.*, the choice of lag). In addition, the basis for standardization used by EPA in the ISA (discussed in more detail in Section 4) may have introduced additional bias to the effect estimates.

Table 2.1 presents the standardized mortality effect estimates as reported by EPA in the ISA.² These mortality effects were mostly statistically significant but small; therefore, they may not be indicative of causation, especially due to many unresolved uncertainties in these estimates (as discussed below, and in more detail in Section 4).

In the ISA, EPA highlighted several studies that were evaluated in the AQCD, including Bell *et al.* (2004), Gryparis *et al.* (2004), and Schwartz (2005). In the analysis of the NMMAPS database, Bell *et al.* (2004) evaluated the association between short-term exposures to ozone in 95 urban communities in the US from 1987-2000. The authors reported variable mortality coefficients (range) across the 95 communities, and the vast majority (89 of 95) of these coefficients were not statistically significant. Despite the variability in the mortality estimates, results were combined across cities and reported as a small pooled national mortality increase (Table 2.1). The authors also investigated possible confounding by coarse and fine particulate matter (PM₁₀ and PM_{2.5}), and reported that results were robust based on multi-pollutant analyses. Risk estimates were attenuated, however, and no longer statistically significant when PM was included in the model. Also, a re-analysis of these data by Smith *et al.* (2009) showed that when PM₁₀ is included in each model, the effect of ozone decreased by 22-33%, which may indicate some confounding effects from PM or other related co-pollutants that were not considered in the model. Lastly, as central-site monitor data were used as surrogates of personal exposures to ozone, the results may be biased.

In their APHEA2 analysis, Gryparis *et al.* (2004) reported city-specific ozone-mortality effect estimates for 21 European cities. Gryparis *et al.* (2004) used post-1990 ozone and mortality data to calculate the percent increase in mortality for 1- and 8-hour maximum ozone concentrations. Pooled estimates were small and not statistically significant (Table 2.1). Like Bell *et al.* (2004), the authors noted substantial heterogeneity across the city-specific estimates. Only eight cities had positive ozone-mortality effect estimates, and only five of these were statistically significant. When adjusting for various co-pollutants in the seasonal analyses, the estimates remained statistically significant but were attenuated with inclusion of nitrogen dioxide (NO₂) or PM₁₀ (Table A.1). As in the all-year analyses, the authors reported significant heterogeneity among effect estimates across the cities. In four cities, the mortality estimates were negative. Estimates in this study may also be biased because of measurement error.

Schwartz (2005) applied a case-crossover design to control for potential confounding by temperature in assessing the association between ozone levels and mortality across 14 US cities. The analysis with temperature-matched controls yielded a very small increased mortality risk (Table 2.1). A seasonal analysis showed statistically significant mortality effects only in the warm season (Table 2.1), which the authors stated could reflect a threshold concentration below which no effects are observed. Effect

¹ EPA used the following equation to standardize the mortality effect estimates (Brown, 2013): $EXP(LN(\text{relative risk}) * (\text{standard increment/increment used in paper}))$.

² Mortality effect estimates shown in Table 2.1 were standardized values reported by EPA; Table A.1 presents mortality effect estimates reported by the authors.

estimates also varied considerably across cities, and only two of the cities appeared to have marginally statistically significant estimates from the results reported in figures (no data available). The authors reported results were robust to controlling for PM_{10} but stated that they could not rule out potential confounding by exposures to other pollutants, such as sulfates (which were not included in the study but are highly correlated with ozone). In addition, effect estimates varied considerably across cities, and only two of the cities appeared to have marginally statistically significant estimates from the results reported in figures (no data available). Lastly, this study also used ambient monitors of maximum hourly concentrations (averaged across all monitors) as surrogates for personal exposures to ozone, which could have biased results due to exposure measurement error.

Table 2.1 All-cause Mortality Effect Estimates from Key Studies in the AQCD and ISA¹

Study	Location	Lag	Averaging Time	Percent Change (95% CI) ^{2,3}	
Year-round Analyses					
Key AQCD Studies	Bell <i>et al.</i> (2004)	NMMAPS, 95 US cities	0-6	24-hr avg	1.04 (0.54, 1.55)
	Schwartz (2005)	14 US cities	0	1-hr max	0.76 (0.13, 1.40)
	Gryparis <i>et al.</i> (2004)	APHEA2, 21 European cities	0-1	1-hr max	0.78 (-0.09, 1.66) ⁴
Key ISA Studies	Bell <i>et al.</i> (2007)	NMMAPS, 98 US cities	0-1	24-hr avg	0.64 (0.34, 0.92)
	Bell and Dominici (2008)	NMMAPS, 98 US cities	0-6	24-hr avg	1.04 (0.54, 1.55)
	Katsouyanni <i>et al.</i> (2009)	APHENA-Europe	DL (0-2)	1-hr max	1.66 (0.47, 2.94)
		APHENA-Canada	DL (0-2)	1-hr max	5.87 (1.82, 9.81)
		APHENA-US	DL (0-2)	1-hr max	3.02 (1.10, 4.89)
	Wong (2010)	PAPA-4 Asian cities	0-1	8-hr avg	2.26 (1.36, 3.16)
	Cakmak <i>et al.</i> (2011)	7 Chilean urban areas	DL (0-6)	8-hr max	3.35 (1.07, 5.75)
Summer Only					
Key AQCD Studies	Bell <i>et al.</i> (2004)	NMMAPS, 95 US cities	0-6	24-hr avg	0.78 (0.26, 1.30)
	Schwartz (2005)	14 US cities	0	1-hr max	1.00 (0.30, 1.80)
	Gryparis <i>et al.</i> (2004)	APHEA2, 21 European cities	0-1	8-hr max	1.80 (0.99, 3.06)
Key ISA Studies	Zanobetti and Schwartz (2008a)	48 US cities	0	8-hr max	1.51 (1.14, 1.87)
	Zanobetti and Schwartz (2008b)	48 US cities	0-3	8-hr max	1.60 (0.84, 2.33)
	Medina-Ramon and Schwartz (2008)	48 US cities	0-2	8-hr max	1.96 (1.14, 2.82)
	Stafoggia <i>et al.</i> (2010)	10 Italian cities	DL (0-5)	8-hr max	9.15 (5.41, 13.0)
	Samoli <i>et al.</i> (2009)	APHEA2, 21 European cities	0-1	8-hr max	1.42 (0.89, 2.02)⁴
	Katsouyanni <i>et al.</i> (2009)	APHENA-Europe	DL (0-2)	1-hr max	2.38 (0.87, 3.91)
		APHENA-Canada	DL (0-2)	1-hr max	3.34 (1.26, 5.38)
		APHENA-US	DL (0-2)	1-hr max	3.83 (1.90, 5.79)
	Franklin and Schwartz (2008)	18 US cities	0	24-hr avg	1.79 (0.90, 2.68)
	Wong (2010)	4 Asian cities	0-1	8-hr max	2.26 (1.36, 3.16)
Cakmak <i>et al.</i> (2011)	7 Chilean cities	DL (0-6)	8-hr max	3.81 (0.08, 6.45)	

Notes:

(1) Adapted from US EPA (2013), Table 6-42.

(2) Single-pollutant models, standardized as reported by EPA: per 40-ppb increase for 1-hour maximum, per 30-ppb in 8-hour maximum, and per 20-ppb for 24-hour average ozone concentrations.

(3) Bolded results are statistically significant.

(4) Standardized effect estimate was calculated using $\text{EXP}(\text{LN}(\text{odds ratio}) * (\text{standard increment} / \text{increment used in paper}))$ – estimate is different from that reported by EPA. We could not confirm the estimate calculated by EPA.

Most of the more recent studies evaluated in the ISA were re-analyses of previous cohorts conducted to evaluate specific uncertainties relevant to time-series studies. In some cases, there were unexplained differences between the mortality estimates reported for the same cities and cohorts. For example, Gryparis *et al.* (2004) reported a statistically non-significant total mortality estimate for 21 European cities (0.78%, 95% CI: -0.09, 1.66, per 20 ppb, standardized³), whereas the more recent APHENA study of these European cities reported a statistically significant estimate that was about two times higher (1.66%; 95% CI: 0.47, 2.94). Given the high statistical power of these studies, it is not clear why there are differences in effect estimates for the re-analyses of the same cohorts and cities.

The variability across ozone-mortality associations is particularly apparent in results from the APHENA study (Katsouyanni *et al.*, 2009) (see Table 2.1). This large multi-continent study combined data from existing multi-city study databases from Canada, Europe (APHEA2), and the US (NMMAPS) to "develop more reliable estimates of the potential acute effects of air pollution on human health [and] provide a common basis for [the] comparison of risks across geographic areas" (Katsouyanni *et al.*, 2009). As shown in Table 2.1, the percent increase in standardized all-cause mortality ranged from 1.66-5.87 per 40 ppb increase in ozone, with the lowest estimates found in Europe and the highest in Canada (Katsouyanni *et al.*, 2009). Results also varied by choice of model and lag period. It is noteworthy that the Canadian all-cause mortality estimates were several times higher than the US and the European estimates for each 40 ppb increase in ozone, yet these cities had the lowest reported 1-hour maximum ozone concentrations (50th percentile range of 7-8 ppb). In contrast, depending on the model used, US cities were found to have considerably lower ozone-mortality effect estimates, and even negative associations, despite having the highest reported ozone concentrations (50th percentile of 35-60 ppb).

We discuss other studies that have assessed specific limitations of epidemiology studies in more detail in Section 4. For example, we examine how different model assumptions (*e.g.*, smoothing functions for control of temporal confounding, choice of lag periods, *etc.*) affect mortality estimates (*e.g.*, Katsouyanni *et al.*, 2009; Samoli *et al.*, 2009; Zanobetti and Schwartz, 2008a,b; Smith *et al.*, 2009), potential confounding effects of PM₁₀ and other co-pollutants on the ozone-mortality relationship (*e.g.*, Bell *et al.*, 2007; Smith *et al.*, 2009; Katsouyanni *et al.*, 2009; Franklin and Schwartz, 2008), and heterogeneity (*e.g.*, Bell and Dominici, 2008; Katsouyanni *et al.*, 2009).

2.1.2 Meta-analyses

In addition to the key multi-city studies, EPA highlighted results from three meta-analyses of short-term ozone mortality studies (Bell *et al.*, 2005; Ito *et al.*, 2005; Levy *et al.*, 2005) as "robust" evidence for ozone-associated effects on mortality. Results for these studies are summarized in Table A.4. The authors of all three analyses, however, stress the high degree of heterogeneity in the estimates across cities, and that the results for many of the cities were not statistically significant. There was also evidence of model selection and publication bias in all of the analyses, which resulted in higher mortality estimates than those reported in large, multi-city studies.

Bell *et al.* (2005) analyzed 144 effect estimates from 39 time-series studies and estimated pooled effects by lag, age group, cause-specific mortality, and concentration metric. The authors compared the results with pooled estimates from the NMMAPS study of 95 urban US communities (Bell *et al.*, 2004). The effect estimates from the meta-analysis were consistently much larger than those from the NMMAPS multi-city analysis, and the pooled estimates were larger when results from studies that reported a single lag were used in the analysis compared to studies that reported results for multiple lags, suggesting that the lag with the largest effect was more likely to be reported.

³ These values were standardized according to the EPA equation $\text{EXP}(\text{LN}(\text{odds ratio}) * (\text{standard increment} / \text{increment used in paper}))$ and are different from the standardized values reported by EPA in the ISA.

Similarly, Ito *et al.* (2005) conducted a meta-analysis of short-term ozone mortality studies and an additional time-series analysis of seven large US cities (*i.e.*, Chicago, Detroit, Houston, Minneapolis-St. Paul, New York City, Philadelphia, and St. Louis). The authors reported conflicting results from analyses of the same cities by different researchers. In Amsterdam, London, and Santiago, associations reported by one set of authors were positive and by another set of authors were negative, strongly indicating bias in model selection. Ito *et al.* (2005) also noted that their summary estimates are approximately twice as large as the combined estimates from a 90-city NMMAPS study (HEI, 2003) and may be biased upward because the "optimal" or "best" lags were chosen from each study (based on statistical, not biological, considerations), whereas the overall estimate from the NMMAPS study is for the fixed 0-day lag for all 90 cities.

Lastly, Levy *et al.* (2005), who conducted a meta-regression of 48 estimates from 28 studies, noted that estimates differed among studies of the same city, suggesting model selection bias and indicating possible publication bias, as multiple studies did not report quantitative estimates if ozone associations were not statistically significant.

2.2 Key Studies Not Included in the Ozone ISA

Several relevant studies were not included in the ISA. With one exception (Sacks *et al.*, 2012), all of these studies were conducted outside the US, mainly in Asia (Cheng and Kan, 2012; Tao *et al.*, 2012; Yang *et al.*, 2012; Shang *et al.*, 2013), Latin America (Reyna *et al.*, 2012; Romieu *et al.*, 2012), and Europe (Atkinson *et al.*, 2012; de Almeida *et al.*, 2011; Garrett and Casimiro, 2011; Faustini *et al.*, 2012; Pascal *et al.*, 2012; Hunova *et al.*, 2013; Moshhammer *et al.*, 2013).

Most of these studies were single-city studies, including two studies in China (Cheng and Kan, 2012; Yang *et al.*, 2012), one study in Seoul, South Korea (Son *et al.*, 2012), two studies in Portugal (de Almeida *et al.*, 2011; Garrett and Casimiro, 2011); one study in Prague, Czech Republic (Hunova *et al.*, 2013), and one study in Mexicali, Baja California, Mexico (Reyna *et al.*, 2012). A study in Rome, Italy, was a summer-only analysis (Faustini *et al.*, 2012). These studies are not discussed in detail here, but instead are summarized in Table A.1.

Several of these studies evaluated issues associated with the investigation of ozone-mortality associations. For example, Yang *et al.* (2012) evaluated the effect estimates for different ozone averaging times, reporting a significant increase in mortality for each interquartile increase in 1- or 8-hour maximum ozone concentrations but not 24-hour average ozone. In addition, Yang *et al.* (2012) assessed confounding effects of co-pollutants, reporting attenuation of mortality effect estimates when co-pollutants were included in statistical models. More details on and examples of limitations of the epidemiology evidence for an ozone-mortality association are discussed in Section 4.

Atkinson *et al.* (2012), Pascal *et al.* (2012), Romieu *et al.* (2012), and Tao *et al.* (2012) conducted new multi-city analyses. Results, as reported by the authors, for key multi-city studies are provided in Table A.1 and standardized results based on EPA's methodology are summarized in Table 2.2. The standardized mortality effect estimates reported in these studies were small and generally within the range of those reported in previous studies, with means ranging from a percent increase of 0.63-4.86%. Some estimates were not statistically significant depending on the model used.

Table 2.2 All-cause Mortality Effect Estimates from Key Multi-city Studies Not in the ISA¹

	Study	Location	Lag	Averaging Time	Percent Increase (95% CI) ^{2,3}
Year-round Analyses					
Asian Study	Tao <i>et al.</i> (2012)	Southern China, 4 cities	1-2	8-hr avg	4.86 (3.76, 6.03)
European Studies	Atkinson <i>et al.</i> (2012)	UK, 5 urban	0-1	8-hr max	2.86 (2.08, 3.58)
		UK, 5 rural areas	0-1	8-hr max	3.46 (2.14, 4.92)
	Pascal <i>et al.</i> (2012)	France, 9 urban areas	0	8-hr max	1.78 (0.59, 2.98)
Latin American Study	Romieu <i>et al.</i> (2012)	Latin America, 9 cities	0-3, FE	24-hr avg	0.87 (0.71, 1.02)
			0-3, RE		0.63 (-0.08, 1.30)
Seasonal Analyses³					
Asian Study	Tao <i>et al.</i> (2012)	Southern China, 4 cities	1-2	8-hr avg	3.88 (1.60, 6.15)
European Study	Atkinson <i>et al.</i> (2012)	UK, 5 urban	0-1	8-hr max	3.88 (2.32, 5.47)
		UK, 5 rural areas	0-1	8-hr max	2.74 (-0.06, 5.53)

Notes:

(1) Bolded results are statistically significant.

(2) Results from single-pollutant models, estimates standardized using the EPA equation: EXP(LN(odds ratio)*(standard increment/increment used in paper)) such that estimates are an increase in mortality per 40-ppb increase in 1-hour maximum, 30-ppb increase in 8-hour maximum or 8-hour average, and 20-ppb increase in 24-hour average ozone concentrations.

(3) Warm season only shown

FE = fixed effects model; RE = random effects model.

Atkinson *et al.* (2012) investigated the association between maximum 8-hour ozone levels and daily all-cause mortality in residents of five urban and five rural areas in the UK. The analysis was conducted using data from 1993-2006 for both all-year and season-specific periods, and it included sensitivity analyses to adjust for PM and alternative temperature metrics. Results were analyzed for individual locations assuming linear, linear-threshold, and spline models. Median all-year ozone concentrations were lower in urban areas (range: 48-54 $\mu\text{g}/\text{m}^3$) than in rural areas (range: 65-74 $\mu\text{g}/\text{m}^3$); ozone levels were highest in spring and lowest in the fall in all areas. In both urban and rural areas, the authors reported statistically significant mortality effects (Table 2.2). In seasonal analyses, an association between ozone exposure and mortality in summer and winter was observed, but not in spring and fall in urban areas (see Table 2.2 for summer-only effects). In rural areas, only fall mortality effect estimates were significantly elevated. The authors also explored whether there was evidence of a threshold for ozone-mortality associations or if effects were modified by temperature and/or confounded by PM₁₀. Overall, the authors reported evidence of a threshold for ozone, effect modification by temperature, and attenuated effects with PM₁₀ adjustment (Section 4).

Pascal *et al.* (2012) analyzed the impact of ozone and temperature on all-cause (non-accidental), respiratory, and CV mortality in nine urban areas in France. Data were collected between 1998 and 2006 and analyzed using a time-stratified, case-crossover model. As the authors did not specify lag time for these data, it was assumed to be zero. In the year-round analyses, there were significant increases in all-cause mortality (Table 2.2). When adjusting for PM_{2.5} in the summer-only analysis, the mortality estimates were no longer statistically significant. Additional analyses indicated that the relationship was

stronger on warm days (*i.e.*, days when the mean temperature equals or exceeds the 97.5th percentile of the temperature distribution) compared with non-warm days.

Romieu *et al.* (2012) conducted a large, multi-city study of mortality (all-natural cause and cause-specific) in Latin America, known as the ESCALA Study (Estudio de Salud y Contaminación del Air en Latonamérica). Six cities in three countries were selected for analysis of ozone (Sao Paolo and Rio de Janeiro, Brazil; Santiago, Chile; Mexico City, Toluca, and Monterrey, Mexico). The authors used generalized linear models (GLMs) with different model specifications [*e.g.*, natural splines with 3, 6, 9, or 12 degrees of freedom (df) per year, and distributed lags for up to 3, 5, or 10 days]. In addition, the authors conducted analyses using both a linear fixed and random effects model, reporting statistically significant effects for the linear fixed effects model but not the random effects model (Table 2.2). The authors reported significant heterogeneity across cities. For example, all-year natural-cause mortality was significantly increased in single-pollutant models for Sao Paolo, Rio de Janeiro, Monterrey, and Mexico City but not Santiago or Toluca. In addition, the authors also reported seasonal variations in effect estimates and attenuation of effect estimates in two pollutant models including PM₁₀.

Tao *et al.* (2012) studied the effect of short-term ozone exposure on all-cause, non-accidental mortality in four cities in the Pearl River Delta of southern China, including Guangzhou, Foshan, Ahongshan, and Zhuahai. The authors collected data from the years 2006-2008 and analyzed the associations using GLMs with Poisson regression. In addition, to determine the appropriate degrees of freedom to control for temporal factors, the authors used partial autocorrelation function (PACF), a statistical technique commonly used. The authors assessed effects by individual lag days 0-6 and two-day periods (lag 0-1 or 1-2). In the single-pollutant model, small statistically significant pooled mortality effects were reported (Table 2.2). When adjusting for PM₁₀, NO₂, sulfur dioxide (SO₂), and carbon monoxide (CO), the increases remained statistically significant but were attenuated, particularly with inclusion of NO₂ in the model. Tao *et al.* (2012) also performed analyses for peak (September-November) *vs.* non-peak periods of ozone exposure (December-August). When the analysis was restricted to peak periods, the association was attenuated. Average annual mean of ozone is 70-85 µg/m³ (137-167 ppb), which is substantially higher than concentrations reported for the US (*e.g.*, Bell *et al.*, 2004, reported average 24-hour ozone concentrations of 26 ppb for 95 NMMAPS cities). Furthermore, air quality data were only available for one or two monitors per city. The authors also noted heterogeneity between the four cities. In the single city analyses, two of the four cities (Foshan and Zhuhai) had reported mortality estimates that did not reach statistical significance.

In addition to the multi-city studies, we identified one meta-analysis that was published after the ISA cutoff for inclusion. Shang *et al.* (2013) performed a literature search of studies on short-term exposure to particulate and gaseous air pollutants conducted in China between 1990 and 2012 (Table A.4). After excluding studies with repeated data or insufficient information, the final meta-analysis included 33 studies. This included eight studies assessing the association between ozone and total mortality, nine assessing the association between ozone and respiratory mortality, and nine assessing ozone and CV mortality. Using a linear random effects model, Shang *et al.* (2013) reported that for each 10 µg/m³ increase in 24-hour average ozone concentrations, all-cause mortality increased by 0.48% (95% CI: 0.38, 0.58). The authors did not consider confounding by co-pollutants or other variables. Average ozone concentrations ranged from 56-86 µg/m³ (110-169 ppb); substantially higher than in most US cities (*e.g.*, 26 ppb average 24-hour ozone concentrations for 95 NMMAPS cities, Bell *et al.*, 2004). The authors tested for possible publication bias, noting little evidence of this in the identified literature. The authors noted that results should be interpreted with caution because of the small number of studies and possible bias from the choice of lags.

2.3 Conclusions

In the AQCD and ISA, EPA relied primarily on multi-city studies that reported relatively small, but statistically significant, pooled estimates of all-cause mortality. Even when evaluating standardized mortality effect estimates to facilitate comparisons across studies, there remain inconsistencies in pooled mortality effects. In addition, several studies published since the ISA was completed indicate these inconsistencies remain. Many of these recent studies were conducted to investigate the inconsistencies observed across and within studies, such as model specification, confounding, inter-city and inter-region heterogeneity, exposure measurement error, and the ozone-mortality concentration-response function (CRF). We discuss these factors, which indicate that the evidence is not robust and does not support EPA's conclusion of a "likely to be causal" relationship between short-term ozone exposure and all-cause mortality, in Section 4.

3 Cause-specific Mortality

EPA highlighted several studies in the ISA, including key studies from the 2006 AQCD, that investigated cause-specific mortality associations with short-term ozone exposures, focusing on respiratory and CV mortality. There are several recent studies that evaluated respiratory and CV mortality that were not included in ISA. Respiratory and CV mortality risks are summarized in Tables A.2 and A.3, respectively.

3.1 Respiratory Mortality

In the ISA (US EPA, 2013), EPA concluded that there is a causal relationship between short-term ozone exposure and respiratory health effects, including respiratory mortality. EPA reported that recent multi-city studies consistently demonstrate associations between ambient ozone and mortality across the US, Europe, and Canada. In particular, EPA highlighted the results from the APHENA study (Katsouyanni *et al.*, 2009) as being supportive of respiratory and CV mortality effects. As we discuss below, the majority of available analyses, including the large APHENA study by Katsouyanni *et al.* (2009), does not show statistically significant increases in respiratory mortality. In fact, a number of estimates yielded negative mortality estimates, particularly in the US, but also in several analyses of Canada and Europe. Furthermore, additional studies published since the ISA predominantly found no associations between ozone and respiratory mortality, even in areas with very high levels of ozone (*e.g.*, >100 ppb in several areas in China).

3.1.1 Key Studies Included in the Ozone ISA

In the ISA, EPA highlights studies by Gryparis *et al.* (2004), Katsouyanni *et al.* (2009), Wong (2010), Samoli *et al.* (2009), Stafoggia *et al.* (2010), and Zanobetti and Schwartz (2008b) in its evaluation of respiratory mortality. Details and results of these studies (as reported by the authors) are summarized in Table A.2. EPA's standardized results are shown below in Table 3.1 for these studies. Results are variable across US, European, and Canadian cities, and many of the mortality estimates were not statistically significant despite the increased power in multi-city studies. Similarly, Wong (2010) reported effects that were not statistically significant for year-round analyses of Asian cities. A few studies reported statistically significant respiratory mortality effects in summer-only analyses (Gryparis *et al.*, 2004; Samoli *et al.*, 2009; Zanobetti and Schwartz 2008b; Katsouyanni *et al.*, 2009 for Canadian cities only; Stafoggia *et al.*, 2010). Variable effect estimates across cities and seasons, confounding, and measurement error add to the uncertainties in these effect estimates (see Section 4).

Table 3.1 Respiratory Mortality Effect Estimates from Key Studies in the AQCD and ISA¹

Study	Location	Lag	Averaging Time	Percent Change (95% CI) ^{2,3}
Key ISA Studies (Year-round Analyses)				
Katsouyanni <i>et al.</i> (2009)	APHENA-US	DL (0-2)	1-hr max	2.54 (-3.32, 8.79)
	APHENA-Canada	DL (0-2)	1-hr max	1.02 (-11.9, 15.9)
	APHENA-Europe	DL (0-2)	1-hr max	1.82 (-2.18, 6.04)
Wong (2010)	4 Asian cities	0-1	8-hr max	2.02 (-0.41, 4.49)
Key AQCD Studies (Seasonal Analyses)				
Gryparis <i>et al.</i> (2004)	21 European cities	0-1	8-hr max	6.75 (4.38, 9.10)
Key ISA Studies (Seasonal Analyses)				
Samoli <i>et al.</i> (2009)	21 European cities	0-1	8-hr max	2.38 (0.65, 4.19)
Zanobetti and Schwartz (2008b)	48 US cities	0-3	8-hr max	2.51 (1.14, 3.89)
Katsouyanni <i>et al.</i> (2009)	APHENA-US	DL (0-2)	1-hr max	4.40 (-2.10, 11.3)
	APHENA-Canada	DL (0-2)	1-hr max	26.1 (13.3, 41.2)
	APHENA-Europe	DL (0-2)	1-hr max	3.83 (-1.33, 9.21)
Stafoggia <i>et al.</i> (2010)	Italian cities	DL (0-5)	8-hr max	17.6 (1.78, 35.5)

Notes:

(1) Adapted from EPA (2013, Table 6-37).

(2) Results from single-pollutant models, standardized by EPA and reported as an increase in mortality per 40-ppb increase in 1-hour maximum, 30-ppb increase in 8-hour maximum, and 20-ppb increase in 24-hour average ozone concentrations.

(3) Bolded results are statistically significant.

3.1.2 Key Studies Not Included in the Ozone ISA

Several studies not included in the ISA or published after the ISA cutoff date for inclusion examined the association between respiratory mortality and short-term ozone exposure (Cheng and Kan, 2012; de Almeida *et al.*, 2011; Hunova *et al.*, 2013; Faustini *et al.*, 2012; Pascal *et al.*, 2012; Romieu *et al.*, 2012; Son *et al.*, 2012; Tao *et al.*, 2012; Yang *et al.*, 2012). Details and results as reported by the authors are summarized in Table A.2, and results standardized using EPA methodology are shown in Table 3.2 to allow comparisons with results in Table 3.1.

Table 3.2 Effect Estimates for Respiratory Mortality from Key Studies Not in the ISA

Study	Location	Lag	Averaging Time	Percent Change (95% CI) ¹
Year-round Analyses				
de Almeida <i>et al.</i> (2011)	Oporto, Portugal	1	8-hr max	6.34 (-2.61, 16.1)
Romieu <i>et al.</i> (2012)	Latin America, 9 cities	0-3, FE	24-hr avg	0.83 (0.04, 1.22) ²
		0-3, RE		0.83 (0.04, 1.22)
Cheng and Kan (2012)	Shanghai, China	1	8-hr avg	4.86 (-0.50, 10.6)
Pascal <i>et al.</i> (2012)	France, 9 urban areas	0	8-hr max	0.0 (-0.06, 6.65)
Tao <i>et al.</i> (2012)	Southern China, 4 cities	1-2	8-hr avg	8.08 (5.35, 10.8)
Yang <i>et al.</i> (2012)	Suzhou, China	1	1-hr max	-2.56 (-5.23, 0.64)
			8-hr max	-0.94 (-3.54, 1.61)
			24-hr avg	-1.39 (-4.32, 1.49)
Seasonal Analyses				
de Almeida <i>et al.</i> (2011)	Oporto, Portugal	1	8-hr max	9.03 (-7.63, 14.5)
Faustini <i>et al.</i> (2012)	Rome, Italy	0-5	8-hr max	9.11 (-14.0, 38.8)
Hunova <i>et al.</i> (2013)	Prague, Czech Republic	1	8-hr max	25.4 (2.98, 51.6) ³
			24-hr avg	33.8 (12.5, 58.2) ³
Pascal <i>et al.</i> (2012)	France, 9 urban areas	0	8-hr max	-1.17 (-11.7, 11.1)
Tao <i>et al.</i> (2012)	Southern China, 4 cities	1-2	8-hr avg	1.42 (-5.63, 6.83)

Notes:

(1) Results from single-pollutant models, converted using EPA's equation: $\text{EXP}(\text{LN}(\text{odds ratio}) * (\text{standard increment/increment used in paper}))$; shown as an increase in mortality per 40-ppb increase in 1-hour maximum, 30-ppb increase in 8-hour maximum, and 20-ppb increase in 24-hour average ozone concentrations (Brown, 2013, personal communication).

(2) Bolded results are statistically significant.

(3) Model included adjustment for PM₁₀.

FE = fixed effects model; NA = not available; NR = not reported; RE = random effects model.

Respiratory mortality effect estimates are variable across studies, ranging from -2.5 to 25%, and the majority of these estimates are not statistically significant. Specifically, in many of the single-city studies, the effect estimates did not achieve statistical significance in year-round or summer-only analyses (de Almeida *et al.*, 2011; Faustini *et al.*, 2012). Only Hunova *et al.* (2013) reported statistically significant increases in respiratory mortality, for either 8-hour maximum or 24-hour average ozone, in summer months (they did not conduct all-year analyses).

Romieu *et al.* (2012) investigated several cause-specific mortality endpoints, including respiratory-related mortality, in their analysis of six Latin American countries (Table 3.1). The authors reported a small but statistically significant percent increase in respiratory mortality (standardized 0.83% per 20 ppb ozone, 95% CI: 0.04, 1.22). The authors reported statistically significant heterogeneity in effect estimates across cities and variation in effects by season. When the authors adjusted for PM₁₀, however, respiratory mortality was no longer statistically significant in any of the analyses, which may indicate confounding by PM or some other factors. In seasonal analyses, results for the cold-season were not statistically significant, but results varied in the warm season. There were significant increases in mortality in Sao Paulo but not Rio de Janeiro, Santiago, or Toluca. In Mexico City, only those 65 years and older had increased mortality (see Table A.2); in Monterrey, ozone was associated with respiratory mortality in all-age analyses, but not in those restricted to people 65 years or older (see Table A.2).

Several of these studies were focused on Asian populations (Cheng and Kan, 2012; Son *et al.*, 2012; Tao *et al.*, 2012, and Yang *et al.*, 2012). Despite assessing similar regions of the world with similar climates, they yielded different results. Three studies did not support an association between short-term ozone exposure and respiratory mortality; two reported positive but not statistically significant results (Cheng and Kan 2012; Son *et al.*, 2012), and the other reported decreases in mortality (Yang *et al.*, 2012). The multi-city study by Tao *et al.* (2012), however, reported significant increases in respiratory mortality in Southern Chinese cities in year-round analyses (see Table 3.1 and Table A.2).

In a multi-city study, Tao *et al.* (2012 reported a statistically significant increase in respiratory mortality (Table 3.1). The authors reported results that were attenuated, but remained statistically significant, in two-pollutant models with PM₁₀, NO₂, SO₂, and CO. Larger decreases were reported when PM₁₀ and NO₂ were included in two-pollutant models (see Table A.2). The authors also evaluated respiratory mortality according to ozone peak and non-peak exposure periods, reporting statistically significant effects only for the non-peak ozone season. These results are contrary to findings in studies in the US and Europe, where mortality effect estimates tend to be larger in analyses restricted to warmer months when ozone levels peak (*e.g.*, Bell *et al.*, 2004; Gryparis *et al.*, 2004).

There are only two meta-analyses of respiratory mortality endpoints (Bell *et al.*, 2005; Shang *et al.*, 2013); results are summarized in Table A.4. Bell *et al.* (2005) meta-analyzed 39 individual studies and did not find a relationship between ozone and respiratory mortality in either US-only studies or US and non-US studies using GLMs. In a recent meta-analyses, however, Shang *et al.* (2013) reported a 0.73% increase in respiratory mortality with each 10 µg/m³ increase in 24-hour average ozone in nine Chinese cities (95% CI: 0.49-0.97). Average ozone concentrations ranged from 56-86 µg/m³ (approximately 110-169 ppb), which is substantially higher than in most contemporary US cities [*i.e.*, Bell *et al.* (2004) reported average 24-hour ozone concentrations of 26 ppb for 95 NMMAPS cities]. Confounding by co-pollutants or other variables were not explored. In addition, publication and model specification errors cannot be ruled out. Therefore, it is unclear how much weight can be placed in these findings.

Overall, recent studies that evaluated the association between respiratory mortality and short-term ozone exposures were inconsistent.

3.2 Cardiovascular Mortality

In the 2006 AQCD, EPA stated, "the evidence is highly suggestive that ozone directly or indirectly contributes to cardiopulmonary-related mortality." In the ISA (US EPA, 2013), however, EPA concluded that there is a likely causal relationship between short-term ozone exposure and CV effects, even though epidemiology studies provide inconsistent evidence. While some studies reported associations between ozone and CV mortality, others reported no statistically significant relationships or reductions in mortality with short-term ozone exposures.

3.2.1 Key Studies Included in the Ozone ISA

There are several epidemiology studies of short-term ozone exposure and CV mortality highlighted in the ISA (Gryparis *et al.*, 2004, Katsouyanni *et al.*, 2009; Zanobetti and Schwartz, 2008a,b; Samoli *et al.*, 2009; Stafoggia *et al.*, 2010; Wong, 2010) (described in Table A.3). EPA standardized the results so they would be comparable across studies (Table 3.3). Results are variable across US, European, and Canadian cities, and many of the mortality estimates are not statistically significant. Only two of the available studies (Katsouyanni *et al.*, 2009; Stafoggia *et al.*, 2010) evaluated potential confounding by co-pollutants (*e.g.*, PM). Katsouyanni *et al.* (2009) reported that the risk of mortality was reduced and no longer

statistically significant when adjusted for PM, and results were inconsistent across cities. Stafoggia *et al.* (2010) reported results that were only marginally statistically significant for CV mortality.

Table 3.3 Effect Estimates for Cardiovascular Mortality from Key Studies in the AQCD and ISA¹

Study	Location	Ages	Lag	Averaging Time	Percent Change (95% CI) ²
Key ISA Studies (Year-round Analyses)					
Katsouyanni <i>et al.</i> (2009)	APHENA-US	≥75	DL (0-2)	1-h max	2.30 (-1.33, 6.04)
	APHENA-Canada		DL (0-2)	1-h max	8.96 (0.75, 18.6)
	APHENA-Europe		DL (0-2)	1-h max	2.06 (-0.24, 4.31)
	APHENA-US	<75	DL (0-2)	1-h max	3.83 (-0.16, 7.95)
	APHENA-Canada		DL (0-2)	1-h max	7.03 (-2.71, 17.7)
	APHENA-Europe		DL (0-2)	1-h max	1.98 (-1.09, 5.13)
Wong (2010)	4 Asian cities	All	0-1	8-hr max	2.20 (0.06, 4.37)
Key AQCD Studies (Seasonal Analyses)					
Gryparis <i>et al.</i> (2004)	21 European cities	All	0-1	8-h max	2.7 (1.29,4.32)
Key ISA Studies (Seasonal Analyses)					
Samoli <i>et al.</i> (2009)	21 European cities		0-1	8-h max	1.48 (0.18, 2.80)
Zanobetti and Schwartz (2008b)	48 US cities		0-3	8-h max	2.42 (1.45, 3.43)
Stafoggia <i>et al.</i> (2010)	10 Italian cities	≥35	DL (0-5)	8-h max	14.3 (6.65, 22.4)
Katsouyanni <i>et al.</i> (2009)	APHENA-US	≥75	DL (0-2)	1-h max	3.18 (-0.47, 6.95)
	APHENA-Canada		DL (0-2)	1-h max	1.50 (-2.79, 5.95)
	APHENA-Europe		DL (0-2)	1-h max	3.67 (0.95, 6.53)
	APHENA-US	<75	DL (0-2)	1-h max	6.78 (2.70, 11.0)
	APHENA-Canada		DL (0-2)	1-h max	-1.02 (-4.23, 2.30)
	APHENA-Europe		DL (0-2)	1-h max	2.22 (-1.48, 6.04)

Notes:

(1) Bolded results are statistically significant.

(2) Results from single pollutant models, standardized by EPA and reported as an increase in mortality per 40-ppb increase in 1-hour maximum, 30-ppb increase in 8-hour maximum, and 20-ppb increase in 24-hour average ozone concentrations.

FE = fixed effects model; NA = not available; NR = not reported; RE = random effects model.

3.2.2 Key Studies Not Included in the Ozone ISA

Several studies evaluating CV mortality were not included in the ISA, including some published after the cutoff for inclusion (Cheng and Kan, 2012; Garrett and Casimiro, 2011; Hunova *et al.*, 2013; Pascal *et al.*, 2012; Romieu *et al.*, 2012; Sacks *et al.*, 2012; Son *et al.*, 2012; Tao *et al.*, 2012; Yang *et al.*, 2012). These studies add to the previous body of evidence regarding CV mortality. In Table 3.4, we show the standardized mortality effect estimates according to EPA's methodology. Results as reported by the authors are summarized in Table A.3. There was inconsistency in the effect estimates across studies, with standardized effect estimates ranging from 0.67-6.09% in year-round analyses. As shown in Table 3.4, not all effect estimates were statistically significant, particular in the seasonal analyses.

Table 3.4 Cardiovascular Mortality Effect Estimates from Key Studies Not in the ISA

Study	Location	Lag	Averaging Time	Percent Change (95% CI) ^{1,21}
Year-round Analyses				
Pascal <i>et al.</i> (2012)	France, 9 urban areas	0	8-hr max	2.38 (0.0, 4.19)
Romieu <i>et al.</i> (2012)	Latin America, 9 cities	0-3, FE	24-hr avg	0.67 (0.43, 0.91)²
		0-3, RE		0.90 (0.35, 1.46)
Sacks <i>et al.</i> (2012)	Philadelphia, PA	0-1	24-hr avg	1.70 (-1.80, 5.30)
Tao <i>et al.</i> (2012)	Southern China, 4 cities	1-2	8-h avg	6.09 (4.25, 8.02)
Yang <i>et al.</i> (2012)	Suzhou, China	1	1-hr max	2.42 (0.76, 4.06)
			8-hr max	2.23 (0.72, 3.71)
			24-hr avg	1.99 (0.30, 3.66)
Seasonal Analyses				
Pascal <i>et al.</i> (2012)	France, 9 urban areas	0	8-hr max	7.89 (3.58, 11.7)
Sacks <i>et al.</i> (2012)	Philadelphia, PA	0-1	24-hr avg	1.10 (-2.60, 5.00)
Tao <i>et al.</i> (2012)	Southern China, 4 cities	1-2	8-h avg	5.78 (2.08, 9.66)
Yang <i>et al.</i> (2012)	Suzhou, China	1	1-hr max	0.91 (-1.25, 3.05)
			8-hr max	1.46 (-0.05, 3.39)
			24-hr avg	2.00 (-0.10, 4.08)

Notes:

(1) Bolded results are statistically significant.

(2) Results from single pollutant models, standardized using EPA's equation: $EXP(LN(odds\ ratio) * (standard\ increment / increment\ used\ in\ paper))$ for an increase in mortality per 40-ppb increase in 1-hour maximum, 30-ppb increase in 8-hour maximum, and 20-ppb increase in 24-hour average ozone concentrations.

FE = fixed effects model; NA = not available; NR = not reported; RE = random effects model.

In addition to all-cause and respiratory mortality, Pascal *et al.* (2012) investigated the association between short-term exposure to ozone and CV mortality in nine French urban areas. In all-year analyses, the authors reported no statistically significant associations between ozone and CV mortality in single- or two-pollutant models adjusting for PM_{2.5}. Statistically significant effects were reported only in the analyses restricted to the summer (Table 3.4). In a two-pollutant model adjusting for PM_{2.5}, however, the relationship was no longer statistically significant (see Table A.3). The authors conducted sensitivity

analyses with a temperature-stratified, case-crossover model (with the highest adjustment for temperature) and observed similar results, concluding that temperature was unlikely a confounder in this study.

Romieu *et al.* (2012) evaluated CV-related mortality in the ESCALA study, as well as other specific CV mortality outcomes, including hypertensive disease, ischemic heart disease, and other forms of heart disease. In the combined analyses of all cities (Sao Paulo and Rio de Janeiro, Brazil; Santiago, Chile; Mexico City, Toluca, and Monterrey, Mexico), the authors reported a small but statistically significant increase in CV mortality with each 10 $\mu\text{g}/\text{m}^3$ in 24-hour average ozone, in both fixed and random effects single-pollutant models (Table 3.4). There was evidence of heterogeneity across the cities; for example, in single-pollutant models, there was no significant increase in CV mortality in Toluca, and in Santiago, Chile, mortality effects were only statistically significant in those 65 years or older. After adjusting for PM_{10} , CV mortality was only statistically significantly increased in Santiago, Chile, and in those 65 years or older in Mexico City. In Toluca and Sao Paulo, no statistically significant increases in CV mortality were observed. Similar inconsistencies in effect estimates across cities were noted in the seasonal analyses (see Table A.3).

Tao *et al.* (2012) also assessed the relationship between ozone and CV mortality. In a single-pollutant model, the authors reported an increase in CV mortality (Table 3.4). The relationship between ozone and respiratory mortality was attenuated in two-pollutant models with either PM_{10} , NO_2 , SO_2 , or CO, but it remained statistically significant (see Table A.3). Mortality effect estimates remained statistically significant in the analyses of peak *vs.* non-peak ozone exposure periods in single- and two-pollutant models adjusted for PM_{10} . Tao *et al.* (2012) also observed heterogeneity among the effect estimates in each of the cities. CV mortality remained statistically significant when the "megacity" of Guangzhou was evaluated separately, but, in two out of three of the medium-sized cities (Foshan and Zhuhai), no statistically significant increases in CV mortality was observed.

Yang *et al.* (2012) assessed the relationship between short-term ozone exposure and cause-specific mortality, including CV endpoints. The authors reported increased CV mortality (Table 3.4). Adjusting for PM_{10} attenuated the CV mortality estimates, but they remained statistically significant.

Sacks *et al.* (2012) is the only study not included in the ISA that analyzed US data. The authors evaluated the effects of different model specifications on the CV-mortality association with short-term ozone concentrations in Philadelphia, Pennsylvania. The authors reported no significant increases in CV mortality regardless of the model used. Study results from Sacks *et al.* (2012) are discussed further in Section 4.2.

Only two meta-analyses evaluated CV-related mortality associations with short-term ozone exposures: the study by Bell *et al.* (2005) of studies of US and non-US cities conducted from 1987-2000, and a recent study by Shang *et al.* (2013) of Chinese cities (see Table A.4). Bell *et al.* (2005) reported statistically significant CV-mortality effects when studies of US and non-US cities were combined (1.11%; 95% CI: 0.68, 1.53 per 10 ppb increase in 24-hour average ozone) in year-round analysis. When studies of US cities were analyzed alone, however, there was no significant increase in mortality (0.85%, 95% CI: -0.66, 2.39 per 10 ppb increase in 24-hour average ozone). In warm-season analyses of US and non-US cities combined, CV mortality was significantly increased 2.45% (95% CI: 0.88, 4.10) for every 10 ppb increase in 24-hour average ozone. The authors noted significant heterogeneity among the risk estimates of the individual cities, as well as evidence of publication bias. CV-mortality effect estimates observed from the meta-analysis were consistently much larger than those from the NMMAPS multi-city analysis, and the pooled estimates were larger when results from studies that reported a single lag (compared to multiple lags) were used in the analysis, suggesting that the lag with the largest effect was more likely to be reported.

Shang *et al.* (2013) evaluated CV mortality in nine studies in China published between 1990 and 2012. Using a linear random effects model, the authors reported a 0.45% increase in CV mortality (95% CI: 0.29, 0.60) with each 10 $\mu\text{g}/\text{m}^3$ increase in 24-hour average ozone. The authors reported that the average ozone concentrations ranged from 56-86 $\mu\text{g}/\text{m}^3$ (approximately 110-169 ppb), which is higher than what is reported in most contemporary US cities (*e.g.*, Bell *et al.*, 2004, reported average 24-hour ozone concentrations of 26 ppb for 95 NMMAPS cities). Shang *et al.* (2013) stated that caution should be used in interpreting these results due to the small number of studies identified and possible model selection bias from the choice of lags.

Collectively, these recent studies show inconsistent results, and many show evidence of between-city heterogeneity, confounding by co-pollutants, and other potential limitations (discussed in detail in Section 4).

3.3 Conclusions

In the ISA (US EPA, 2013), EPA concluded that there is a causal relationship between short-term ozone exposure and respiratory health effects, including respiratory mortality. However, the majority of available analyses, including the large APHENA study by Katsouyanni *et al.* (2009) on which EPA relied heavily, does not show statistically significant increases in respiratory mortality from short-term ozone exposure. In fact, a number of estimates yielded negative mortality estimates, particularly in the US, but also in several analyses of Canada and Europe. Furthermore, additional studies published since the ISA predominantly found no associations between ozone and respiratory mortality, even in areas with very high levels of ozone.

With regard to CV mortality, EPA concluded that there is a likely causal relationship between short-term ozone exposure and CV effects. While some studies report associations between ozone and CV mortality, others report no statistically significant relationships with short-term ozone exposures.

The epidemiology evidence regarding respiratory- and CV-related mortality associations with short-term ozone exposures is inconsistent across cities and regions. As discussed in Section 4, this could be due to model assumptions, potential confounding effects of PM_{10} and other co-pollutants, inter-city and inter-region heterogeneity, exposure measurement error, and the ozone-mortality concentration-response (C-R) relationship. Overall, the evidence is not robust and does not support EPA's causality determinations in the ozone ISA.

4 Limitations of the Epidemiology Evidence

Many studies published since the 2006 ozone AQCD are re-analyses of multi-city datasets. The principal purpose of these studies was to address specific uncertainties associated with time-series epidemiology studies *via* extensive sensitivity analyses that determine the relative impact of uncertainties on effect estimates (*e.g.*, Katsouyanni *et al.*, 2009 and Smith *et al.*, 2009). These uncertainties include the choice of ozone averaging time, model selection (including choice of lag time), the confounding effects of co-pollutants and other factors (*e.g.*, temperature), modifying effects that may explain the observed heterogeneity in mortality effect estimates across cities and regions, exposure measurement error, and the shape of the CRF. In the 2006 AQCD, EPA acknowledged the significance of these uncertainties and concluded that the overall evidence was "highly suggestive" of an association between mortality and short-term exposures to ozone (US EPA, 2006, p. 6-140). As discussed below, new evidence only serves to further highlight these uncertainties, yet EPA downplayed or did not fully acknowledge them in the ISA. Because the new studies do not resolve these uncertainties, the body of evidence is not sufficiently robust to support a "likely causal" determination for all-cause and CV mortality nor a causal association for respiratory mortality.

4.1 Ozone Averaging Time

The ozone averaging times used in calculating ozone-related effect estimates vary across epidemiology studies. The most common averaging times are the maximum 1-hour average within a 24-hour period (1-hour maximum), the maximum 8-hour average within a 24-hour period (8-hour maximum), and the 24-hour average (24-hour average.). In addition, the effect estimates are reported for an incremental change in ozone, which also differs across studies but is often reported as 10 ppb or 10 $\mu\text{g}/\text{m}^3$. This poses challenges in comparing results across studies. In the ISA, EPA standardized the mortality effect estimates to facilitate comparisons. The increments for the different averaging times were based on the observed ratios of measured ambient ozone concentrations from monitors across the US for the different averaging times. EPA derived a ratio for these different ozone metrics of 2:1.5:1 for 1-hour maximum:8-hour maximum:24-hour average. All ozone effect estimates were then standardized using the increments of 20 ppb for 24-hour average, 30 ppb for 8-hour maximum, and 40 ppb for 1-hour maximum ozone concentrations, by applying the following equation: $\text{EXP}(\text{LN}(\text{odds ratio}) * (\text{standard increment} / \text{increment used in paper}))$ (US EPA, 2013; Brown *et al.*, 2013, personal calculation). It is important to note that, although it addresses the ozone averaging time and the associated increment for reporting mortality estimates, this standardization does not address other important methodological differences across studies that also complicate comparisons (*e.g.*, lag times).

Researchers have investigated whether the ratios EPA applied to standardize mortality effect estimates were the most appropriate. For example, Anderson and Bell (2010) evaluated the ratios used to standardize mortality effect estimates by EPA and others and analyzed data from 78 communities in the US (2000 and 2004) to determine if ratios vary across regions and seasons. They noted that different studies used different ratios to standardize results across studies that used different ozone averaging times. For example, Thurston and Ito (2001) applied a ratio of 2.5:1.33:1 (1-hour maximum:8-hour maximum:24-hour average), which differs from EPA's ratio. Anderson and Bell (2010) also found that the ratios for different ozone metrics varied across communities and over time. Average ozone metric ratios ranged from 1.08-1.26 for the 1:8-hour ratio, from 1.23-1.83 for the 8:24-hour ratio, and from 1.35-2.20 for the 1:24-hour ratio. Furthermore, there were no clear regional patterns. The ratios also varied by

season; for most communities, the 1:8-hour ratio and the 8:24-hour ratio were highest in the spring. The authors noted that a possible reason for the variability in these ratios is the diurnal cycle of ozone concentrations, which generally peak in the afternoon, although the diurnal pattern also differs seasonally and across locations. Anderson and Bell (2010) concluded that using a standard ratio to convert ozone metrics may introduce error, distorting the ozone pollution patterns and the resulting health effect estimates. They suggested that separate conversion methods be used for warm vs. cool seasons to reduce uncertainty.

To avoid standardization and any error introduced by applying the ozone ratios, some researchers present results for different ozone averaging times. For example, Yang *et al.* (2012), Hunova *et al.* (2013), and Moshhammer *et al.* (2013) presented all-cause mortality effect estimates for all three common ozone averaging times; the results showed differences in effect estimates depending on which ozone averaging time was used (Table 4.1).

Table 4.1 Short-term Ozone and All-cause Mortality in Studies Reporting Several Averaging Times

Averaging Time	Lag (d)	Co-Pollutants	Increment ¹	% Change	95% CI
Yang <i>et al.</i> (2012)					
1-hr max	1	None	70.6 µg/m ³	1.84	0.07, 3.60
8-hr max			59.6 µg/m ³	2.15	0.36, 3.93
24-hr avg			33.3 µg/m ³	1.33	-0.37, 3.03
1-hr max	1	PM ₁₀	70.6 µg/m ³	0.99	-0.78, 2.75
8-hr max			59.6 µg/m ³	1.43	-0.36, 3.22
24-hr avg			33.3 µg/m ³	0.93	-0.77, 2.63
Hunova <i>et al.</i> (2013)					
24-hr avg	1	None	Per 10 µg/m ³	0.60	-0.50, 1.69
8-hr max				0.00	-0.80, 0.80
24-hr avg	2			-0.10	-0.90, 0.70
8-hr max				0.00	-0.60, 0.50
Moshhammer <i>et al.</i> (2013)					
1-hr max	0	None	Per 10 µg/m ³	0.57	0.41, 0.73
	1			0.56	0.31, 0.73
	2			0.20	0.00, 0.41
8-hr max	0			0.60	0.42, 0.78
	1			0.51	0.31, 0.70
	2			0.27	0.03, 0.50
24-hr avg.	0			0.51	0.28, 0.74
	1			0.09	-0.14, 0.33
	2			-0.12	-0.37, 0.14

Note:

(1) Incremental change in ozone concentration corresponding to % change in mortality, as reported in original study.

Overall, one of the challenges in comparing across studies that evaluate mortality associations with short-term ozone exposure is that they use different ozone exposure averaging times and report results for different increments of ozone exposures. In an attempt to standardize mortality effect estimates across studies, EPA applied a function based on ratios of measured ozone concentrations across the US. These ratios, however, may not account for differences in ozone concentrations across regions and seasons.

Therefore, the application of these ratios in the ISA may have generated biased standardized mortality effect estimates (see Sections 2 and 3).

4.2 Model Specification

Model selection is an important source of uncertainty that has been investigated in recent epidemiology studies. Researchers have evaluated how the control of temporal factors, such as weather and season, and lag times (used to define ozone exposures relative to mortality) impact mortality effect estimates.

4.2.1 Short-term Temporal Factors

In time-series analyses, daily mortality associations are modeled against daily (or lagged) ozone exposures and other co-variates to assess how short-term ozone exposures are correlated with mortality. Short-term temporal factors, such as daily weather and season, can bias results from this type of analysis. Temporal confounders, in fact, tend to account for a significant fraction of the associations in time-series studies of mortality; for in ozone studies, temporal cofounders are particularly important to consider because ozone has strong seasonal cycles and is formed under high temperature conditions. Several approaches have been used to adjust for temporal trends and weather effects in recent time-series ozone mortality studies. These include parametric and non-parametric smoothers with different degrees of freedom (*i.e.*, the number of values that are free to vary) per year, typically ranging from 4-12. To determine the appropriate number of degrees of freedom, researchers typically use statistical diagnostics such as Akaike's Information Criteria (AIC), PACF, or dispersion of the regression model, but these do not guarantee that temporal confounding is controlled for adequately.

The most recent time-series analyses have relied primarily on parametric (*e.g.*, natural splines) or non-parametric [*e.g.*, locally estimated smoothing splines (LOESS)] smoothing functions, which provide flexible ways to fit mortality estimates as a function of temperature and other weather variables. Issues arise due to the significant correlations between weather and ozone and weather and mortality. In addition, year-round analyses do not account for correlation structures that likely change across season; this can lead to biased effect estimates. This is an important issue for ozone, because the relationship between ozone and temperature varies with season much more than for other pollutants (*e.g.*, PM). Thus, those studies that have included seasonal analyses when evaluating mortality effects of ozone exposure are much more robust than those that do not.

The importance of model selection and control for temporal confounding is highlighted in several sensitivity analyses, most recently in the APHENA study (Katsouyanni *et al.*, 2009). The APHENA study, which included datasets from US, Canadian, and European multi-city studies, included extensive sensitivity analyses exploring the use of different smoothing functions. Results indicated that there were significant differences when different model specifications were used (*e.g.*, penalized *vs.* natural spline functions).

In Table 4.2, the APHENA ozone-mortality effect estimates are presented for two different model specifications. Specifically, in column 1, standardized ozone-mortality effect estimates (*i.e.*, per 40 ppb ozone increment in 1-hour maximum ozone) are shown for a model using natural splines and 8 degrees of freedom per year (NS/8 df/year); in column 2, the adjusted (per 40 ppb of ozone) mortality estimates are shown based on a penalized spline (PS) model, and PACF-derived degrees of freedom (PACF/PS). Katsouyanni *et al.* (2009) noted that the PACF/PS model showed strong performance and lower bias and thus may be a more appropriate model to use, but the authors noted that there was no "best" model to use overall. As shown in Table 4.2, with the exception of Canada, the PACF/PS model yielded mortality

effect estimates that were lower and not statistically significant compared to the NS/8 df/year model. These differences are important as they can change the interpretation of the results.

Table 4.2 Katsouyanni *et al.* (2009) Results by Location for All-cause, Cardiovascular, and Respiratory Mortality

Location	Percent Change (95% CI) ¹ 8 df/year, Natural Spline	Percent Change (95% CI) ² PACF, Penalized Spline
US		
All-cause	1.42 (0.08, 2.78)	-4.56 (-7.12, -2.08)
Cardiovascular, age ≥75	1.10 (-1.33, 3.67)	-6.80 (-10.96, -2.64)
Cardiovascular, age <75	-0.16 (-3.02, 2.86)	-4.08 (-7.20, -0.88)
Respiratory	2.46 (-1.87, 6.86)	-10.32 (-17.36, -3.28)
Canada		
All-cause	4.15 (1.90, 6.45)	5.44 (3.44, 7.52)
Cardiovascular, age ≥75	5.62 (0.95, 10.7)	8.00 (3.84, 12.0)
Cardiovascular, age <75	1.10 (-4.08, 6.61)	3.52 (-1.36, 8.0)
Respiratory	0.87 (-6.40, 8.96)	2.00 (-5.04, 8.8)
Europe		
All-cause	1.02 (0.39, 1.66)	0.72 (-0.08, 0.17)
Cardiovascular, age ≥75	1.10 (-0.47, 2.70)	0.48 (-1.12, 2.00)
Cardiovascular, age <75	1.34 (-0.24, 2.94)	0.96 (-0.80, 2.64)
Respiratory	1.42 (-1.02, 3.83)	0.16 (-2.40, 2.81)

Notes:

(1) Results as reported in EPA (2013), Table 6-45. Results are for all-year analyses, all ages (except CV). Effect estimates are for a 40 ppb increase in 1-hour ozone concentration at lag 1 and are for models with 8 df/year and using natural splines.

(2) Results as reported in Katsouyanni *et al.* (2009), as the model with least bias, standardized to a 40 ppb increase in 1-hour ozone, lag 1.

Bold numbers are statistically significant.

The impact of model selection on mortality effect estimates was investigated in a recent study of air pollution and CV mortality in Philadelphia, Pennsylvania (May 1992-September 1995) by Sacks *et al.* (2012). The authors applied several previously used regression models to PM and gaseous air pollution data in both single- and multi-pollutant models. The models evaluated included models that were used in the APHEA2 study (Samoli *et al.*, 2005), NMMAPS (Dominici *et al.*, 2005), a study in California (Ostro *et al.*, 2008), a study in Canada (Burnett and Goldberg, 2003), and two Harvard Studies in US cities (Zanobetti and Schwartz, 2008c, 2009). The models applied different temporal adjustment (smoothing function and degrees of freedom) and differed in how they controlled for weather (*i.e.*, the weather covariates). As shown in Table 4.3, the CV mortality estimates varied greatly depending on the model, with estimates ranging from -1.6 to 2.2%; none were statistically significant. The authors noted that, unlike PM and other gases that were evaluated, ozone-mortality effect estimates were inconsistent in both year-round and seasonal analyses.

Table 4.3 Sacks *et al.* (2012) Results for Cardiovascular Mortality by Model Specification in Year-round Analysis

Model, Temporal Adjustment	Weather Co-variates	% Change	Source of Model
APHEA2, GAM, penalized splines	Same-day temperature (k = 10) Lag 1–3 day temperature (k = 10) Relative humidity (k = 10)	1.7 (-1.8, 5.3)	Samoli <i>et al.</i> (2005)
California, GLM, 4 df/year	Same-day temperature (4 df) Barometric pressure (4 df)	0.2 (-3.4, 3.9)	Ostro <i>et al.</i> (2008)
Canada, GLM, 8 df/year	Same-day temperature (3 df) Lag 1 day temperature (3 df)	0.5 (-3.1, 4.3)	Burnett and Goldberg (2003)
NMMAPS, GLM, 7 df/year	Same-day temperature (6 df) Lag 1–3 day temperature (6 df) Same-day dew point (3 df) Lag 1–3 day dew point (3 df)	2.2 (-1.8, 6.4)	Dominici <i>et al.</i> (2005)
9 U.S. cities, GLM, 6 df/year	Lag 1 day temperature (3 df) Lag 1 day relative humidity (3 df)	2.2 (-1.8, 6.4)	Zanobetti and Schwartz (2009)
118 U.S. cities, GLM, 8 df/year	Same-day apparent temperature (4 df)	1.3 (-2.1, 4.9)	Zanobetti and Schwartz (2008c)

Notes:

Adapted from Sacks *et al.* (2012), Tables 1 and 4.

df = degree of freedom; GAM = generalized additive model; GLM = generalized linear model; k = number of basic functions included for each covariate. An indicator variable for day of week was also included for each model.

4.2.2 Lag Time

Lag time refers to the time between an exposure and the occurrence of a health effect. For example, if one is evaluating the association between ozone exposure and a health effect occurring two days later, this would be a lag of 2 days. If one is evaluating a health effect that occurs within two days, this would be a lag of 0-2 days. Researchers often evaluate multiple lag times and sometimes only report findings for statistically significant lags, without consideration of whether the lag is biologically plausible.

For ozone, researchers traditionally have analyzed lag times of up to a few days, because short-term ozone associations are considered to represent effects from acute exposures. A few recent studies, however, have examined the effects of longer lag times, employing distributed lag models that yield summary estimates for all included lag days and using a function that accounts for colinearities in effects that are summed across multiple days. These approaches have further complicated comparisons across studies, as the effect estimates reported for single- vs. multi-day lag models are not comparable, even if the reported estimates are for the same increment of ozone exposure (*e.g.*, per 10 ppb ozone). Bias associated with the selection of lags has been investigated in several meta-analyses (Bell *et al.*, 2005; Levy *et al.*, 2005). The authors of these meta-analyses noted that 0-day lag models tend to be larger than estimates from longer lags.

Several studies have reported mortality effect estimates for different lag times (see Table 4.4). Zanobetti and Schwartz (2008b) conducted a time-series study using generalized linear models that controlled for season, day of the week, and temperature to evaluate the association between mortality and ozone in 48 US cities during the summer months (June-August) between 1989 and 2000. The aim of the study was to determine if there was evidence of mortality displacement, *i.e.*, that deaths associated with exposure to ozone occurred in people that were dying, and exposure merely hastened but did not cause death. To evaluate this, the authors compared the mortality effect estimates at lag 0, lag 0-3, lag 4-20, and a distributed lag model (0-20). As shown in Table 4.4, the standardized estimate was a 0.16% (95% CI:

0.1, 0.22) increase in all-cause mortality for a 10 $\mu\text{g}/\text{m}^3$ increase in 8-hour maximum ozone concentrations at lag 0⁴ vs. 0.26% (95% CI: 0.03, 0.48) increase for the unconstrained distributed lag model (lag 0-20). Similar results were reported for CV- and respiratory-cause mortality. The effects were statistically significant only for the lags up to 3 days, with negative effects (*i.e.*, mortality decreases) observed for the sum of lags 4-20. One way to interpret this is that ozone hastens death within 3 days but prevents it between 4 and 20 days. Since this is unlikely, the authors concluded that, based on these results, there was no evidence of mortality displacement.

In a similar study, Samoli *et al.* (2009) investigated the temporal pattern of effects in a summer-only (June-August) re-analysis of data from the APHEA2 study of 21 European cities using unconstrained distributed lag models with lags up to 20 days. The authors reported total mortality and CV effects similar to Zanobetti and Schwartz (2008b) for the lag 0 and 0-1, but they reported null and negative findings for the distributed lag model for total and CV mortality. Even more divergent results were reported for respiratory mortality, with no effects at lag 0, small, statistically significant effects at lags 0-1, and effects approximately 10 times higher using the distributed lag model (0-20) – *i.e.*, a completely opposite direction to the Zanobetti and Schwartz (2008b) results.

⁴ We adjusted the mortality effect estimates to reflect a 10 $\mu\text{g}/\text{m}^3$ increase in ozone for comparison with other study results. The study investigators reported results in terms of a 10 ppb increase in ozone (equivalent to about 20 $\mu\text{g}/\text{m}^3$).

Table 4.4 All-cause Mortality Effect Estimates by Lag for a 10 µg/m³ Increase in Ambient Ozone Concentration¹

Study	Lags Examined	% Change in Mortality (95% Confidence Interval)		
		All-cause	Cardiovascular	Respiratory
Katsouyanni <i>et al.</i> (2009) ² - European Cities	0-1	0.25 (0.10, 0.40)	0.37 (0.09, 0.66)	0.31 (-0.10, 0.72)
	1	0.29 (0.19, 0.39)	0.39 (0.13, 0.65)	0.58 (0.25, 0.91)
	0-2	0.34 (0.16, 0.53)	0.51 (0.17, 0.86)	0.57 (-0.08, 1.22)
Katsouyanni <i>et al.</i> (2009) ² -US Cities	0-1	0.57 (0.35, 0.79)	0.56 (0.16, 0.96)	0.66 (-0.02, 1.34)
	1	0.49 (0.29, 0.69)	0.49 (0.15, 0.83)	0.77 (0.17, 1.37)
	0-2	0.65 (0.33, 0.97)	0.65 (0.03, 1.27)	0.73 (-0.39, 1.85)
Samoli <i>et al.</i> (2009) ³	0	0.28 (0.11, 0.45)	0.43 (0.18, 0.69)	0.36 (-0.21, 0.94)
	0-1	0.24 (0.15, 0.34)	0.33 (0.19, 0.48)	0.40 (0.11, 0.7)
	0-20	0.01 (-0.41, 0.42)	-0.32 (-0.92, 0.28)	3.66 (2.25, 5.08)
Zanobetti and Schwartz (2008b) ⁴	0	0.16 (0.1, 0.22)	0.24 (0.15, 0.32)	0.27 (0.13, 0.41)
	0-3	0.26 (0.14, 0.38)	0.40 (0.24, 0.56)	0.42 (0.19, 0.64)
	0-20	0.26 (0.03, 0.48)	0.24 (-0.005, 0.5)	0.30 (-0.20, 0.81)
	4-20	-0.01 (-0.18, 0.16)	-0.12 (-0.34, 0.11)	-0.12 (-0.54, 0.3)

Notes:

(1) Bold indicates statistically significant results.

(2) Percentage change in mortality (and 95% confidence intervals) per 10 µg/m³ increase in 1-hour maximum ozone during the summer months for previous day (lag 1), average of same and previous day (lag 0-1), and the distribution lag model (lag 0-2), all with penalized splines in 21 European cities and 95 US cities. Data are for all ages except for cardiovascular mortality (age ≥75 years). No ozone-mortality associations were statistically significant when the model controlled for PM₁₀.

(3) Percentage change in mortality (and 95% confidence intervals) per 10 µg/m³ increase in 8-hour maximum ozone during the summer months for same day (lag 0), average of same and previous day (lag 0-1), and the penalized distribution lag model (lag 0-20) in 21 European cities.

(4) Percentage change in mortality (and 95% confidence intervals) per 20 µg/m³ (10 ppb) increase in 8-hour maximum ozone during the summer months for the same day (lag 0) and the distributed lag (lags 0-3, 0-20, and 4-20) model in 48 US cities.

(5) Percent change in mortality (95% CI) per 10 µg/m³ increase in ozone (8-hour), estimated from Figure 1 in Stafoggia *et al.* (2010) for distributed lag models 0-1 and 0-5.

In general, selection of lag period should depend on the mechanism of the effect. Analyzing numerous lags and reporting only the statistically significant effects biases the estimates away from the null. In addition, multiple comparisons increase the likelihood that statistically significant associations are due to chance. Several of the most recent ozone-mortality studies appear to have reported only the largest or most significant mortality effect estimates without *a priori* consideration of the most appropriate or biologically relevant lag. For example, Reyna *et al.* (2012) investigated lags of 0-7 days but only reported the results of a the most significant lag time. For ozone, the most significant lag was 7 days, and this was the only lag for which results were reported.

4.2.3 Conclusions

The results of studies from both those included and not included in the ISA show that the choice of model specification can have a significant effect on the results, in many cases changing the interpretation of the findings. Importantly, APHENA investigators concluded that there was no single method that was "adequate or preferred for selecting the underlying model and the degrees of freedom for confounder control" (Katsouyanni *et al.*, 2009). Therefore, there remains significant uncertainty in the best choice of model to evaluate the potential mortality effects of ozone exposure. Likewise, the choice of lag in ozone-mortality evaluations results in divergent results across studies. It is important to evaluate results for the same lag period across studies to determine if results are robust, particularly when the most biologically plausible lag period is unknown. Furthermore, reporting only the statistically significant findings for many lag specifications can lead to model selection bias.

4.3. Confounding

4.3.1 Co-pollutants

Confounding by co-pollutants, weather, or other factors not included in epidemiology studies of mortality associations with short-term ozone exposures remains a major source of uncertainty that has not been resolved by recent studies. In fact, evidence from recent studies affirms that this issue remain relevant and important. Specifically, as discussed below, several of the studies EPA evaluated in the ISA, and many of the more recent studies not reviewed in the ISA, investigated confounding of PM₁₀, PM_{2.5}, and some PM components. A few studies also explored confounding effects of temperature.

Bell *et al.* (2007) specifically investigated potential confounding effects of PM₁₀ and PM_{2.5} on the ozone-mortality association in analyses of the NMMAPS data for 98 cities for the years 1987-2000. The authors used three methods: 1) estimating correlations between daily ozone and daily PM concentrations, stratified by ozone or PM levels; 2) constructing time-series models with PM as a covariate; and 3) including PM as a covariate, but considering only days with ozone below a specified value (a subset modeling analysis). As noted by the authors, there were limitations to the PM data availability due to the 3rd or 6th day sampling schedule for PM in most cities, and because PM_{2.5} data were only available after 1999. Therefore, only a subset of the data was available for the evaluation of confounding effects.

Overall, the authors reported low correlations between ozone and PM₁₀ and PM_{2.5} that varied significantly by region and season, with the highest correlations (0.44) in the summer in the Northeast and Industrial Midwest. Negative or no correlations were observed in the Southwest and Northwest (with a range of -0.20 to 0.10 for seasonal correlation coefficients). The overall percent increase in all-cause (non-accidental) mortality associated with a 10 ppb increase in ozone (24-hour, average of lag 0-1) was 0.32% (95% CI: 0.17, 0.46) for all the data, which was lower than the 0.52% (95% CI: 0.27, 0.77) per 10 ppb increase in ozone (24 hour, constrained distributed lag) reported previously for 95 NMMAPS US cities (Bell *et al.*, 2004). Smaller effects were obtained for the data limited to the days (and communities) with available PM₁₀ and PM_{2.5} data: 0.29% (95% CI: 0.03, 0.55) and 0.22% (95% CI: -0.22, 0.65), respectively. Adjustment for PM₁₀ or PM_{2.5} resulted in a slight reduction of the mortality estimates to 0.21% for both PM fractions; neither of the adjusted estimates were statistically significant.

The authors concluded that there was no evidence of confounding by PM based on the correlation and regression analyses adjusting for PM, but they cautioned that the analyses were limited by the data availability. Interestingly, the authors maintained that this type of analysis was possible because of the large dataset, which included 14 years of data and a large number of cities. While effect estimates were

not greatly reduced with inclusion of PM, results were no longer statistically significant, providing some evidence of potential confounding. In addition, the regional heterogeneity observed for the correlation between PM₁₀ and ozone, with higher observed correlation in the Northeast and Industrial Midwest, is consistent with higher reported mortality estimates for these regions (*e.g.*, as reported by Dominici *et al.*, 2005; HEI 2003; Smith *et al.*, 2009). This may be indicative of regional confounding effects. Regional heterogeneity is discussed further in Section 4.4.

Smith *et al.* (2009) reproduced the analysis of the NMMAPS study by Bell *et al.* (2004) and examined the inter-city variability and sensitivity of the ozone-mortality relationship to various modeling assumptions, including confounding effects of temperature and co-pollutants (PM₁₀ and SO₂). Using the constrained distributed lag model of Bell *et al.* (2004) to estimate national average effects for ozone, Smith *et al.* (2009) reported an increase in non-accidental mortality of 0.40% per 10 ppb increase in 24-hour ozone when fitted to days in which lag 1 PM₁₀ data were available (but not included in the model) and an increase of 0.31% per 10 ppb increase in 24-hour ozone when the analysis was repeated with PM₁₀ included as a co-pollutant. Other ozone metrics and model specifications were investigated, and the authors demonstrated reduced ozone effects of 22-33% across the various models when including PM₁₀. Moreover, Smith *et al.* (2009) recreated the scatterplots presented in Bell *et al.* (2007) using the Bayesian-adjusted mortality effect estimates (the preferred estimates used by Bell *et al.*, 2007) and found that a much larger fraction of the estimates (89 of 93) were below the diagonal line (*i.e.*, were lower with PM₁₀ adjustment) compared to the plot using the raw estimates. Lastly, Smith *et al.* (2009) also considered an alternative model using a distributed lag to control for meteorology, which resulted in reduced mortality estimates. This suggests additional confounding by temperature that was not accounted for in earlier analyses.

Evidence of confounding effects was also reported for the APHENA study of cities in the US, Europe, and Canada. Katsouyanni *et al.* (2009) assessed potential co-pollutant confounding in both all-year analyses and seasonal (summer-only) analyses, presenting estimates of mortality with and without adjustment for PM₁₀. All-year mortality estimates were largely not statistically significant; however, in the few cases where statistically significant estimates were observed for ozone-only single-pollutant models (*e.g.*, all-cause mortality in Canadian and US cities, and CV mortality in those ≥ 75 years old in Canadian cities), the PM₁₀-adjusted effects were not statistically significant. The notable exception was all-cause mortality across European cities, where the effect estimate was essentially unchanged and remained significant with PM₁₀ adjustment. Therefore, inconsistent potential confounding effects were observed and point to the need for further exploration of this issue. EPA, however, does not place enough weight on the confounding evidence in the US and Canadian studies by citing data availability limitations.

Confounding by PM₁₀ appears to be more pronounced in the summer-only analyses, as most mortality estimates were statistically significant (and larger than the all-year estimates), but significantly reduced and often not statistically significant, with the inclusion of PM₁₀ (Figure 4.1). As with the year-round analyses, the notable exception was all-cause mortality in European cities. In this case, the effect estimate was reduced by almost 40%, although it remained statistically significant.

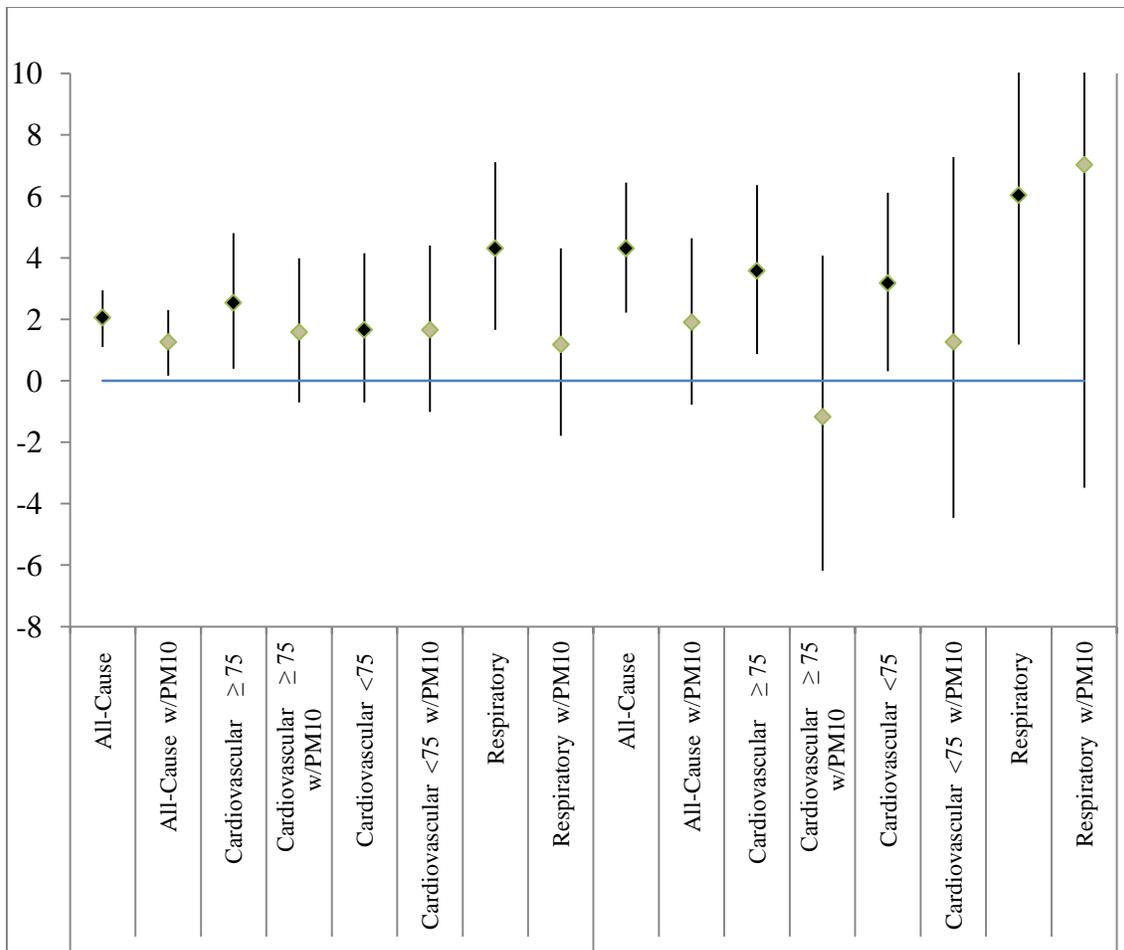


Figure 4.1 Percent Change in All-cause, Cardiovascular, and Respiratory Mortality for Single- and Co-pollutant Models from the APHENA Study, Summer-only Analysis (Katsouyanni *et al.*, 2009). Effect estimates are for a 40 ppb increase in 1-hour maximum ozone concentrations at lag 1 from a 8 df/year model using natural splines. Dark diamonds are single-pollutant estimates and light diamonds are co-pollutant estimates with PM₁₀. (Source: US EPA, 2013, Table 6-45)

Franklin and Schwartz (2008) analyzed data from 2000 -2005 from 18 US communities to determine the association between ozone and non-accidental mortality after adjustment for PM_{2.5}, sulfate, organic carbon (OC), and nitrate. They reported a pooled estimate across all communities of a 0.89% increase in mortality (95% CI: 0.45, 1.33) per 10 ppb increase in same-day 24-hour average ozone levels (summertime only). Effect estimates were slightly reduced with adjustment for PM_{2.5} (0.79%, 95% CI: 0.27, 1.31), but they were more substantially reduced and became non-significant with adjustment for sulfate, OC, and nitrate (0.58, 0.54, and 0.62%, respectively, per 10 ppb increase in ozone). However, the authors noted that there were sample size and data quality issues associated with the OC and nitrate data.

Several of the studies not included in the ISA investigated the effects of co-pollutants on the association between short-term ozone exposure and all-cause or cause-specific mortality (Pascal *et al.*, 2012,; Tao, *et al.*, 2012; Yang *et al.*, 2012; Moshhammer *et al.*, 2013). In year-round, all-cause mortality analyses, effect estimates were generally unchanged in some studies (*e.g.*, certain pollutants in Tao *et al.*, 2012) while attenuated in others (certain pollutants in Tao *et al.*, 2012; Yang *et al.*, 2012); in others, effect estimates increased (*e.g.*, Moshhammer *et al.*, 2013; Pascal *et al.*, 2012).

Tao *et al.* (2012) adjusted for the effects of PM₁₀, NO₂, SO₂, and CO. All-cause mortality in all analyses was statistically significantly increased, but, for models inclusive of PM₁₀ and NO₂, the effects were attenuated (0.54% and 0.43% per 10 µg/m³ 8-hour average ozone, respectively, in comparison with ozone-only increases of 0.81%). Also, Yang *et al.* (2012) reported decreased all-cause mortality estimates with adjustment for PM₁₀ (0.99%, 95% CI: -0.78, 2.75 per 76 µg/m³ increase in 1-hour maximum ozone) compared with 1.84% (95% CI: 0.07, 3.60) for the ozone-only model.

An increase in the mortality effect estimates was reported by Moshhammer *et al.* (2013) when the authors adjusted for NO₂ [from 0.51% (95% CI: 0.28, 0.74) to 1.04% (95% CI: 0.81, 1.45) per 10 µg/m³ increase in 24-hour average ozone]. When adjusting for PM_{2.5}, Pascal *et al.* (2012) noted an increased effect of ozone (0.30%, 95% CI: 0.10, 0.50 increased to 0.50, 95% CI: 0.20, 0.80 per 10 µg/m³ of 8-hour maximum ozone). In summer-only analyses, however, Pascal *et al.* (2012) reported an attenuation in the effect of ozone when PM_{2.5} was included in the model (0.80%, 95% CI: 0.50, 1.20 decreased to 0.70%, 95% CI: -0.10, 1.50 after inclusion of PM_{2.5}). Complete results of all single- and multi-pollutant analyses are presented in Table A.1.

Overall, results are inconsistent for confounding, with some studies suggesting that co-pollutants confound the relationship between ozone and mortality or act as surrogates for other confounders. Only one study (Pascal *et al.*, 2012) considered the effect of PM_{2.5}, which is more highly correlated with ozone than other co-pollutants, and it found inconsistent results across analyses.

4.3.2 Temperature

The potential confounding effects of temperature on the ozone-mortality association are evident in findings from Zanobetti and Schwartz (2008a). The authors examined ozone-mortality associations by season and summer month (May-September) in 48 US cities from 1989-2000. The authors found the highest ozone-mortality risk estimates at lag 0 in the summer season, with July having the highest ozone-mortality estimate among the summer months and August having a diminished estimate. As shown in Table 4.5, ozone-mortality estimates were only statistically significant in the spring and summer months, which also had the highest ozone concentrations and temperatures. The highest monthly estimate was in July (0.65%) and the lowest was in August (0.28%), although ozone concentrations were similarly high in both months. The authors hypothesized that this is indicative of possible adaptation to ozone-mortality effects. Alternatively, the observed seasonal heterogeneity may be indicative of potential confounding effects that are not accounted for in the model. Given that there is no known mechanism by which ozone causes mortality, either directly or indirectly, it is difficult to conceive how adaptivity could affect overall mortality rates (*e.g.*, would people that adapt to ozone exposure be immune from any lethal effects?). While adaptation to ozone exposures has been reported in humans (Folinsbee *et al.*, 1980) and animals (Hamade *et al.*, 2010) for some CV and pulmonary function parameters, there is still no evidence to support how these clinical effects would extend to mortality outcomes.

Table 4.5 Percent Increase in Total Mortality by Season and Month and Corresponding Daily 8-hour Mean Concentrations

Season/ Month	% Increase	95% CI		Ozone Concentration ppb (8-hr mean)		
				Mean	Min	Max
Season						
Winter	-0.13	-0.56	0.29	17	2	41
Spring	0.35	0.16	0.54	42	6	91
Summer	0.50	0.38	0.62	48	7	103
Autumn	0.05	-0.14	0.24	34	3	91
Month						
May	0.48	0.28	0.68	45	10	90
June	0.46	0.24	0.68	47	11	95
July	0.65	0.47	0.82	49	12	98
August	0.28	0.11	0.46	48	9	96
September	-0.09	-0.35	0.16	40	6	91

Source: Zanobetti and Schwartz (2008a); adapted from US EPA (2013), Table 6-52.

Sacks *et al.* (2012) evaluated the effect of various model specifications for temperature on the ozone and cardiovascular-mortality association, including the methodologies applied in the APHEA2 study (Samoli *et al.*, 2005), NMMAPS study (Dominici *et al.*, 2005), and by Zanobetti and Schwartz (2008c, 2009). They noted that variability in risk estimates across models was observed in single-pollutant analyses, indicating that ozone is more temperature-dependent than other air pollutants, and that careful control for the potential confounding effect of weather is needed for ozone. They cautioned, however, that it was not clear what model was best suited to do this. In addition, the authors noted that it was unclear whether temperature terms actually "control" for the effects of weather, or if they act as surrogates for pollutants in the middle range of temperature. Furthermore, the authors posited that the uniform method often applied in multi-city ozone-mortality studies to adjust for temperature and weather may not be appropriate and could explain some of the regional heterogeneity seen in these studies. In Table 4.3, we summarize the results based on weather co-variables included in each of the models evaluated.

Overall, recent studies provide evidence that temperature is an important confounder in air pollution studies of mortality, and it is especially important to control for weather in studies of ozone. To date, there is no ideal model to appropriately control for temporal and weather confounding effects. Instead, studies have shown that there are significant differences for different model specifications. This is a concern, as it complicates the interpretation of these results.

4.3.3 Conclusions

Overall, studies exploring potential confounding of ozone-mortality associations by PM₁₀ and PM_{2.5} have reported conflicting evidence. Some researchers have discounted the confounding effects of PM₁₀ altogether (*e.g.*, Bell *et al.*, 2007), yet others have found that effect estimates are significantly reduced with inclusion of these pollutants (*e.g.*, Smith *et al.*, 2009, Katsouyanni *et al.*, 2009, Tao *et al.*, 2012). Therefore, studies have arrived at entirely different conclusions regarding the importance of co-pollutant confounding in the ozone-mortality associations, even when based on analyses of the same dataset (Bell *et al.*, 2007; Smith *et al.*, 2009).

Studies have also evaluated the effects of temporal trends and weather (*e.g.*, temperature) on mortality estimates (Bell and Dominici, 2008; Ren *et al.*, 2008; Zanobetti and Schwartz, 2008a; Sacks *et al.*, 2012). These remain important confounders. Some researchers have postulated that the observed heterogeneity in ozone mortality studies may be explained by these confounding effects. As there is no ideal model to

control for temporal and weather confounding effects, and ozone is particularly sensitive to model specification, this remains a significant source of uncertainty in studies that evaluate associations between ozone and mortality.

4.4 Heterogeneity

As discussed above, EPA relied heavily on the findings from large multi-city epidemiology studies of short-term ozone-mortality effects to support its upgraded causality determination for short-term ozone exposure and mortality. These studies have generally reported pooled ozone-mortality effect estimates that are small but statistically significant for all-cause mortality, with more mixed results for cause-specific mortality (*e.g.*, CV and respiratory). Importantly, most multi-city studies have reported significant heterogeneity in ozone-mortality effect estimates across cities, and some researchers have questioned the methods used to pool these divergent estimates into one overall estimate. In addition, several of the recent studies and re-analyses have explored factors that could contribute to the observed heterogeneity. For example, as part of the APHENA and NMMAPS projects, investigators assessed whether community-specific characteristics, such as race, income, unemployment, transportation use, and other factors, could explain the heterogeneity; findings have been inconclusive.

The APHENA study was conducted principally to determine the consistency among results from studies carried out in multiple cities in Canada, Europe, and the US, but it also addressed the extent of heterogeneity across cities in these different regions and possible contributing factors (Katsouyanni *et al.*, 2009). The authors used data that were collected for: 1) the APHEA2 study (Europe); 2) NMMAPS (US cities); and 3) multi-city research on the health effects of air pollution in 12 Canadian cities. Although Katsouyanni *et al.* (2009) did not present city-specific estimates, these data are available from studies that have analyzed the same multi-city databases (*e.g.*, the APHEA2 and NMMAPS projects). For example, Gryparis *et al.* (2004) presents city-specific ozone-mortality effect estimates for 23 European cities. The authors reported substantial heterogeneity across the city-specific estimates, with pooled estimates that were small and not statistically significant. In addition, only eight cities had positive ozone-mortality effect estimates for both 1- and 8-hour averaging times; only five of these were statistically significant.

Similarly, Samoli *et al.* (2009) presented results showing a large amount of heterogeneity across city-specific ozone-respiratory mortality estimates (summertime only), with only three out of the 21 cities showing significant effects either for the average 0-1 lag (Basel, London) or the distributed lag (0-20) model (the Netherlands), but not both. Notably, 11 of the 21 cities had negative or close to null results while the rest were not statistically significant, thus complicating the interpretation of the pooled results (Figure 4.2). Importantly, the estimates for the distributed lag model are more heterogeneous and much more uncertain (*i.e.*, had larger CIs), which raises questions regarding the authors' finding of large and significant pooled estimates for respiratory mortality with a distributed lag.

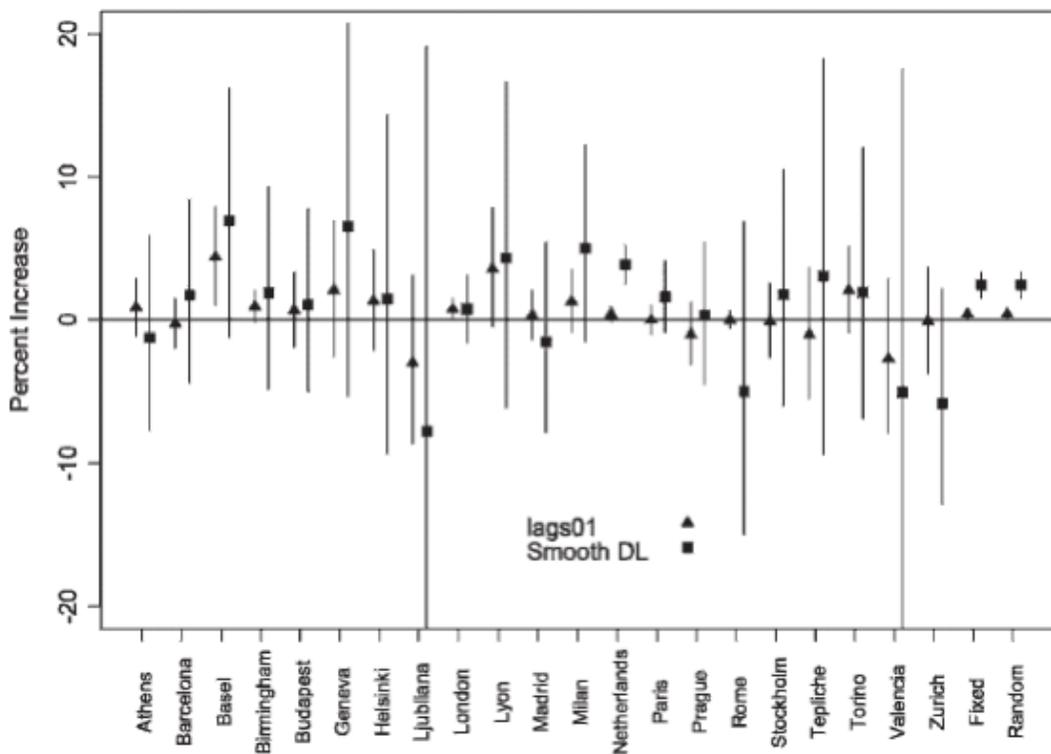


Figure 4.2 Percent Increase in Respiratory Mortality with 95% Confidence Intervals per 10 µg/m³ Increase in Ozone (8-hour Maximum) in the Summertime (June-August).
 (Source: Figure 1 from Samoli *et al.*, 2009)

Bell and Dominici (2008) assessed whether community-specific characteristics (such as race, income, urbanization, transportation use, and other factors) could explain the heterogeneity of ozone-mortality effect estimates across the 98 US communities that were part of the NMMAPS. Across all communities, the authors reported a 0.52% increase in all-cause (non-accidental) mortality (95% CI: 0.28, 0.77) for a 10 ppb increase in ozone levels from the previous week, consistent with the prior NMMAPS analysis (Bell *et al.*, 2004). However, regional results showed a great deal of heterogeneity, with a range of increases in mortality of -0.06 to 1.44% for a 10 ppb increase in ozone that generally failed to achieve statistical significance, except for the Northeast and the Industrial Midwest. Several of the community-level variables were evaluated to determine if they were effect modifiers (*i.e.*, factors that impact the magnitude of the effect when stratified by that factor). There was little change in the overall percent in mortality risk associated with a 10 ppb increase in ozone without and without these factors (range of 0.46-0.54%), and significant heterogeneity remained after adjustment for these factors. However, for several factors, the differences were statistically significant (*e.g.*, greater number of unemployed or African American, higher fraction of people using public transportation, lower temperatures, and lower prevalence of air conditioner use). Furthermore, the authors emphasized several limitations associated with their analyses, including misclassification errors associated with using community-level descriptors rather than individual-level data; use of ambient measurements as surrogates of personal exposures; and failure to include other important factors that may explain the observed heterogeneity (*e.g.*, underlying health status of the population, smoking, *etc.*).

Smith *et al.* (2009) reproduced the Bell *et al.* (2004) analysis of the NMMAPS data, presenting results for the raw mortality estimates, estimates using a regional model, and the original estimates from Bell *et al.* (2006) as Bayesian-adjusted values. As shown in Figure 4.3, both the raw ozone-mortality (with a range

of -4.1% to 6.3% per 10 ppb increase in daily ozone concentrations) and the regional estimates were more heterogeneous than the original Bayesian-adjusted estimates. Smith *et al.* (2009) further analyzed the regional ozone-mortality estimates and confirmed statistically significant differences across regions, with significant effects reported in the Midwest and Northeast, small and largely null effect estimates in the Southeast, and negative or null estimates in the rest of the US, including Southern California (which includes cities with the highest reported ozone levels). The authors noted that "quoting a single value as a national average is misleading if there is substantial heterogeneity."

Smith *et al.* (2009) also evaluated several factors that can potentially act as mortality effect modifiers, including temperature and PM₁₀. For temperature, effect modification was only significant in the summertime. Interestingly, regional analyses showed temperature effect modification to be significant only in the Northeast and Industrial Midwest regions. Similarly, PM₁₀ was found to modify the ozone-mortality effect, with a significant regional effect only in the Northeast. These results are consistent with the results from Bell *et al.* (2007), who reported that the strongest correlations between ozone and PM₁₀ were in the Northeast in the summertime.

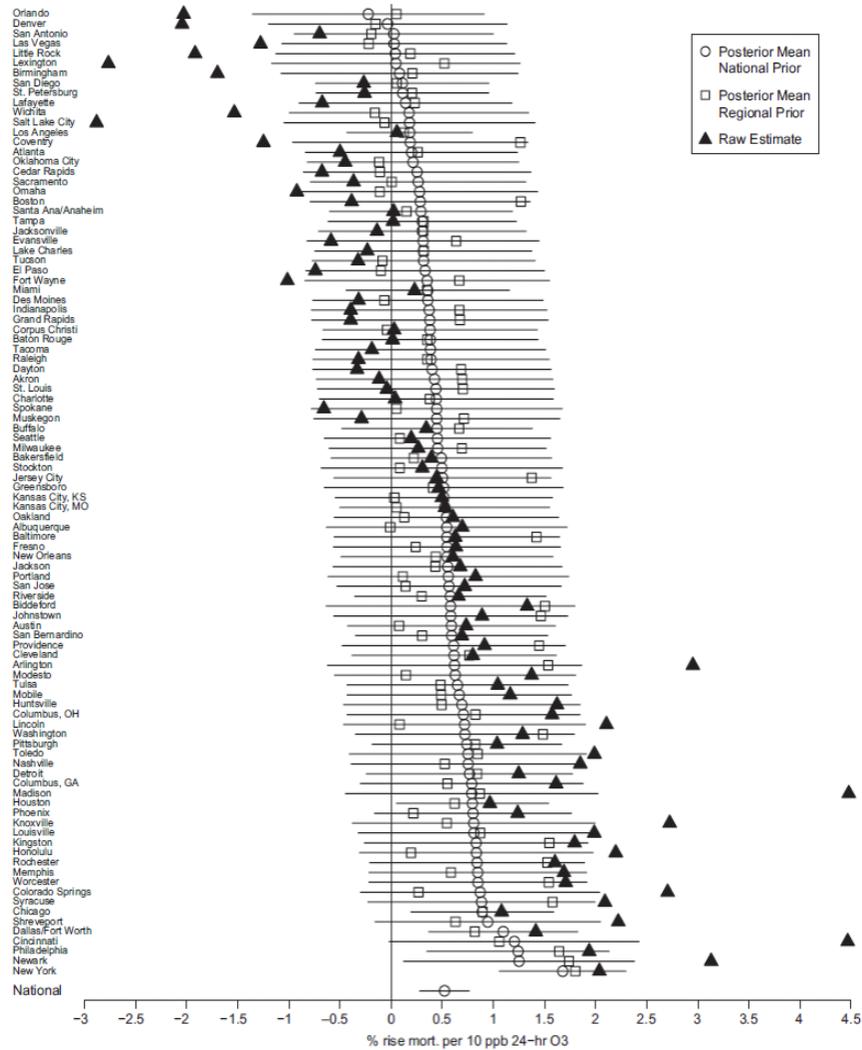


Figure 4.3 Percent Increase in All-cause Mortality per 10 ppb Increase in Daily Ozone (Year-round Analysis). The raw maximum likelihood estimates (triangles) are shown together with the Bayesian estimates (circles) from Bell *et al.* (2004) and the regional estimates (squares). (Source: Figure 1 from Smith *et al.*, 2009)

Similarly, Ren *et al.* (2008) analyzed the NMMAPS data to assess whether temperature was a significant modifier of the effects of ozone on mortality in 60 eastern US cities, finding further evidence of regional heterogeneity in ozone-mortality associations. In the Northeast, ozone exposure was reported to be significantly associated with all-cause mortality, with stronger and more significant associations across cities with higher temperatures compared with those with lower temperatures (*e.g.*, overall percent increases in mortality of 6.22, 95% CI: 4.77, 7.56 vs. 2.22, 95% CI: 1.19, 3.13). In the Southeast, however, there was little difference in the effect estimates for low and high temperatures, and estimates were not statistically significant. The authors hypothesized that the regional differences in effect modification by temperature could be explained by differences in air conditioning use and the amount of outdoor activity, which may lead to differential personal exposures in different regions. Alternatively, the authors suggested that adaptation may be a contributing factor to their findings, and modeling limitations may make it difficult to separate out the separate effects of ozone and temperature. Further, ozone may

act as a surrogate for other environmental influences related to temperature (*e.g.*, the larger photochemical mix of pollutants). As noted by the authors, "biomedical mechanisms for such interactions [between ozone, temperature and mortality] are very complex because causal pathways for both risks are unclear and the biological or physiological reactions are complicated." Overall, the patterns of regional effect modification may be indicative of confounding or due to variations in personal exposure to ozone. In any case, the issue remains unresolved, further casting doubt on the validity of pooled "national" estimates of mortality.

Zanobetti and Schwartz (2008b) conducted a time-series study using generalized linear models and controlling for season, day of the week, and temperature to evaluate the association between mortality and ozone in 48 US cities between 1989 and 2000. As with other multi-city studies, there was significant variability in city-specific total mortality effect estimates, ranging from about -4 to 13% (as estimated from Figure 4.4 shown below). The authors, however, report a small statistical measure of heterogeneity, probably due to overlapping effect estimates that occur due to the large CIs for many cities. Importantly, a large majority of the city-specific estimates were not statistically significant. As seen in Figure 4.4, only four out of the 48 cities in the study appear to have statistically significant total mortality effect estimates, and 21 estimates appear to be either negative or close to null. In contrast to the findings by Bell and Dominici (2008), income, poverty status, and central air conditioning use were not observed to modify the overall effects of ozone on CV or respiratory mortality. As with other studies, the researchers were unable to identify factors that may explain the heterogeneity in effect estimates for these cities.

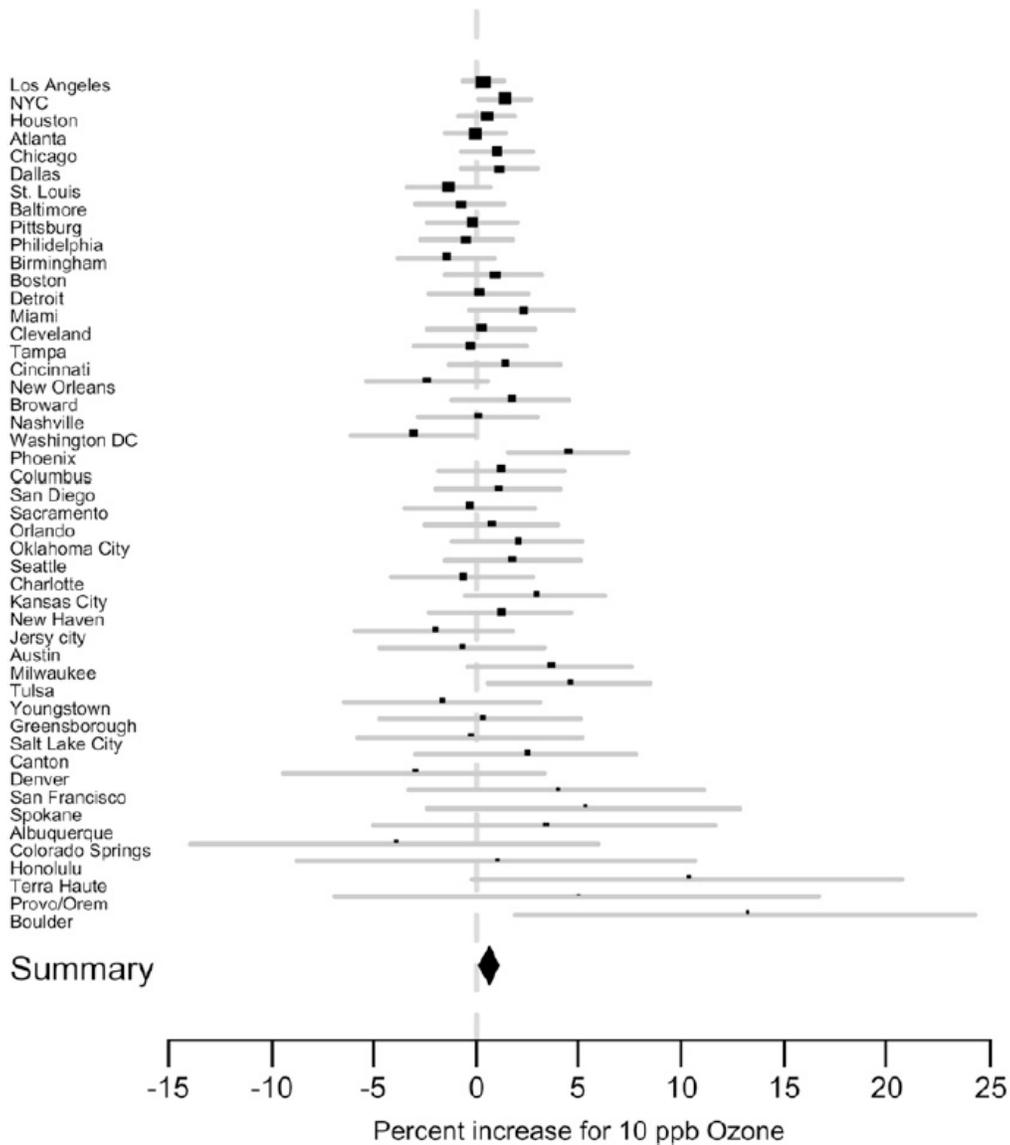


Figure 4.4 Percent Increase in Total Mortality per 10 ppb Increase in 8-hour Ozone by City (June-August). The triangle represents the pooled mortality estimate. (Source: Figure 1 from Zanobetti and Schwartz, 2008b)

Franklin and Schwartz (2008) observed a large degree of heterogeneity in community-specific effect estimates in their time-series study of 18 US communities, with null effects reported in 10 of the 18 communities, including the communities with the highest daily ozone concentrations (*i.e.*, Fresno). As mentioned previously, effect estimates were slightly reduced with adjustment for PM_{2.5} but were significantly reduced and became non-significant with adjustment for sulfate. Importantly, adjustment for sulfate affected the mortality effect estimates differentially across communities (see Figure 4.5).

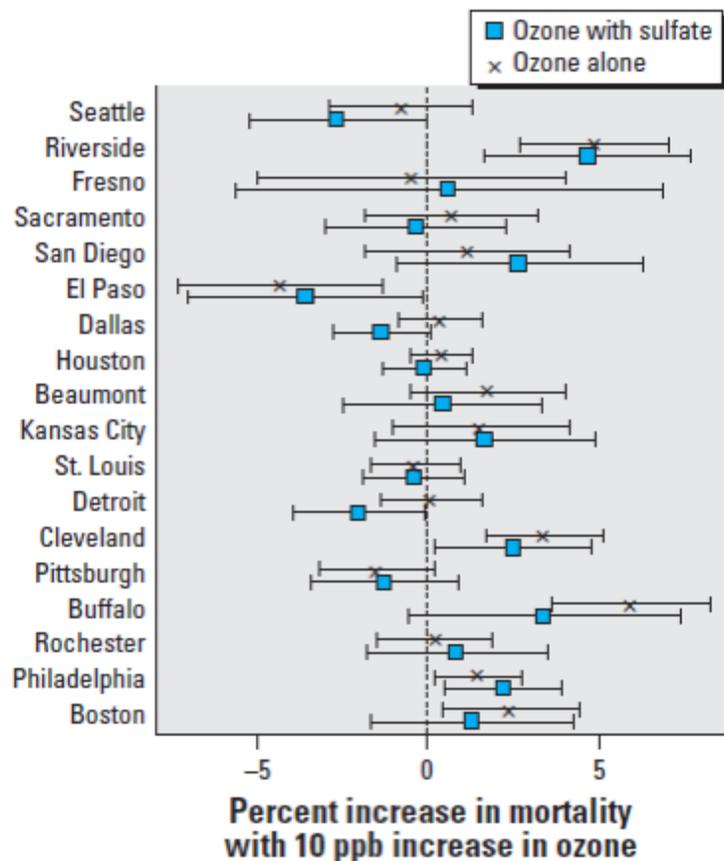


Figure 4.5 City-specific Percent Increase in Total Mortality per 10 ppb Increase in Same-day 24-hour Ozone With and Without Adjustment for Particulate Sulfate. (Source: Figure 2 from Franklin and Schwartz, 2008)

Studies conducted in Asia have also reported significant heterogeneity across studies. In the PAPA study of four Chinese cities (Bangkok, Hong Kong, Shanghai, and Wuhan), Wong (2010) reported the smallest all-cause mortality estimates for ozone compared with other pollutants that were evaluated (*i.e.*, NO₂, SO₂, and PM₁₀), ranging from 0.31-0.63% per 10 µg/m³ in 8-hour average ozone concentration (lag 0-1 day) for all ages. All estimates were statistically significant except for in the city of Wuhan, China, and were only marginally significant for Shanghai and Hong Kong (Figure 4.6). Interestingly, the smallest effect estimates for all-cause mortality were reported for the most populous cities, Shanghai (13.2 million inhabitants) and Wuhan (7.8 million inhabitants), and these cities had the highest ozone concentrations. For example, for Wuhan, the median ozone concentration for the study period was 81.5 µg/m³ (42 ppb) and the maximum was 258.5 µg/m³ (132 ppb).

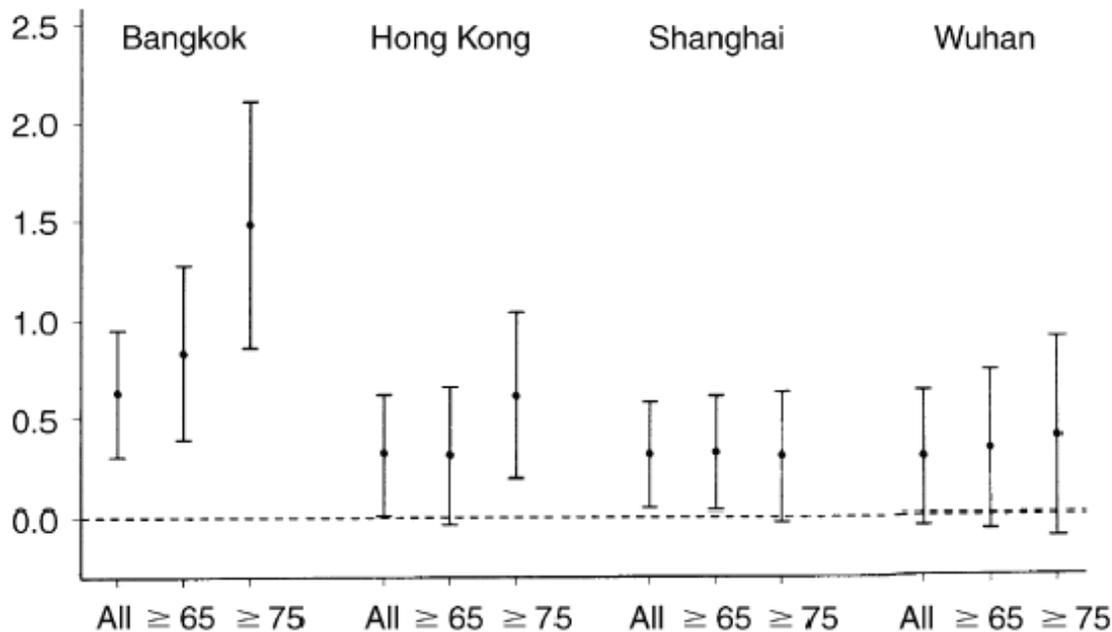


Figure 4.6 Percent Increase in All-cause Mortality with 95% Confidence Intervals per 10 $\mu\text{g}/\text{m}^3$ Ozone. (Source: Wong, 2010, Figure 4, p. 388)

In the more recent study by Tao *et al.* (2012), the authors reported total (non-accidental) mortality effect estimates that varied from 0.22-0.64% per 10 $\mu\text{g}/\text{m}^3$ increase in 8-hour average ozone concentrations (1-2 day lag) (Table A.1). The authors reported 8-hour ozone concentrations for two of the three medium-sized cities, Zhongshan and Zhuhai, that were somewhat higher [85.7 $\mu\text{g}/\text{m}^3$ (43.7 ppb) and 85.5 $\mu\text{g}/\text{m}^3$ (43.6 ppb), respectively] than for the much larger "megacity" of Guangzhou [78.2 $\mu\text{g}/\text{m}^3$ (40 ppb)] and the other medium-sized city of Foshan [70.7 $\mu\text{g}/\text{m}^3$ (36.1 ppb)]. As discussed above, the authors noted differential mortality estimates for peak and non-peak ozone exposure periods. Peak ozone periods in this subtropical/tropical area of China typically occur in the fall (September-November) with average 8-hour ozone concentrations of 117 $\mu\text{g}/\text{m}^3$ (60 ppb) and 67 $\mu\text{g}/\text{m}^3$ (34 ppb) in the non-peak season (Tao *et al.*, 2012). The authors reported counterintuitive results for total and CV mortality, observing estimates that were higher in the non-peak period in single-pollutant models. This contrasts with the results from Bell *et al.* (2004) and others who have reported the opposite findings for US and European studies. In two-pollutant models with PM_{10} , however, Tao *et al.* (2012) observed higher estimates for the peak period. This may indicate potential confounding by PM_{10} or some other factor. In the case of respiratory mortality, mortality estimates were very small and not statistically significant for the peak period, but estimates were statistically significant and much larger in the non-peak period for both single- and two-pollutant models (see Table A.3).

Other multi-city studies not included in the ISA reported significant heterogeneity in effect estimates across cities. For example, Romieu *et al.* (2012) investigated all-cause and cause-specific mortality in six Latin American cities (Sao Paulo and Rio de Janeiro, Brazil; Santiago, Chile; Mexico City, Toluca, and Monterrey, Mexico). The effect estimates for all-age, all natural-cause mortality varied from statistically significantly negative (-0.47%) in Toluca to statistically significantly positive (0.73%) in Monterrey. The all-cause mortality estimate per 10 $\mu\text{g}/\text{m}^3$ daily 8-hour maximum ozone concentration was also statistically significant in Mexico City (0.22%, 95% CI: 0.17, 0.27) and marginally significant in Sao Paulo and Rio de Janeiro (0.18%, 95% CI: 0.07, 0.28 and 0.13%, 95% CI: 0.02, 0.24, respectively) (Romieu *et al.*, 2012, Table 12). Inconsistent findings were also observed in seasonal analyses. For example, in the cold season, negative estimates were reported for the Brazilian cities and Santiago,

whereas positive and statistically significant estimates were reported for the Mexican cities. In contrast, in the warm season, significant findings were reported for the Brazilian cities and two Mexican cities (Mexico City and Monterrey) and negative results were reported Santiago. In Toluca, effects were not statistically significant in the warm season.

In conclusion, EPA relied heavily on pooled estimates of ozone-related mortality derived from large multi-city studies in the ISA, often pointing to the obvious advantage of increased statistical power to observe effects at low levels of exposure. While these studies are generally considered to be superior to meta-analyses because a similar methodology is applied to calculate effects from raw data across multiple cities, there are several limitations to relying on pooled estimates. As discussed above, researchers have found that city-specific estimates vary from city to city; this variability is clearly not captured in the pooled estimates, which this has raised questions about the appropriateness of their use. There is also a need to better understand the observed heterogeneity of risk estimates across cities and regions; this remains an important area of research. Until heterogeneity is better understood, including an understanding the divergent trends in observed effect estimates (*e.g.*, higher mortality estimates in non-peak periods in Asia *vs.* in peak periods in US and European cities), confounders or effect modifiers (either known or unknown) cannot be ruled out.

4.5 Measurement Error

A significant source of uncertainty in epidemiology studies of mortality associations with short-term ozone exposures is measurement error. Exposure measurement error refers to the uncertainty associated with the estimated exposure that is used to represent the personal exposure of an individual or population. Measurement error can bias effect estimates toward or away from the null. All of the epidemiology ozone mortality studies evaluated in the ISA, as well as more recent studies not included in the ISA, rely on data from central ambient monitoring sites to provide community-average ambient ozone exposure concentrations to represent personal exposures. These central-site ambient monitors, however, are poor measures of individual exposures, and thus exposure measurement error is a major source of uncertainty in these studies.

Personal ozone exposures are typically much lower than ambient ozone levels and, more importantly, often show little or no correlation with concentrations measured at the central ambient sites. For example, for a Baltimore-based cohort of 56 subjects, Sarnat *et al.* (2001) reported no correlation between ambient and personal ozone measurements in winter or summertime sampling periods. For a similarly designed study conducted in Boston, Sarnat *et al.* (2005) reported comparable results, finding no correlation between ambient and personal ozone concentrations for wintertime sampling data (correlation slope of 0.04) and only a moderate correlation between ambient and personal ozone concentrations for summertime sampling data (0.27).

Brauer *et al.* (2002) discussed the effect of measurement error on the detection thresholds for health effects. The authors conducted simulations with varying individual thresholds to determine how measurement error affected the ability to detect a non-linear exposure-response relationship or a threshold for PM_{2.5} and sulfate using personal exposure data and ambient monitoring data from Vancouver, Canada. Results showed that personal exposures were more highly correlated with ambient levels of sulfate as opposed to PM_{2.5}. In the PM_{2.5} simulation, there was no threshold seen at the lowest value of the threshold parameter (20 µg/m³), even though no effects were observed in individuals at or below this level. The authors concluded that a threshold can be obscured at the population level – even if there is a threshold at the individual level – when surrogate measures of air pollutants (in the form of ambient concentrations) are not highly correlated with personal exposures (Brauer *et al.*, 2002). Although this

study did not investigate ozone specifically, issues with measurement error from central ambient air monitors also apply to ozone.

Exposure measurement error most likely influences the shapes of the ozone-mortality CRF. Gradient recently assessed how the various kinds of exposure measurement error can contribute to bias in CRFs (Rhombert *et al.*, 2011). In this study, we demonstrated the importance of investigating potential biases in air pollution CRFs that may be caused by exposure measurement error. For example, Meng *et al.* (2005) hypothesized that potential biases can arise in PM_{2.5} associations because of seasonal variations in infiltration behavior. Their data showed that seasonal differences in infiltration behavior not only coincide with fluctuations in ambient particle concentrations, but they also vary with location. In particular, in summertime, when PM_{2.5} concentrations are generally higher, Meng *et al.* (2005) observed an increase in infiltration factors in New Jersey homes due to the opening of windows to increase home ventilation, but a reduction in infiltration factors in Texas homes as people instead relied on air conditioners. Meng *et al.* (2005) further suggested that exposure measurement error from differences in infiltration behavior possibly could contribute to bias in chronic health studies because its size can differ between communities and differentially impact the personal ambient relationships – *e.g.*, mean ambient PM_{2.5} concentrations could be higher in City A *vs.* City B but, due to differences in particle infiltration behavior in the two cities, mean exposures to ambient PM_{2.5} could be higher in City B *vs.* City A.

Although Meng *et al.* (2005) developed this hypothetical scenario for PM_{2.5}, like the Brauer *et al.* (2002) evaluation, it is entirely applicable – if not more likely – for ozone. For ozone, it is well established that relatively weak personal-ambient ozone correlations and low personal-ambient attenuation factors are a function of the interplay of a number of individual-, season-, and city-specific factors, including time-activity patterns, building characteristics, and ventilation practices. In the ISA, EPA discussed how ambient ozone concentrations and the relationship between personal ozone exposure and ambient concentrations show strong seasonal influences. Because ozone concentrations are typically higher during the summertime, ozone infiltration into indoor spaces can be at a maximum in communities relying upon the opening of windows for ventilation and cooling; thus, differences between central-site ambient ozone measurements and personal ozone exposures are minimized. In communities that rely upon air conditioning for cooling, however, ozone infiltration into indoor spaces can be at a minimum during the warm season, resulting in greater differences between central-site ambient ozone measurements and personal ozone exposures.

Exposure measurement error likely occurs in all ozone mortality studies discussed here, yet none of these studies address it adequately. Although EPA acknowledged this source of uncertainty in the ISA, it was not given sufficient weight in the evaluation and interpretation of study results.

4.6 Ozone Concentration-response Function

Several recent epidemiology studies have conducted analyses to determine the shape of the CRF and the possible existence of a threshold for ozone mortality. It is well recognized that such analyses are complicated by the noise in the observational data and uncertainties in the statistical models, which may hide the existence of a threshold. Specifically, as noted by EPA (2013), the interpretation of pooled ozone-mortality CRFs is complicated by the heterogeneity in effect estimates across regions and cities, as well as the uncertainties associated with the appropriate lag periods and averaging times. EPA (2013) stated in the ISA that "a national or combined analysis may not be appropriate to identify whether a threshold exists in the [ozone]-mortality [CRF]" (p. 6-257). Thus, EPA (2013) concluded that "the evaluation of the [ozone]-mortality C-R relationship did not find any evidence that supports a threshold for the association between short-term exposure to [ozone] and mortality" (p. 6-257).

Despite this conclusion in the ISA, EPA described several recent studies that evaluated the ozone-mortality C-R relationship (Bell *et al.*, 2006; Xia and Tong, 2006; Stylianou and Nicolich, 2009; Katsouyanni *et al.*, 2009). Bell *et al.* (2006) applied four statistical methods to the NMMAPS data to assess whether a threshold exists for ozone-mortality (using a 24-hour ozone averaging period): 1) a subset analysis in which the ozone-mortality association is assessed below a specific concentration (*e.g.*, 5-60 ppb); 2) a threshold analysis, which assumes that the ozone-mortality association is only observed above a certain value; and 3) and 4) two different non-linear models using natural cubic splines. The authors reported that, for a 10 ppb increase in ambient ozone concentrations, a threshold was observed at around 10 ppb for 24-hour average ozone concentrations; however, there was a large amount of uncertainty in the mortality estimates at levels below about 30 ppb (as shown in Figure 2 of Bell *et al.*, 2006), making it difficult to interpret the findings below 30 ppb. Similarly, using the spline approach, the authors concluded that the CRF was near linear at concentrations above 10 ppb, with no association evident below these levels. As shown below in Figure 4.7, however, the shape of the curve does not appear linear and effect estimates become statistically significant only at about 40 ppb, indicating that ozone-mortality estimates below that level are highly uncertain.

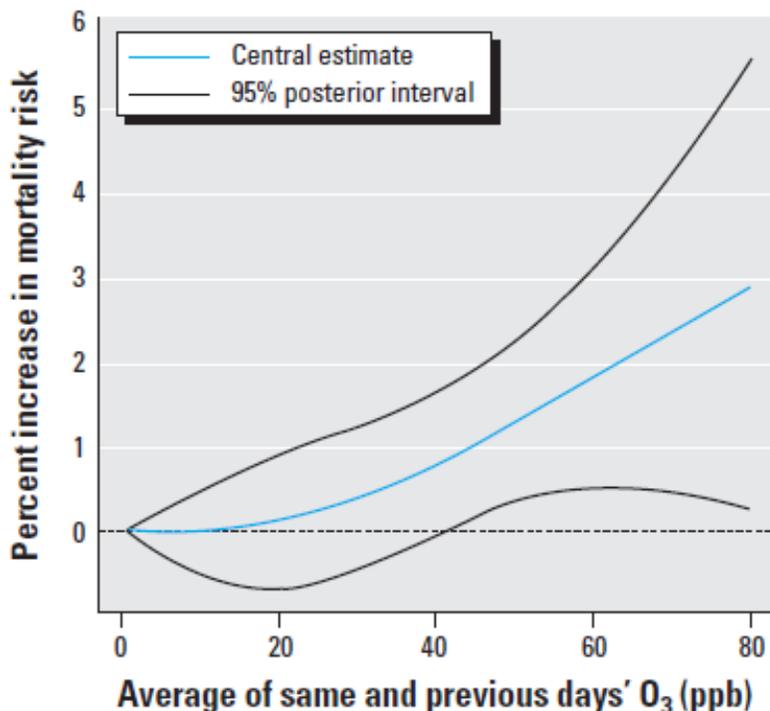


Figure 4.7 Combined Concentration-response Curve for Ozone and Non-accidental Mortality Using Non-linear Spline Approach. Results showing the percent increase in daily (24-hour average.) non-accidental mortality at various ozone concentrations. (Source: Figure 3 from Bell *et al.*, 2006)

Both Stylianou and Nicolich (2009) and Xia and Tong (2006) reported the existence of thresholds. Xia and Tong (2006) applied an updated generalized additive model (GAM), which accounted for cumulative and non-linear effects of ozone, and found evidence of a threshold at 25 ppb ozone for circulatory and respiratory mortality in Hong Kong and for CV mortality in three US cities (Chicago, Illinois, El Paso, Texas, and Pittsburgh, Pennsylvania), based on a 24-hour ozone averaging time. In another study,

Stylianou and Nicolich (2009) used the same model proposed by Xia and Tong (2006) to investigate a potential threshold in nine major US cities that were part of NMMAPS but used a 3-day weighted mean concentration of ozone. The authors found evidence of thresholds for ozone-associated total mortality, but the results varied across cities. Importantly, the relative risk functions varied in shape and direction across cities, including negative functions across most of the ozone concentration range in Miami, Los Angeles, and Seattle. Overall, the authors found an average threshold concentration at which the mortality relative risk was positive and statistically significantly of 32 ppb (range: 21-44 ppb, 6 cities) for total mortality, 28 ppb for CV mortality (range: 16-38 ppb, 4 cities), and 25 ppb (range: 17-39 ppb, 3 cities) for respiratory mortality.

In the ISA, EPA did not present the findings of another recent study by Smith *et al.* (2009) that provides evidence of a threshold. Smith *et al.* (2009) evaluated the ozone-mortality association above various cutoffs in the range of 15-60 ppb. The authors reported different slopes within the three brackets they evaluated (0-40, 40-60, and 60-80 ppb), indicating a non-linear CRF. The authors noted that the finding of statistically significant mortality effects at very low levels of ozone is not consistent with clinical studies of human lung function response to ozone, which show no effects at 40 ppb (*e.g.*, Adams, 2006). The biological plausibility of low ozone effects has also been questioned by researchers (*e.g.*, Vedal *et al.*, 2003).

Wong (2010) investigated the relationship between mortality and short-term ozone in four cities in Asia, including Wuhan, Shanghai, and Hong Kong, China, and Bangkok, Thailand. The authors calculated combined city estimates and performed city-specific analyses to evaluate heterogeneity between the four cities. As shown in Figure 4.8., the CRFs for all-cause mortality differed between cities, and Bangkok appeared to be the only city with a near-linear CRF. Shanghai and Wuhan showed an absence of linearity between 50 and 100 $\mu\text{g}/\text{m}^3$ ozone (~26 to ~52 ppb), where the function appeared to be almost flat.

Several studies that were not included in the ISA have investigated the ozone-mortality CRF (Atkinson *et al.*, 2012; Yang *et al.*, 2012). Atkinson *et al.* (2012) specifically investigated the CRF in five urban and five rural cities in the UK. The authors found evidence of a threshold in London of 65 $\mu\text{g}/\text{m}^3$ (33 ppb) and one of the rural communities (Aston Hill) of 88 $\mu\text{g}/\text{m}^3$ (45 ppb). In seasonal (summer-only) analyses, there was evidence of threshold ozone levels in both urban and rural areas. The authors evaluated linear, linear-threshold, and spline models. They applied statistical tests for linearity and found limited evidence for linearity, but CRFs were non-linear, at least for a portion of the ozone concentration range, and the CRF varied by region (urban or rural) and season. The authors also reported effect modification in sensitivity analyses with temperature, with no observed mortality effects for mean temperatures below 20°C. Yang *et al.* (2012) also reported CRFs for ozone-mortality in the Chinese city of Suzhou. They found linear relationships for total and CV mortality, but no associations for respiratory mortality.

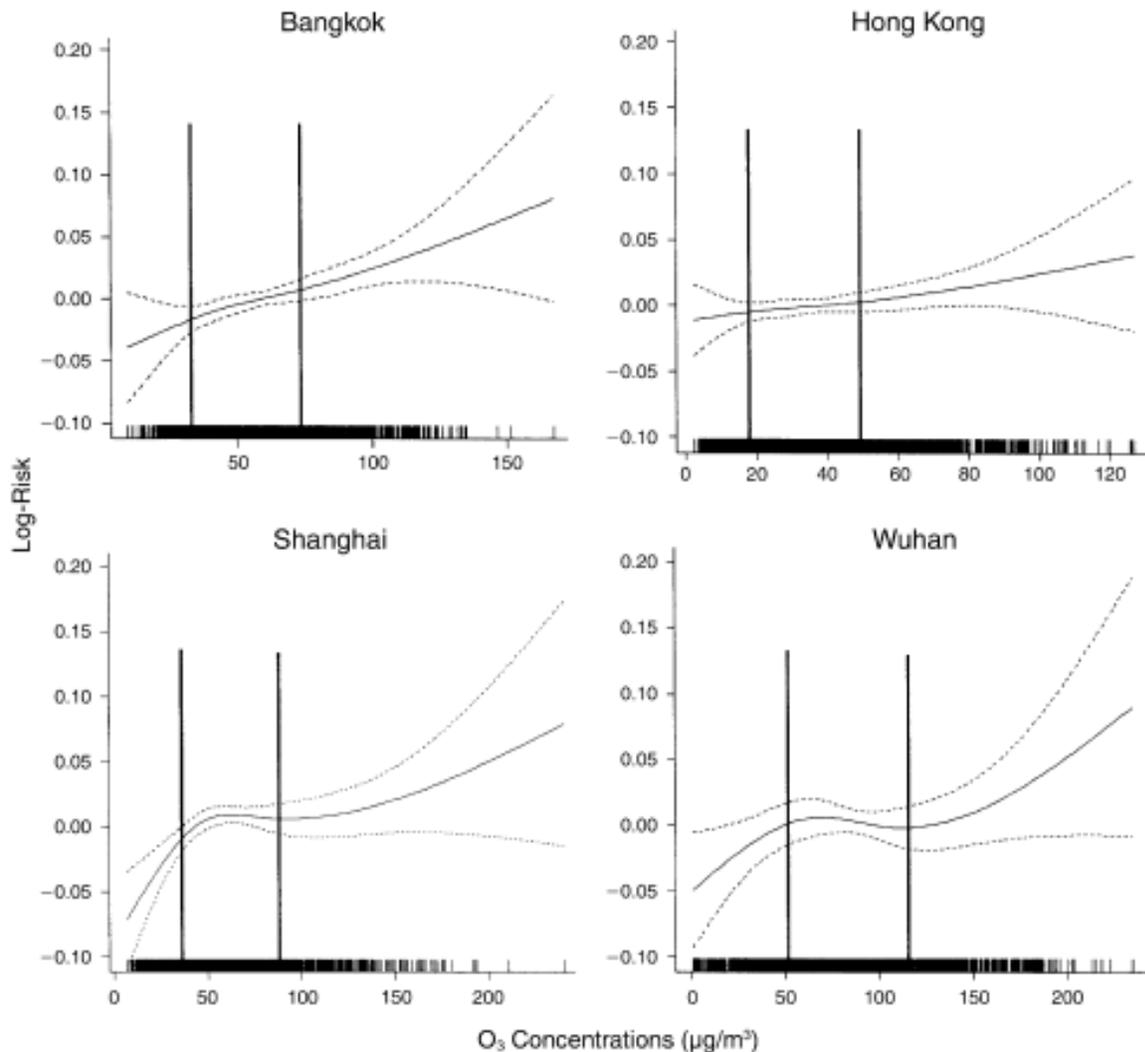


Figure 4.8 Concentration-response Curves for 3 Chinese Cities and 1 Thai City (Adapted from Wong, 2010)

There are several factors that limit the ability of studies to assess ozone CRFs and potential thresholds. As discussed in Section 4.5, it is well known that exposure measurement error can bias regression results, which tends to flatten and apparently linearize the CRF (Rhomberg *et al.*, 2011). For ozone, which has been shown to have poor correlations between ambient and personal exposure, Brauer *et al.* (2002) reported that the use of poorly correlated ambient air measurements as a surrogate for personal exposure obscures the ability to detect thresholds. Heterogeneity across cities also makes it difficult to identify a threshold (Rhomberg *et al.*, 2011). As discussed in Section 4.4, all of the multi-city studies observed substantial heterogeneity in mortality effect estimates across cities.

In the ISA, EPA concluded that there is no evidence to support a threshold for short-term ozone exposure and mortality, yet several studies have found evidence of non-linearities and possible ozone thresholds, even considering the uncertainties described above that make it difficult to discern a threshold. At present, methodological limitations make it difficult to evaluate CRFs in epidemiology studies, however, both the controlled human exposure studies and proposed modes of actions of ozone effects support the existence of a threshold at exposures at least as high as the current NAAQS.

5 Conclusions

In the 2013 ozone ISA, EPA upgraded its causality determinations for short-term ozone exposure and all-cause and CV mortality to likely to be causal. It also maintained that there is a causal relationship between short-term ozone exposure and respiratory effects, including respiratory mortality. However, EPA generally failed to provide adequate justification for these upgrades. The ozone-mortality epidemiology studies available since the 2006 AQCD do not substantially add to the overall body of findings and are not sufficiently robust to support the upgrade. In particular, many studies on which EPA relied are simply extensions or re-analyses of previous analyses, and, as such, do not constitute new evidence. In addition, results are not consistent across studies.

Important sources of uncertainty that were identified in the 2006 AQCD, including model specification (*e.g.*, lags), confounding, exposure measurement error, and linearity assumptions for the ozone-mortality CRF, remain in the studies evaluated in the ISA, as well as studies published since the ISA was completed. In fact, new studies confirm rather than resolve these uncertainties; EPA appears to have downplayed this. One of the most significant unresolved issues involves the substantial heterogeneity among city-specific ozone-mortality effects, which raises questions regarding the practice of pooling estimates of mortality across a large number of cities. Importantly, the reasons for the observed variability across cities and regions remains poorly understood. Studies have also reported conflicting evidence for confounding effects, and the proper control for confounding effects from temperature is not well established. Lastly, a remaining challenge is how to interpret results considering exposure measurement error. This source of bias results from the use of central-site monitors to represent personal exposures, which tend to be poorly correlated, especially for ozone exposures

Overall, the epidemiology evidence regarding short-term ozone exposure is not supportive of EPA's upgraded causality determinations for all-cause and CV mortality nor for maintaining a causal determination for respiratory mortality. New studies fall short of resolving major uncertainties and, without a well understood (if even plausible) biological mode of action, the weight of evidence remains limited or suggestive at best. EPA should reconsider these causality determinations.

References

Adams, WC. 2006. "Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses." *Inhal. Toxicol.* 18(2):127-136.

Anderson, GB; Bell, ML. 2010. "Does one size fit all? The suitability of standard ozone exposure metric conversion ratios and implications for epidemiology." *J. Expo. Sci. Environ. Epidemiol.* 20(1):2-11.

Atkinson, RW; Yu, D; Armstrong, BG; Pattenden, S; Wilkinson, P; Doherty, RM; Heal, MR; Anderson, HR. 2012. "Concentration-response function for ozone and daily mortality: Results from five urban and five rural U.K. populations." *Environ. Health Perspect.* 120(10):1411-1417.

Bell, ML; Dominici, F. 2008. "Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 US communities." *Am. J. Epidemiol.* 167(8):986-997.

Bell, ML; Dominici, F; Samet, JM. 2005. "A meta-analysis of time-series studies of ozone and mortality with comparison to the National Morbidity, Mortality, and Air Pollution Study." *Epidemiology* 16(4):436-445.

Bell, ML; Kim, JY; Dominici, F. 2007. "Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies." *Environ. Health Perspect.* 115(11):1591-1595.

Bell, ML; McDermott, A; Zeger, SL; Samet, JM; Dominici, F. 2004. "Ozone and short-term mortality in 95 US urban communities, 1987-2000." *JAMA* 292:2372-2378.

Bell, ML; Peng, RD; Dominici, F. 2006. "The exposure-response curve for ozone and risk of mortality and the adequacy of current ozone regulations." *Environ. Health Perspect.* 114(4):352-356.

Brauer, M; Brumm, J; Vedal, S; Petkau, AJ. 2002. "Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects." *Risk Anal.* 22(6):1183-1193

Brown, J. [US EPA]. 2013. Email to S. Sax (Gradient) re: Standardization of ozone mortality estimates. 2p., April 30.

Burnett, RT; Goldberg, MS. 2003. "Size-fractionated particulate mass and daily mortality in eight Canadian cities." In Health Effects Institute. 2003. "Revised Analyses of Time Series Studies of Air Pollution and Health." p85-89.

Cakmak, S; Dales, RE; Rubio, MA; Vidal, CB. 2011. "The risk of dying on days of higher air pollution among the socially disadvantaged elderly." *Environ. Res.* 111(3):388-393.

Cheng, Y; Kan, H. 2012. "Effect of the interaction between outdoor air pollution and extreme temperature on daily mortality in Shanghai, China." *J. Epidemiol.* 22(1):28-36.

de Almeida, SP; Casimiro, E; Calheiros, J. 2011. "Short-term association between exposure to ozone and mortality in Oporto, Portugal." *Environ. Res.* 111(3):406-410.

Dominici, F; McDermott, A; Daniels, M; Zeger, SL; Samet, JM. 2005. "Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities." *J. Toxicol. Environ. Health A* 68(13-14):1071-1092.

Faustini, A; Stafoggia, M; Cappai, G; Forastiere, F. 2012. "Short-term effects of air pollution in a cohort of patients with chronic obstructive pulmonary disease." *Epidemiology* 23(6):861-879.

Folinsbee, LJ; Bedi, JF; Horvath, SM. 1980. "Respiratory responses in humans repeatedly exposed to low concentrations of ozone." *Am. Rev. Respir. Dis.* 121(3):431-439.

Franklin, M; Schwartz, J. 2008. "The impact of secondary particles on the association between ambient ozone and mortality." *Environ. Health Perspect.* 116(4):453-458.

Garrett, P; Casimiro, E. 2011. "Short-term effect of fine particulate matter (PM_{2.5}) and ozone on daily mortality in Lisbon, Portugal." *Environ. Sci. Pollut. Res. Int.* 18(9):1585-1592.

Gryparis, A; Forsberg, B; Katsouyanni, K; Analitis, A; Touloumi, G; Schwartz, J; Samoli, E; Medina, S; Anderson, HR; Niciu, E; Wichmann, H-E; Kriz, B; Kosnik, M; Skorkovsky, J; Vonk, JM; Dortbudak, Z. 2004. "Acute effects of ozone on mortality from the "Air Pollution and Health: A European Approach" project." *Am. J. Respir. Crit. Care Med.* 170:1080-1087.

Hamade, AK; Misra, V; Rabold, R; Tankersley, CG. 2010. "Age-related changes in cardiac and respiratory adaptation to acute ozone and carbon black exposures: Interstrain variation in mice." *Inhal. Toxicol.* 22(Suppl. 2):84-94.

Health Effects Institute (HEI). 2003. "Revised Analyses of Time-Series Studies of Air Pollution and Health." 306p., May.

Hunova, I; Maly, M; Rezacova, J; Branis, M. 2013. "Association between ambient ozone and health outcomes in Prague." *Int. Arch. Occup. Environ. Health* 86(1):385-394.

Ito, K; De Leon, SF; Lippmann, M. 2005. "Associations between ozone and daily mortality: Analysis and meta-analysis." *Epidemiology* 16(4):446-457.

Katsouyanni, K; Samet, JM; Anderson, HR; Atkinson, R; Le Tertre, A; Medina, S; Samoli, E; Touloumi, G; Burnett, RT; Krewski, D; Ramsay, T; Dominici, F; Peng, RD; Schwartz, J; Zanobetti, A. 2009. "Air Pollution and Health: A European and North American Approach (APHENA)." HEI Research Report 142. 132p., October 29.

Kim, SY; Lee, JT; Hong, YC; Ahn, KJ; Kim, H. 2004. "Determining the threshold effect of ozone on daily mortality: An analysis of ozone and mortality in Seoul, Korea, 1995-1999." *Environ. Res.* 94(2):113-119.

Langstaff, J. 2003. Email to J. Pinto re: Percentiles of 1996-2000 ozone concentrations. 22p., September 17.

- Levy, JI; Chemerynski, SM; Sarnat, JA. 2005. "Ozone exposure and mortality: An empiric Bayes metaregression analysis." *Epidemiology* 16(4):458-468.
- Medina-Ramon, M; Schwartz, J. 2008. "Who is more vulnerable to die from ozone air pollution?" *Epidemiology* 19(5):672-679.
- Meng, QY; Turpin, BJ; Korn, L; Weisel, CP; Morandi, M; Colome, S; Zhang, JJ; Stock, T; Spektor, D; Winer, A; Zhange, L; Lee, JH; Giovanetti, R; Cui, W; Kwon, J; Alimokhtari, S; Shendell, D; Jones, J; Farrar, C; Maberti, S. 2005. "Influence of ambient (outdoor) sources on residential indoor and personal PM2.5 concentrations: Analyses of RIOPA data." *J. Expo. Anal. Environ. Epidemiol.* 15:17-28.
- Moshhammer, H; Hutter, HP; Kundi, M. 2013. "Which metric of ambient ozone to predict daily mortality?" *Atmos. Environ.* 65:171-176.
- Ostro, BD; Feng, WY; Broadwin, R; Malig, BJ; Green, RS; Lipsett, MJ. 2008. "The impact of components of fine particulate matter on cardiovascular mortality in susceptible subpopulations." *Occup. Environ. Med.* 65(11):750-756.
- Pascal, M; Wagner, V; Chatignoux, E; Falq, G; Corso, M; Blanchard, M; Host, S; Larrieu, S; Pascal, L; Declercq, C. 2012. "Ozone and short-term mortality in nine French cities: Influence of temperature and season." *Atmos. Environ.* 62:566-572.
- Ren, C; Williams, GM; Mengersen, K; Morawska, L; Tong, S. 2008. "Does temperature modify short-term effects of ozone on total mortality in 60 large eastern US communities? An assessment using the NMMAPS data." *Environ. Int.* 34(4):451-458.
- Reyna, MA; Bravo, ME; Lopez, R; Nieblas, EC; Nava, ML. 2012. "Relative risk of death from exposure to air pollutants: A short-term (2003-2007) study in Mexicali, Baja California, México." *Int. J. Environ. Health Res.* 22(4):370-386.
- Rhomberg, LR; Chandalia, JK; Long, CM; Goodman, JE. 2011. "Measurement error in environmental epidemiology and the shape of exposure-response curves." *Crit. Rev. Toxicol.* 41(8):651-671.
- Romieu, I; Gouveia, N; Cifuentes, LA; de Leon, AP; Junger, W; Vera, J; Strappa, V; Hurtado-Diaz, M; Miranda-Soberanis, V; Rojas-Bracho, L; Carbajal-Arroyo, L; Tzintzun-Cervantes, G. 2012. "Multicity Study of Air Pollution and Mortality in Latin America (The ESCALA Study)." HEI Research Report 171. Accessed on March 20, 2013 at <http://pubs.healtheffects.org/view.php?id=389>, 120p., October.
- Sacks, JD; Ito, K; Wilson, WE; Neas, LM. 2012. "Impact of covariate models on the assessment of the air pollution-mortality association in a single- and multipollutant context." *Am. J. Epidemiol.* 176(7):622-634.
- Samet, JM; Zeger, SI; Dominici, F; et al. 2000. "The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity, mortality, and air pollution in the United States." Health Effects Institute (Cambridge, MA), HEI Research Report 94, Part II. 84p., June.
- Samoli, E; Analitis, A; Touloumi, G; Schwartz, J; Anderson, HR; Sunyer, J; Bisanti, L; Zmirou, D; Vonk, JM; Pekkanen, J; Goodman, P; Paldy, A; Schindler, C; Katsouyanni, K. 2005. "Estimating the exposure-response relationships between particulate matter and mortality within the APHEA multicity project." *Environ. Health Perspect.* 113(1):88-95.

- Samoli, E; Zanobetti, A; Schwartz, J; Atkinson, R; LeTertre, A; Schnindler, C; Perez, L; Cadum, E; Pekkanen, J; Paldy, A; Touloumi, G; Katsouyanni, K. 2009. "The temporal pattern of mortality responses to ambient ozone in the APHEA project." *J. Epidemiol. Community Health* 63(12):960-966.
- Sarnat, JA; Brown, KW; Schwartz, J; Coull, BA; Koutrakis, P. 2005. "Ambient gas concentrations and personal particulate matter exposures: Implications for studying the health effects of particles." *Epidemiology* 16:385-395.
- Sarnat, JA; Schwartz, J; Catalano, PJ; Suh, HH. 2001. "Gaseous pollutants in particulate matter epidemiology: Confounders or surrogates?" *Environ. Health Perspect.* 109(10):1053-1061.
- Schwartz, J. 2005. "How sensitive is the association between ozone and daily deaths to control for temperature?" *Am. J. Respir. Crit. Care Med.* 171:627-631.
- Shang, Y; Sun, Z; Cao, J; Wang, X; Zhong, L; Bi, X; Li, H; Liu, W; Zhu, T; Huang, W. 2013. "Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality." *Environ. Int.* 54:100-111.
- Smith, RL; Xu, B; Switzer, P. 2009. "Reassessing the relationship between ozone and short-term mortality in U.S. urban communities." *Inhal. Toxicol.* 21(Suppl. 2):37-61.
- Son, JY; Lee, JT; Kim, H; Yi, O; Bell, ML. 2012. "Susceptibility to air pollution effects on mortality in Seoul, Korea: A case-crossover analysis of individual-level effect modifiers." *J. Expo. Sci. Environ. Epidemiol.* 22(3):227-234.
- Stafoggia, M; Forastiere, F; Faustini, A; Biggeri, A; Bisanti, L; Cadum, E; Cernigliaro, A; Mallone, S; Pandolfi, P; Serinelli, M; Tessari, R; Vigotti, MA; Perucci, CA. 2010. "Susceptibility factors to ozone-related mortality: A population-based case-crossover analysis." *Am. J. Respir. Crit. Care Med.* 182(3):376-384.
- Stylianou, M; Nicolich, MJ. 2009. "Cumulative effects and threshold levels in air pollution mortality: Data analysis of nine large US cities using the NMMAPS dataset." *Environ. Pollut.* 157(8-9):2216-2223.
- Tao, Y; Huang, W; Huang, X; Zhong, L; Lu, SE; Li, Y; Dai, L; Zhang, Y; Zhu, T. 2012. "Estimated acute effects of ambient ozone and nitrogen dioxide on mortality in the Pearl River Delta of southern China." *Environ. Health Perspect.* 120(3):393-398.
- Thurston, GD; Ito, K. 2001. "Epidemiological studies of acute ozone exposures and mortality." *J. Expo. Anal. Environ. Epidemiol.* 11(4):286-294.
- US EPA. 2006. "Air Quality Criteria for Ozone and Related Photochemical Oxidants (Volume I of III)." National Center for Environmental Assessment-RTP Division, EPA 600/R-05/004aF. Accessed on December 15, 2010 at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923>, 821p., February.
- US EPA. 2013. "Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Final)." National Center for Environmental Assessment (NCEA), EPA/600/R-10/076F. 1251p., February.
- Vedal, S; Brauer, M; White, R; Petkau, J. January 2003. "Air pollution and daily mortality in a city with low levels of pollution." *Environ. Health Perspect.* 111(1):45-51.

Wong, CM. 2010. "Public Health and Air Pollution in Asia (PAPA): A combined analysis of four studies of air pollution and mortality." HEI Research Report 154 Part 5. In Public Health and Air Pollution in Asia (PAPA): Coordinated Studies of Short-Term Exposure to Air Pollution and Daily Mortality in Four Cities. Health Effects Institute, Boston, MA. Accessed on August 03, 2012 at <http://pubs.healtheffects.org/getfile.php?u=595,p377-431>., November.

Xia, Y; Tong, H. 2006. "Cumulative effects of air pollution on public health." *Stat. Med.* 25 (20):3548-3559.

Yang, C; Yang, H; Guo, S; Wang, Z; Xu, X; Duan, X; Kan, H. 2012. "Alternative ozone metrics and daily mortality in Suzhou: The China Air Pollution and Health Effects Study (CAPES)." *Sci. Total Environ.* 426:83-89.

Zanobetti, A; Schwartz, J. 2008a. "Is there adaptation in the ozone mortality relationship: A multi-city case-crossover analysis." *Environ. Health* 7:22.

Zanobetti, A; Schwartz, J. 2008b. "Mortality displacement in the association of ozone with mortality: An analysis of 48 cities in the United States." *Am. J. Respir. Crit. Care Med.* 177(2):184-189.

Zanobetti, A; Schwartz, J. 2008c. "Temperature and mortality in nine US cities." *Epidemiology* 19(4):563-570.

Zanobetti, A; Schwartz, J. 2009. "The effect of fine and coarse particulate air pollution on mortality: A national analysis." *Environ. Health Perspect.* 117(6):898-903.

Appendix A

Summary of Studies of Short-term Ozone Exposure and Mortality

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Key Studies Included in the ISA (Year-round Analyses)										
Bell <i>et al.</i> (2004)	NMMAPS, 95 US cities	40% of US pop (NR)	1987-2000	Overdispersion linear	24-hr avg	(DL) 0-6	None	10 ppb	0.52	0.27, 0.77
						0			0.24	0.11, 0.39¹
						1			0.17	0.05, 0.17¹
						2			0.15	0.02, 0.26¹
						3			0.05	-0.07, 0.17 ¹
Gryparis <i>et al.</i> (2004)	APHEA2, 23 European cities	>50 mil. (6-347/d)	At least 3 years post-1990	GAM	1-hr max	0-1	None	10 µg/m ³	0.10	-0.11, 0.26
					8-hr max	0-1	None		0.03	-0.18, 0.21
Schwartz (2005)	14 US cities	NR (>1 mil.)	1986-1993	Log linear	1-hr max	0	None	10 ppb	0.23	0.01, 0.44
							Temp		0.19	0.03, 0.35
Bell <i>et al.</i> (2007)	NMMAPS, 98 US cities	NR (NR)	1987-2000	Log linear	24-hr avg	0-1	None	10 ppb	0.32	0.17, 0.46
							PM _{2.5}		0.21	-0.22, 0.64
Bell and Dominici (2008)	NMMAPS, 98 US cities	Mean 996,300 per city (NR)	1987-2000	Bayesian hierarchical regression	24-hr avg	0-6	None	10 ppb	0.52	0.28, 0.77
							PM ₁₀		0.52	0.27, 0.77
							PM _{2.5}		0.53	0.28, 0.78
	NMMAPS, industrial Midwest		1987-2000	Bayesian hierarchical regression	24-hr avg	0-6	None	10 ppb	0.73	0.11, 1.35
									1.44	0.78, 2.10
									0.08	-0.92, 1.09
									0.21	-0.46, 0.88
									0.38	-0.07, 0.85
									-0.06	-0.92, 0.81
Urban Midwest	1987-2000	Bayesian hierarchical regression	24-hr avg	0-6	None	10 ppb	-0.05	-1.28, 1.19		

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Kaysouyanni <i>et al.</i> (2009)	APHENA-Europe	200,000-~7 mil (NR)	1990-1997	GLM, natural splines, 8 <i>df</i>	1-hr max	DL (0-2)	None	10 µg/m ³	0.21	0.06, 0.37
						1	PM ₁₀		0.16	0.06, 0.25
				DL (0-2)		None	0.14		-0.01, 0.29	
				1		PM ₁₀	0.09		0.00, 0.18	
	APHENA-Canada	100,000->2 mil (NR)	1987-1996	GLM, natural splines, 8 <i>df</i>	1-hr max	DL (0-2)	None		0.73	0.23, 1.2
						1	PM ₁₀		0.4	-0.28, 1.1
				DL (0-2)		None	0.79		0.30, 1.30	
				1		PM ₁₀	0.67		0.05, 1.30	
	APHENA-US	250,000->9 mil (NR)	1987-1996	GLM, natural splines, 8 <i>df</i>	1-hr max	DL (0-2)	None		0.38	0.14, 0.61
						1	PM ₁₀		0.13	-0.18, 0.44
				DL (0-2)		None	0.54		0.16, 0.92	
				1		PM ₁₀	0.68		0.38, 0.98	
Wong (2010)	PAPA (4 cities, Asia)	NR (Mean: 8.1-16.2/d/city)	1996-2004	GLM, natural splines	8-hr max	0-1	None, all cities	10 µg/m ³	0.38	0.23, 0.53
Cakmak <i>et al.</i> (2011)	Chile, 7 cities	421,000-1.3 mil (NR)	1997-2007	Log-linear (Poisson), natural splines	8-hr max	DL (0-6)	None	36 ppb	4.59	1.50, 7.79
							Age <64 yrs		3.25	-0.70, 7.33
							65-74		3.25	-1.82, 8.43
							75-84		7.05	1.39, 12.7
							≥85		6.11	1.19, 11.1
Key Studies Not Included in the ISA (Year-round Analyses)										
de Almeida <i>et al.</i> (2011)	Oporto Metropolitan Area, Portugal	1.2 mil (NR)	2000-2004	GAM, penalized spines	8-hr max	1	All ages	10 µg/m ³	0.89	0.32, 1.47
							>65 yrs		1.04	0.38, 1.71

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Garrett and Casimiro (2011)	Lisbon, Portugal	0.5 mil (NR)	2004-2006	GAM	1-hr max	2	All ages	10 µg/m ³	0.96	0.56, 1.34
							≥65 yrs		1.11	0.58, 1.63
Hunova <i>et al.</i> (2013)	Prague, Czech Republic	1.2 mil (915/day)	2002-2006	Negative binomial regression	24-hr avg	1	None	10 µg/m ³	0.60	-0.50, 1.69
					8-hr max				0.00	-0.80, 0.80
					24-hr avg	2			-0.10	-0.90, 0.70
					8-hr max				0.00	-0.60, 0.50
Atkinson <i>et al.</i> (2012)	United Kingdom, 5 urban and 5 rural areas	≥10,000 per city (NR)	1993-2006	Linear, urban	8-hr max	0-1	None	10 µg/m ³	0.48	0.35, 0.60
		<10,000 per town (NR)		Linear, rural					0.58	0.36, 0.81
Cheng and Kan (2012)	Shanghai, China	6.3 mil (173,911)	2001-2004	GAM, penalized splines	8-hr avg	0 ²	15 th %ile temp ³	10 µg/m ³	2.17	1.46, 2.88
							85 th %ile ³		0.42	0.05, 0.79
							15 th -85 th %ile ³		0.66	0.32, 1.00
Pascal <i>et al.</i> (2012)	Nine urban areas in France	245,000-6 mil per city (724,289)	1998-2006	Time-stratified case-crossover	8-hr max	0 ²	None	10 µg/m ³	0.30	0.10, 0.50
							PM _{2.5}		0.50	0.20, 0.80
Reyna <i>et al.</i> (2012)	Mexicali, Baja California, Mexico	856,000 (Mean: 9/day)	2003-2007	Log-linear (Poisson)	24-hr avg	7	None	0.016 ppm	-1.71	-0.50, 1.28
Romieu <i>et al.</i> (2012)	Latin America, 9 cities	34 mil. (103,557)	1997-2005	Linear, fixed effect	24-hr avg	0-3	None	10 µg/m ³	0.22	0.18, 0.26
				Linear, random effects					0.16	-0.02, 0.33
Son <i>et al.</i> (2012)	Seoul, South Korea	NR (261,952)	2000-2007	Logistic regression	8-hr max	0-1	None	14.5 ⁴ ppb	0.51	-0.44, 1.46

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Tao <i>et al.</i> (2012)	Southern China, 4 cities	14.1 mil (NR)	2006-2008	GLM w/Poisson	8-hr avg	1-2	None	10 µg/m ³	0.81	0.63, 1.00
							PM ₁₀		0.54	0.34, 0.75
							NO ₂		0.43	0.23, 0.64
							SO ₂		0.70	0.51, 0.90
							CO		0.72	0.53, 0.91
Yang <i>et al.</i> (2012)	Suzhou, China	2.1 mil (37,571)	2006-2008	GAM w/ penalized splines	1-hr max	1	None	70.6 µg/m ³	1.84	0.07, 3.60
					8-hr max			59.6 µg/m ³	2.15	0.36, 3.93
					24-hr avg			33.3 µg/m ³	1.33	-0.37, 3.03
					1-hr max	1	PM ₁₀	70.6 µg/m ³	0.99	-0.78, 2.75
					8-hr max			59.6 µg/m ³	1.43	-0.36, 3.22
					24-hr avg			33.3 µg/m ³	0.93	-0.77, 2.63
Moshammer <i>et al.</i> (2013)	Vienna, Austria	1.5 mil (NR)	1991-2009	GAM w/Poisson	1-hr max	0	None	10 µg/m ³	0.57	0.41, 0.73
						1			0.56	0.39, 0.73
						2			0.20	0.00, 0.41
					8-hr max	0			0.60	0.42, 0.78
						1			0.51	0.31, 0.70
						2			0.27	0.03, 0.50
					24-hr avg	0			0.51	0.28, 0.74
						1			0.09	-0.14, 0.33
						2			-0.12	-0.37, 0.14
						0			1.04	0.81, 1.45
						NO ₂				
Key Studies Included in the ISA (Seasonal Analyses)⁵										
Bell <i>et al.</i> (2004) ⁶	NMMAPS, 95 US cities	40% of US pop (NR)	1987-2000	Overdispersion linear	24-hr avg	(DL) 0-6	None	10 ppb	0.39	0.13, 0.65
Gryparis <i>et al.</i> (2004)	APHEA2, 21 European cities	>50 mil. (6-347/d)	At least 3 years post-1990	GAM	8-hr max	0-1	None	10 µg/m ³	0.31	0.17, 0.52
							SO ₂		0.31	0.13, 0.51
							NO ₂		0.23	0.07, 0.41
							PM ₁₀		0.27	0.08, 0.49
							CO		0.44	0.29, 0.59

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Kim <i>et al.</i> (2004)	Seoul, South Korea	NR (NR)	1995-1999	Linear	1-hr max	1	None	21.5 ppb	1.88	0.52, 3.23
				Threshold					3.76	1.98, 5.53
Schwartz (2005) ⁶	14 US cities	NR (>1 mil.)	1986-1993	Log-linear	1-hr max	0	None	10 ppb	0.26	0.07, 0.44
							Temp		0.37	0.11, 0.62
Bell and Dominici (2008)	NMMAPS, 98 US cities	Mean 996,300 per city (NR)	1987-2000	Bayesian hierarchical regression	24-hr avg	0-6	None	10 ppb	0.52	0.28, 0.76
Zanobetti and Schwartz (2008a)	48 US cities	> 2.7 mil (6.9 mil)	1989-2000	Logistic regression	8-hr max	0	None	10 ppb	0.50	0.38, 0.62
Zanobetti and Schwartz (2008b)	48 US cities	106,000-8 mil/city (1.6 mil)	1989-2000	GLM	8-hr max	0-3	None	10 ppb	0.53	0.28, 0.77
						0			0.32	0.20, 0.43
						0-20			0.51	0.05, 0.96
						4-20			-0.02	-0.35, 0.31
						0	Mean temp at 25 th %ile		0.56	-0.09, 1.21
Medina-Ramon and Schwartz (2008)	48 US cities	NR (>2.7 mil)	1989-2000	Pooled city-specific logistic regression	8-hr max	0-2	None	10 ppb	0.65	0.38, 0.93
							≥65 yrs		1.10	0.44, 1.77
							Women only		0.58	0.18, 0.98
Stafoggia <i>et al.</i> (2010)	Adults >35 y.o. in 10 Italian cities	NR (127,860)	2001-2005	Linear	8-hr max	DL (0-5)	None	10 µg/m ³	1.50	0.90, 2.10
							PM ₁₀		1.50	0.90, 2.20

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Samoli <i>et al.</i> (2009)	APHEA2, 21 European cities	>60 mil. (>571,798)	At least 3 years post-1990	Linear regression, fixed effects	8-hr max	0	None	10 µg/m ³	0.28	0.11, 0.45
						0-1			0.24	0.15, 0.34
						0-20, U	None		0.01	-0.40, 0.41
						0-20, P			0.01	-0.41, 0.42
				Random effects		0	None		0.28	0.07, 0.48
						0-1			0.22	0.08, 0.35
						0-20, U	None		-0.54	-1.28, 0.20
						0-20, P			-0.56	-1.30, 0.19
Katsouyanni <i>et al.</i> (2009)	APHENA-Europe	200,000-~7 mil (NR)	1990-1997	GLM, natural splines	1-hr max	DL (0-2)	None	10 µg/m ³	0.30	0.11, 0.49
	APHENA-Canada	>100,000-~2 mil (NR)	1987-1996			1	PM ₁₀		0.16	0.02, 0.29
					1-hr max	DL (0-2)	None		0.42	0.16, 0.67
						1	PM ₁₀		NR	NR
					APHENA-US	>250,000-~9 mil (NR)	1987-1996		1-hr max	DL (0-2)
	1	PM ₁₀	0.24							-0.10, 0.58
Franklin and Schwartz (2008)	18 US cities	NR (>424,000)	2000-2005	Log-linear (Poisson)	24-hr avg	0	None	10 ppb	0.89	0.45, 1.33
Key Studies Not Included in the ISA (Seasonal Analyses)⁵										
de Almeida <i>et al.</i> (2011)	Oporto Metropolitan Area, Portugal	1.2 mil (NR)	2000-2004	GAM, penalized spines	8-hr max	1	All ages	10 µg/m ³	0.95	0.30, 1.60
							>65 yrs		0.99	0.24, 1.75

Table A.1 Epidemiology Studies of Short-term Ozone Exposure and All-cause Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Atkinson <i>et al.</i> (2012)	United Kingdom, 5 urban and 5 rural areas	≥10,000 per city (NR)	1993-2006	Linear, urban	8-hr max	0-1	Mean temp	10 µg/m ³	0.65	0.39, 0.91
		<10,000 per town (NR)		Linear, rural					0.46	-0.01, 0.92
Faustini <i>et al.</i> (2012)	Rome, Italy	145,681 (15,884)	2005-2009	Log-linear (Poisson)	8-hr max	0-5	None	27.1 µg/m ³	0.40	-2.10, 3.10
Pascal <i>et al.</i> (2012)	Nine urban areas in France	245,000-6 mil per city (724,289)	1998-2006	Time-stratified case-crossover	8-hr max	0 ²	None	10 µg/m ³	0.80	0.50, 1.20
							PM _{2.5}		0.70	-0.10, 1.50
Reyna <i>et al.</i> (2012)	Mexicali, Baja California, Mexico	856,000 (Mean: 9/day)	2003-2007	Log-linear (Poisson)	24-hr avg	7	None	0.015 ppm	-1.82	-5.01, 1.28
Tao <i>et al.</i> (2012)	Southern China, 4 cities	14.1 mil (NR)	2006-2008	GLM w/Poisson	8-hr avg	1-2	None	10 µg/m ³	0.65	0.27, 1.02
							PM ₁₀		0.77	0.32, 1.22
Yang <i>et al.</i> (2012)	Suzhou, China	2.1 mil (37,571)	2006-2008	GAM w/ penalized splines	1-hr max	1	None, warm season	70.6 µg/m ³	0.42	-1.84, 2.68
					8-hr max			59.6 µg/m ³	0.66	-1.67, 2.98
					24-hr avg			33.3 µg/m ³	0.37	-1.73, 2.46
					1-hr max		None, cool season	70.6 µg/m ³	4.45	1.34, 7.55
					8-hr max			59.6 µg/m ³	5.07	1.91, 8.22
					24-hr avg			33.3 µg/m ³	2.20	-0.90, 5.29
Moshammer <i>et al.</i> (2013)	Vienna, Austria	1.5 mil (NR)	1991-2009	GAM w/Poisson	1-hr max	0	None	10 µg/m ³	0.15⁷	0.08, 0.22
					8-hr max				0.13⁷	0.05, 0.20
					24-hr avg				0.09 ⁷	-0.02, 0.19

Notes:

Bolded results are statistically significant.

(1) Estimated from figure in original study using GetData Graph Digitizer.

(2) Lag 0 assumed.

(3) Cheng and Kan (2012) examined the effects of various percentiles of temperature; "normal" temperature which corresponds to the 15th-85th percentiles are shown.

(4) Calculated using the mean and standard deviation provided in the study report (Son *et al.*, 2012).

(5) Estimates are for the warm season only, unless otherwise specified.

(6) Estimates adjusted for PM₁₀ are not shown, authors noted no change in mortality effect estimates (Bell *et al.*, 2004; Schwartz, 2005).

(7) Estimate from Figure 2 in study report (Moshammer *et al.*, 2013). Aug. PM_{2.5} = augmented PM_{2.5}, or PM_{2.5} concentrations predicted using the coefficient of haze and NO₂ concentrations.

CO = carbon monoxide; df = degree of freedom; DL = distributed lag; GAM = generalized additive model; GLM = generalized linear model; NO₂ = nitrogen dioxide; NR = not reported; P = penalized distributed lag; PACF = partial autocorrelation function; PM = particulate matter; pop. = population; SO₂ = sulfur dioxide; U = unconstrained distributed lag.

Table A.2 Epidemiology Studies of Short-term Ozone Exposure and Respiratory Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age (yrs)	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval	
Key Studies Included in the ISA (Year-round Analyses)												
Katsouyanni <i>et al.</i> (2009)	APHENA- Europe	200,000- ~7 mil (NR)	1990-1997	All ages	GLM, natural splines, 8 <i>df</i>	1-hr max	DL (0-2)	None	10 µg/m ³	0.23	-0.28, 0.75	
				≥75			0.14			-0.45, 0.74		
				All			1			PM ₁₀	0.18	-0.13, 0.48
				≥75			0.07			-0.28, 0.42		
				All ages			DL (0-2)			None	0.01	-0.50, 0.51
				≥75			-0.09			-0.67, 0.49		
	All	GLM, penalized splines, PACF	1	PM ₁₀	0.04	-0.25, 0.33						
	≥75		-0.06	-0.44, 0.31								
	All		DL (0-2)	None	0.13	-1.60, 1.90						
	≥75		-0.6	-2.70, 1.60								
	All		1	PM ₁₀	2.6	-1.70, 7.10						
	≥75		0.16	-2.80, 3.20								
	APHENA- Canada	100,000- >2 mil (NR)	1987-1996	All	GLM, natural splines, 8 <i>df</i>	DL (0-2)	None	0.30	-1.40, 2.00			
				≥75		-0.14		-2.20, 2.00				
				All		1		PM ₁₀	1.20	-0.92, 3.50		
				≥75		0.14		-2.50, 2.90				
				All		DL (0-2)		None	0.32	-0.43, 1.08		
				≥75		0.14		-0.85, 1.13				
	APHENA-US	250,000- >9 mil (NR)	1987-1996	All	GLM, natural splines, 8 <i>df</i>	1	PM ₁₀	0.44	-0.55, 1.43			
				≥75		0.36	-0.79, 1.50					
				All		DL (0-2)	None	-0.71	-1.82, 0.41			
				≥75		-1.16	-2.57, 0.24					
				All		1	PM ₁₀	-0.89	-2.11, 0.33			
				≥75		-0.71	-2.22, 0.81					

Table A.2 Epidemiology Studies of Short-term Ozone Exposure and Respiratory Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age (yrs)	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Wong (2010)	PAPA (4 cities, Asia)	NR (Mean: 8.1- 16.2/d/city)	1996-2004	All ages	GLM, natural splines	8-hr max	0-1	None, all cities	10 µg/m ³	0.34	-0.07, 0.75
								None, 3 Chinese cities		0.23	-0.22, 0.68
								None		0.99	-0.99, 1.98
	NO ₂	0.98	-0.75, 2.10								
	SO ₂	0.99	-0.98, 1.99								
	PM ₁₀	0.97	-0.73, 1.99								
	Bangkok only ¹	NR (Mean: 8.1/d/city)	1999-2003	Key Studies Not Included in the ISA (Year-round Analyses)							
de Almeida <i>et al.</i> (2011)	Oporto Metropolitan Area, Portugal	1.2 mil (NR)	2000-2004	All ages	GAM, penalized spines	8-hr max	1	None	10 µg/m ³	1.05	-0.45, 2.57
				>65 yrs						1.16	-0.42, 2.78
Cheng and Kan (2012)	Shanghai, China	6.3 mil (173,911)	2001-2004		GAM, penalized splines	8-hr avg	0	15 th %ile temp ²	10 µg/m ³	2.79	1.13, 4.46
								85 th %ile ²		0.53	-0.46, 1.53
								15 th -85 th %ile ²		0.81	-0.09, 1.72
Pascal <i>et al.</i> (2012)	Nine urban areas in France	245,000-6 mil per city (724,289)	1998-2006	All	Time- stratified case- crossover	8-hr max	0	None	10 µg/m ³	0.0	-1.10, 1.10
								PM _{2.5}		0.0	-1.50, 1.60
Romieu <i>et al.</i> (2012)	Latin America, 9 cities	34 mil (103,557)	1997-2005	All	Linear, fixed effects	24-hr avg	DL (0-3)	All ages	10 µg/m ³	0.21	0.10, 0.31
								≥65 yrs		0.12	0.00, 0.24
					All ages			0.21		0.10, 0.31	
					≥65 yrs			0.11		-0.04, 0.27	
Son <i>et al.</i> (2012)	Seoul, South Korea	NR (261,952)	2000-2007	Adults ≥35 yrs	Logistic regression	8-hr max	0-1	None	14.5 ³ ppb	2.04	-1.91, 6.15

Table A.2 Epidemiology Studies of Short-term Ozone Exposure and Respiratory Mortality

Study	Cohort/Region	Pop. (Deaths)	Time Period	Age (yrs)	Model	Averaging Time	Lag (d)	Co-pollutants/Co-variates	Increment	% Change	95% Confidence Interval
Tao <i>et al.</i> (2012)	Southern China, 4 cities	14.1 mil (NR)	2006-2008	All	GLM w/Poisson	8-hr avg	1-2	None	10 µg/m ³	1.33	0.89, 1.76
								PM ₁₀		0.87	0.39, 1.36
								NO ₂		0.58	0.10, 1.06
								SO ₂		1.16	0.71, 1.61
								CO		1.17	0.72, 1.61
Yang <i>et al.</i> (2012)	Suzhou, China	2.1 mil (37,571)	2006-2008	All	GAM w/penalized splines	1-hr max	1	None	70.6 µg/m ³	-3.95	-9.04, 1.13
						8-hr max			59.6 µg/m ³	-1.85	-6.91, 3.22
						24-hr avg			33.3 µg/m ³	-2.30	-7.09, 2.50
						1-hr max	1	PM ₁₀	70.6 µg/m ³	-4.38	-9.46, 0.71
						8-hr max			59.6 µg/m ³	-2.26	-7.39, 2.86
						24-hr avg			33.3 µg/m ³	-2.46	-7.26, 2.33
Moshammer <i>et al.</i> (2013)	Vienna, Austria	1.5 mil (NR)	1991-2009	All	GAM w/Poisson	1-hr max	0	None	10 µg/m ³	1.29	0.55, 2.04
						8-hr max				1.29	0.43, 2.15
						24-hr avg				1.07	0.01, 2.15
Key Studies Included in the ISA (Seasonal Analyses)⁴											
Gryparis <i>et al.</i> (2004)	21 European cities	>50 mil. (6-347/d)	At least 3 years post-1990	All	GAM	8-hr max	0-1	None	10 µg/m ³	1.13	0.74, 1.51
						1-hr max	0-1	None		1.13	0.62, 1.48
Samoli <i>et al.</i> (2009)	21 European cities	>60 mil. (>571,798)	At least 3 years post-1990	NR	Linear regression, fixed effects	8-hr max	0	None	10 µg/m ³	0.36	-0.21, 0.94
							0-1			0.40	0.11, 0.70
							0-20, U			3.35	1.90, 4.83
							0-20, P			3.66	2.25, 5.08
					Random effects	8-hr max	0	None	10 µg/m ³	0.36	-0.21, 0.94
							0-1			0.40	0.11, 0.70
							0-20, U			3.35	1.90, 4.83
							0-20, P			3.66	2.25, 5.08

Table A.2 Epidemiology Studies of Short-term Ozone Exposure and Respiratory Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age (yrs)	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval	
Zanobetti and Schwartz (2008b)	48 US cities	106,000- 8 mil/city (1.6 mil)	1989-2000	All	GLM	8-hr max	0	None	10 ppb	0.54	0.26, 0.81	
							0-20			0.61	-0.41, 1.65	
							0-3			0.83	0.38, 1.28	
							4-20			-0.24	-1.08, 0.60	
Katsouyanni <i>et al.</i> (2009)	APHENA-US	250,000- >9 mil (NR)	1987-1996	All ages	GLM, natural splines	1-hr max	DL (0-2)	None	10 µg/m ³	0.55	-0.27, 1.37	
				>75			0.51	-0.55, 1.57				
				All ages			0.87	-0.45, 2.19				
				>75	1		PM ₁₀	0.56		-1.00, 2.12		
				All ages	GLM, penalized splines		DL (0-2)	None		0.73	-0.39, 1.85	
				<75			0.79	-0.65, 2.23				
				All ages			1	PM ₁₀		0.99	-0.33, 2.31	
	<75	0.72	-0.88, 2.32									
	APHENA- Canada	100,000- >2 mil (NR)	1987-1996	All ages	GLM	1-hr max	DL (0-2)	None		3.0	1.60, 4.50	
	≥75	2.3	0.28, 4.40									
	APHENA- Europe	200,000- ~7 mil (NR)	1990-1997	All ages	GLM, natural splines	1-hr max	DL (0-2)	None		0.48	-0.17, 1.13	
				≥75						0.31	-0.44, 1.06	
				All ages						1	PM ₁₀	0.15
				≥75	-0.02					-0.46, 0.43		
All ages				GLM, penalized splines	DL (0-2)				None	0.57	-0.08, 1.22	
≥75					0.43				-0.32, 1.18			
All ages					1				PM ₁₀	0.20	-0.19, 0.58	
≥75	0.05	-0.39, 0.50										
Stafoggia <i>et al.</i> (2010)	10 Italian cities	NR (127,860)	2001-2005	Adults >35	Linear	8-hr max	DL (0-5)	None	10 µg/m ³	2.8	0.3, 5.3	
								PM ₁₀		1.5	-1.2, 4.4	

Table A.2 Epidemiology Studies of Short-term Ozone Exposure and Respiratory Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age (yrs)	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Key Studies Not Included in the ISA (Seasonal Analyses)⁴											
de Almeida <i>et al.</i> (2011)	Oporto Metropolitan Area, Portugal	1.2 mil (NR)	2000-2004	All ages	GAM, penalized spines	8-hr max	1	None	10 µg/m ³	1.48	-1.34, 2.33
				>65 yrs						1.50	-1.42, 2.46
Faustini <i>et al.</i> (2012)	Rome, Italy	145,681 (15,884)	2005-2009	Adults ≥35	Log-linear (Poisson)	8-hr max	0-5	None	27.1 µg/m ³	4.10	-6.70, 16.3
Hunova <i>et al.</i> (2013)	Prague, Czech Republic	1.2 mil (915/day)	2002-2006	All	Negative binomial regression	24-hr avg	1	PM ₁₀	10 µg/m ³	7.70	3.05, 12.4
						8-hr max				3.92	0.50, 7.33
						24-hr avg	2			3.92	0.60, 7.23
						8-hr max				3.34	0.90, 5.83
Pascal <i>et al.</i> (2012)	Nine urban areas in France	245,000-6 mil per city (724,289)	1998-2006	All	Time- stratified case- crossover	8-hr max	0	None	10 µg/m ³	-0.20	-2.10, 1.80
								PM _{2.5}		-1.50	-4.60, 1.70
Tao <i>et al.</i> (2012)	Southern China, 4 cities	14.1 mil (NR)	2006-2008	All	GLM w/Poisson	8-hr avg	1-2	None	10 µg/m ³	0.24	-0.63, 1.13
								PM ₁₀		0.08	-0.98, 1.16

Notes:

Bolded results are statistically significant.

(1) These values estimated from Figure 10 in study report (Wong, 2010).

(2) Cheng and Kan (2012) examined the effects of various percentiles of temperature; results for "normal" temperature which corresponds to the 15th-85th percentiles are shown.

(3) Calculated using the mean and standard deviation provided in the study report.

(4) Warm season only unless otherwise specified.

CO = carbon monoxide; df = degree of freedom; DL = distributed lag; GAM = generalized additive model; GLM = generalized linear model; P = penalized distributed lag; NO₂ = nitrogen dioxide; NR = not reported; PACF = partial autocorrelation function; PM = particulate matter; pop. = population; SO₂ = sulfur dioxide; U = unconstrained distributed lag.

Table A.3 Epidemiology Studies of Short-term Ozone Exposure and Cardiovascular Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval			
Key Studies Included in the ISA (Year-round Analyses)														
Wong (2010)	PAPA (4 cities, Asia)	NR (Mean: 7.0- 6.2/d/city)	1996- 2004	All	GLM, natural splines	8-hr max	0-1	None, all cities	10 µg/m ³	0.37	0.01, 0.73			
								None, 3 Chinese cities		0.29	-0.09, 0.68			
	Bangkok only	NR (Mean: 8.1/d/city)	1999- 2003					None		0.80	0.00, 1.60			
								NO ₂		0.25	-0.85, 1.25			
								SO ₂		0.85	0.00, 1.75			
								PM ₁₀		0.10	-0.90, 1.10			
Katsouyanni <i>et al.</i> (2009)	APHENA-US	250,000- >9 mil (NR)	1987- 1996	≥75	GLM, natural splines, 8 <i>df</i>	1-hr max	DL (0-2)	None	10 µg/m ³	0.29	-0.17, 0.75			
				<75			0.48			-0.02, 0.98				
				≥75			GLM, penalized splines, PACF	1		PM ₁₀	0.06	-0.60, 0.72		
				<75				DL (0-2)		None	0.17	-0.47, 0.82		
				≥75	DL (0-2)		None	-0.68			-1.36, -0.01			
				<75	1			PM ₁₀		-0.23	-0.94, 0.47			
				≥75	GLM, natural splines, 8 <i>df</i>		DL (0-2)	None		-0.97	-1.83, -0.11			
				<75			1			PM ₁₀	-0.17	-0.8, 0.46		
	≥75	GLM, penalized splines, PACF	DL (0-2)	None			1.10	0.095, 2.20						
	<75		1				PM ₁₀	0.87		-0.35, 2.10				
	APHENA- Canada	100,000- >2 mil (NR)	1987- 1996	≥75	GLM, natural splines, 8 <i>df</i>		None	DL (0-2)		None	10 µg/m ³	0.24	-1.20, 1.70	
				<75				1				PM ₁₀	-0.34	-2.00, 1.40
				≥75			GLM, penalized splines, PACF	DL (0-2)		None		1.30	0.28, 2.30	
				<75				1				PM ₁₀	0.92	-0.26, 2.10
				≥75	GLM, natural splines, 8 <i>df</i>		DL (0-2)	None		0.15		-1.1, 1.4		
				<75			1			PM ₁₀		0.07	-1.4, 1.6	
				≥75			GLM, penalized splines, PACF	DL (0-2)		None		0.26	-0.03, 0.54	
				<75				1				PM ₁₀	0.25	-0.14, 0.64
	APHENA- Europe	200,000- ~7 mil (NR)	1990- 1997	≥75	GLM, natural splines, 8 <i>df</i>		None	DL (0-2)		None		10 µg/m ³	0.15	-0.07, 0.37
				<75				1					PM ₁₀	0.22
				≥75			GLM, penalized splines, PACF	DL (0-2)		None			0.13	-0.15, 0.41
				<75				1					PM ₁₀	0.25
				≥75	GLM, natural splines, 8 <i>df</i>		DL (0-2)	None		0.06			-0.15, 0.28	
				<75			1			PM ₁₀			0.21	-0.04, 0.45
≥75				GLM, penalized splines, PACF		DL (0-2)	None	0.26	-0.03, 0.54					
<75						1		PM ₁₀	0.25	-0.14, 0.64				

Table A.3 Epidemiology Studies of Short-term Ozone Exposure and Cardiovascular Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval	
Key Studies Not Included in the ISA (Year-round Analyses)												
Garrett and Casimiro (2011)	Lisbon, Portugal	0.5 mil (NR)	2004-2006	All ages	GAM	1-hr max	2	None	10 µg/m ³	1.95	1.18, 2.72	
				≥65						1.84	1.03, 2.64	
de Almeida <i>et al.</i> (2011)	Oporto Metropolitan Area, Portugal	1.2 mil (NR)	2000-2004	All ages	GAM, penalized splines	8-hr max	1	None	10 µg/m ³	0.93	0.12, 1.74	
				≥65						1.18	0.32, 2.06	
Cheng and Kan (2012)	Shanghai, China	6.3 mil (173,911)	2001-2004	NR	GAM, penalized splines	8-hr avg	0	15 th %ile temp ¹	10 µg/m ³	2.57	1.53, 3.62	
								85 th %ile ¹		0.62	0.06, 1.18	
								15 th -85 th %ile ¹		0.88	0.37, 1.40	
Pascal <i>et al.</i> (2012)	Nine urban areas in France	245,000-6 mil per city (724,289)	1998-2006	All	Time-stratified case-crossover	8-hr max	0	None	10 µg/m ³	0.40	0.00, 0.70	
								PM _{2.5}		0.30	-0.10, 0.80	
Romieu <i>et al.</i> (2012)	Latin America, 9 cities	34 mil (103,557)	1997-2005	All	Linear, fixed effects	24-hr avg	DL (0-3)	CP: All ages	10 µg/m ³	0.22	0.16, 0.27	
								≥65 yrs		0.30	0.24, 0.36	
								Linear, random effects		All ages	0.23	0.11, 0.36
								≥65 yrs		0.33	0.20, 0.46	
								Linear, fixed effects		CV: All ages	0.17	0.11, 0.23
								≥65 yrs		0.23	0.16, 0.30	
								Linear, random effects		All ages	0.23	0.09, 0.37
≥65 yrs	0.30	0.14, 0.46										
Sacks <i>et al.</i> (2012)	Philadelphia, PA	NR (17,968)	1992-1995	All	GAM, penalized splines	24-hr avg	0-1	None	20 ppb	1.70	-1.80, 5.30	
					GLM, 4 df/year					0.20	-3.40, 3.90	
					GLM, 7 df/year					2.20	-1.80, 6.40	
Son <i>et al.</i> (2012)	Seoul, South Korea	NR (261,952)	2000-2007	Adults ≥35 yrs	Logistic regression	8-hr max	0-1	None	14.5 ² ppb	1.26	-1.32, 3.92	

Table A.3 Epidemiology Studies of Short-term Ozone Exposure and Cardiovascular Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variables	Increment	% Change	95% Confidence Interval
Tao <i>et al.</i> (2012)	Southern China, 4 cities	14.1 mil (NR)	2006- 2008	All	GLM w/Poisson	8-hr avg	1-2	None	10 µg/m ³	1.01	0.71, 1.32
								PM ₁₀		0.71	0.37, 1.05
								NO ₂		0.62	0.29, 0.96
								SO ₂		0.92	0.60, 1.23
								CO		0.89	0.58, 1.20
Yang <i>et al.</i> (2012)	Suzhou, China	2.1 mil (37,571)	2006- 2008	All	GAM w/ penalized splines	1-hr max	1	None	70.6 µg/m ³	4.31	1.34, 7.27
						8-hr max			59.6 µg/m ³	4.47	1.43, 7.51
						24-hr avg			33.3 µg/m ³	3.33	0.50, 6.16
						1-hr max		PM ₁₀	70.6 µg/m ³	3.32	0.28, 6.35
						8-hr max			59.6 µg/m ³	3.64	0.60, 6.68
						24-hr avg			33.3 µg/m ³	2.90	0.07, 5.73
Hunova <i>et al.</i> (2013)	Prague, Czech Republic	1.2 mil (915/day)	2002- 2006	NR	Negative binomial regression	24-hr avg	1	None	10 µg/m ³	0.70	-0.80, 2.18
						8-hr max				-0.30	-1.41, 0.80
						24-hr avg	2			0.50	-0.60, 1.59
						8-hr max				0.30	-0.50, 1.19
Moshammer <i>et al.</i> (2013)	Vienna, Austria	1.5 mil (NR)	1991- 2009	All	GAM w/Poisson	1-hr max	0	None	10 µg/m ³	0.47	0.26, 0.69
						8-hr max				0.51	0.26, 0.76
						24-hr avg				0.62	0.30, 0.93
Key Studies Included in the ISA (Seasonal Analyses)											
Gryparis <i>et al.</i> (2004)	21 European cities	>50 mil. (6-347/d)	At least 3 years post-1990	All	GAM, random effects	8-hr max	0-1	None	10 µg/m ³	0.46	0.22, 0.73
						1-hr max	0-1	None		0.45	0.22, 0.69

Table A.3 Epidemiology Studies of Short-term Ozone Exposure and Cardiovascular Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variates	Increment	% Change	95% Confidence Interval
Samoli <i>et al.</i> (2009)	21 European cities	>60 mil. (>571,798)	At least 3 years post-1990	All	Linear regression, fixed effects	8-hr max	0	None	10 µg/m ³	0.43	0.18, 0.69
							0-1			0.33	0.19, 0.48
							0-20, U			-0.33	-0.93, 0.29
							0-20, P			-0.32	-0.92, 0.28
					Random effects	8-hr max	0	None	10 µg/m ³	0.37	0.05, 0.69
							0-1			0.25	0.03, 0.47
							0-20, U			-0.62	-1.47, 0.24
							0-20, P			-0.57	-1.39, 0.26
Zanobetti and Schwartz (2008b)	48 US cities	106,000- 8 mil/city (1.6 mil)	1989- 2000	All	GLM	8-hr max	0	None	10 ppb	0.47	0.30, 0.64
							0-20			0.49	-0.01, 1.00
							0-3			0.80	0.48, 1.13
							4-20			-0.23	-0.67, 0.22
Katsouyanni <i>et al.</i> (2009)	APHENA-US	250,000- >9 mil (NR)	1987- 1996	≥75	GLM, natural splines, 8 <i>df</i>	1-hr max	DL (0-2)	None	10 µg/m ³	0.40	-0.06, 0.86
				<75			0.84			0.34, 1.34	
				≥75			PM ₁₀	-0.15		-0.81, 0.51	
				<75				0.16		-0.58, 0.90	
				≥75	GLM, penalized splines		DL (0-2)	None		0.65	0.03, 1.27
				<75			0.96			0.24, 1.68	
				≥75			PM ₁₀	-0.09		-0.75, 0.57	
				<75				0.22		-0.52, 0.96	
	APHENA- Canada	100,000- >2 mil (NR)	1987- 1996	≥75	GLM, natural splines, 8 <i>df</i>	DL (0-2)	None	0.19	-0.36, 0.74		
				<75				-0.13	-0.55, 0.29		
				≥75	GLM, penalized splines	0.51		-0.36, 1.40			
				<75		-0.23		-0.81, 0.35			
	APHENA- Europe	200,000- ~7 mil (NR)	1990- 1997	≥75	GLM, natural splines, 8 <i>df</i>	DL (0-2)	None	0.46	0.12, 0.81		
				<75				0.28	-0.19, 0.75		
				≥75		PM ₁₀		0.20	-0.09, 0.50		
				<75				0.21	-0.13, 0.55		
				GLM, penalized splines	DL (0-2)	None	0.51	0.17, 0.86			
							<75	0.29	-0.18, 0.76		
							≥75	0.24	-0.04, 0.52		
							<75	0.21	-0.12, 0.54		

Table A.3 Epidemiology Studies of Short-term Ozone Exposure and Cardiovascular Mortality

Study	Cohort/ Region	Pop. (Deaths)	Time Period	Age	Model	Averaging Time	Lag (d)	Co-pollutants/ Co-variables	Increment	% Change	95% Confidence Interval	
Stafoggia <i>et al.</i> (2010)	10 Italian cities	NR (127,860)	2001- 2005	>35	Linear, cardiac	8-hr max	DL (0-5)	None	10 µg/m ³	2.3	1.10, 3.50	
								PM ₁₀		2.3	1.10, 3.60	
					Linear, cerebrovascular			None		1.4	0.10, 2.60	
								PM ₁₀		1.2	-0.20, 2.60	
Key Studies Not Included in the ISA (Seasonal Analyses)												
de Almeida <i>et al.</i> (2011)	Oporto Metropolitan Area, Portugal	1.2 mil (NR)	2000- 2004	All ages	GAM, penalized splines	8-hr max	1	None	10 µg/m ³	1.58	0.45, 2.73	
				≥65						1.78	0.56, 2.73	
Faustini <i>et al.</i> (2012)	Rome, Italy	145,681 (15,884)	2005- 2009	Adults >35	Log-linear (Poisson)	8-hr max	0-5	None	27.1 µg/m ³	3.60	-1.20, 8.70	
Pascal <i>et al.</i> (2012)	Nine urban areas in France	245,000-6 mil per city (724,289)	1998- 2006	All	Time-stratified case-crossover	8-hr max	0	None	10 µg/m ³	1.30	0.60, 1.90	
								PM _{2.5}		0.90	-0.20, 2.0	
Sacks <i>et al.</i> (2012)	Philadelphia, PA	NR (17,968)	1992- 1995	All	GAM, penalized splines	24-hr avg	0-1	None	20 ppb	1.10	-2.60, 5.00	
					GLM, 4 df/year					-1.10	-4.90, 2.80	
					GLM, 7 df/year					1.90	-2.50, 6.60	
Tao <i>et al.</i> (2012)	Southern China, 4 cities	14.1 mil (NR)	2006- 2008	All	GLM w/Poisson	8-hr avg	1-2	None	10 µg/m ³	0.96	0.35, 1.58	
								PM ₁₀		1.33	0.59, 2.08	
Yang <i>et al.</i> (2012)	Suzhou, China	2.1 mil (37,571)	2006- 2008	All	GAM w/ penalized splines	1-hr max	1	Warm season	70.6 µg/m ³	1.62	-2.19, 5.44	
						8-hr max				2.92	-1.01, 6.85	
						24-hr avg				3.36	-0.17, 6.89	
						1-hr max				70.6 µg/m ³	6.14	0.99, 11.30
						8-hr max				59.6 µg/m ³	6.20	1.01, 11.38
						24-hr avg				33.3 µg/m ³	2.40	-2.73, 7.53

Notes:

Bolded results are statistically significant.

(1) Cheng and Kan (2012) examined the effects of various percentiles of temperature; results for "normal" temperature which corresponds to the 15th-85th percentiles are shown.

(2) Calculated using the mean and standard deviation provided in the study report.

CO = carbon monoxide; CP = cardiopulmonary; CV = cardiovascular; df = degree of freedom; DL = distributed lag; GAM = generalized additive model; GLM = generalized linear model; NO₂ = nitrogen dioxide; NR = not reported; P = penalized distributed lag; PACF = partial autocorrelation function; PM = particulate matter; pop. = population; SO₂ = sulfur dioxide; U = unconstrained distributed lag.

Table A.4 Meta-analyses of Short-term Ozone Exposure and Mortality

Study	Cohort/ Region	# of studies	Study Dates	Model	Avg Time	Lag (d)	Co-pollutants/ Co-variables	Outcome	Increment	% Change	95% Confidence Interval	
Key Studies Included in the ISA (Year-round Analyses)												
Bell <i>et al.</i> (2005)	NMMAPS (US) and non-US	39	1987-2000	GLM, natural splines, US only	24-hr avg	Varied (0-2)	None	All-Cause	10 ppb	0.84	0.48, 1.20	
				PM			0.74			0.06, 1.43		
				GLM, US and non-US		Varied (0-2)	None			0.87	0.55, 1.18	
							PM			0.97	-0.03, 1.98	
				GLM, natural splines, US only		Varied (0-2)	0			None	1.05	0.42, 1.69
							1				0.86	-0.65, 2.40
				GLM, US and non-US		Varied (0-2)	None			Respiratory	0.65	-1.84, 3.21
				GLM, natural splines, US only							0.47	-0.51, 1.47
GLM, US and non-US	Varied (0-2)	None	CV	0.85	-0.66, 2.39							
GLM, natural splines, US only				1.11	0.68, 1.53							
Ito <i>et al.</i> (2005)	US and non-US	43	1990-2003	GLM, random effects	1-hr max	0-1	None	All-cause	10 ppb	0.39	0.26, 0.51	
		33			PM _{2.5}		0.37			0.20, 0.54		
		43			24-hr avg		None		20 ppb	1.60	1.10, 2.00	
		33			PM _{2.5}		1.50			0.80, 2.20		
Levy <i>et al.</i> (2005)	US and non-US	28	1980-1998	Linear	1-hr max	0	None	All-cause	10 µg/m ³	0.21	0.16, 0.26	
Studies Not Included in the ISA (Year-round Analyses)												
Shang <i>et al.</i> (2013)	China	8	1995-2008	Linear (random effects)	24-hr avg	NR	None	All-cause	10 µg/m ³	0.48	0.38, 0.58	
		9						Respiratory		0.73	0.49, 0.97	
		9						CV		0.45	0.29, 0.60	

Table A.4 Meta-analyses of Short-term Ozone Exposure and Mortality

Study	Cohort/ Region	# of studies	Study Dates	Model	Avg Time	Lag (d)	Co-pollutants/ Co-variates	Outcome	Increment	% Change	95% Confidence Interval
Key Studies Included in the ISA (Seasonal Analyses)¹											
Bell <i>et al.</i> (2005)	NMMAPS (US) and non-US	39	1987-2000	GLM, natural splines, US only	24-hr avg	Varied (0-2)	None	All-cause	10 ppb	1.34	-0.45, 3.17
				US and non- US						1.50	0.72, 2.29
				US and non- US				CV		2.45	0.88, 4.10
Ito <i>et al.</i> (2005)	US and non-US	10	1990-2003	GLM, random effects	24-hr avg	0-1	None	All-cause	20 ppb	3.50	2.10, 4.90
Levy <i>et al.</i> (2005)	US and non-US	28	1980-1998	Linear	1-hr max	0	None	All-cause	10 µg/m ³	0.43	0.29, 0.56

Notes:

Bolded results are statistically significant.

(1) Estimates are for the warm season only, unless otherwise specified.

CV = cardiovascular; GLM = generalized linear model; NR = not reported; PM = particulate matter.

Long-Term Ozone Exposure and Respiratory Morbidity

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Abbreviations

AQCD	Air Quality Criteria Document
BAL	Bronchoalveolar Lavage
CHIS	California Health Interview Survey
CHS	Children's Health Study
CI	Confidence Interval
CO	Carbon Monoxide
ED	Emergency Department
EGEA	Epidemiology Study on Genetics and Environment of Asthma
EPA	Environmental Protection Agency
FEF	Forced Expiratory Flow
FEV ₁	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
HA	Hospital Admission
HDMA	House Dust Mite Allergen
HR	Hazard Ratio
IQR	Interquartile Range
ISA	Integrated Science Assessment
LPS	Lipopolysaccharides
MMEF	Maximal Mid-expiratory Flow
NAAQS	National Ambient Air Quality Standard
NHIS	National Health Interview Survey
NO ₂	Nitrogen Dioxide
NYC	New York City
OR	Odds Ratio
PEFR	Peak Expiratory Flow Rate
PM	Particulate Matter
ppb	Parts per Billion
RR	Relative Risk
SD	Standard Deviation
SO ₂	Sulfur Dioxide
SoCAB	California's South Coast Air Basin

Executive Summary

In the 2006 ozone *Air Quality Criteria Document* (AQCD), EPA concluded that evidence was "suggestive but inconclusive for respiratory health effects from long-term [ozone] exposure." (US EPA, 2013) In the *Integrated Science Assessment for Ozone and Related Photochemical Oxidants – Final Report* (ISA), EPA upgraded its causality determination based largely on what it considered coherent new epidemiology evidence, concluding there is "likely to be a causal relationship."

Most of the new onset asthma studies reviewed in the ISA were conducted as part of the Children's Health Study (CHS) in California. One analysis reported an association between playing three or more sports in a high-ozone exposure community and increased risk of developing asthma, but it is unclear whether ozone actually plays a role in this association. Also, some polymorphisms in genes in inflammation and oxidative stress pathways were reported to impact asthma risk, but there is no evidence that ozone plays a role in new onset asthma in children with higher-risk genotypes. Overall, the CHS does not provide evidence that exposure to ozone is associated with new onset asthma.

EPA cited recent cross-sectional studies as providing support for associations between ozone and asthma prevalence or symptoms, but these studies are inconsistent and not supportive of this association. The most robust analyses were conducted as part of the CHS, and these do not indicate increased risks. Although most of the other studies accounted for some potential confounders, they are limited by residual confounding and exposure measurement error or misclassification.

The evidence regarding long-term exposure to ozone and asthma hospital admission and emergency department visits is mixed. Of four California studies available, only one reported any statistically significant associations, but there was a lack of exposure-response. Only a study of New York State infants reported an increased risk of asthma hospitalization. There were potential limitations of all of these studies that may impact the interpretation of study results.

Long-term ozone effects on pulmonary function have been investigated in several epidemiology studies, of which the longitudinal CHS is the largest and most comprehensive, and indicates no associations. Most recent studies all report no effects. Overall, as EPA noted, there is "little new evidence to build upon the very limited studies of pulmonary function" (US EPA, 2013).

Evidence regarding effects of ozone exposure on pulmonary structure comes primarily from studies of non-human primates. Although structural changes were noted in each study, the clinical significance of these changes is not clear. These studies used very high ozone concentrations, and there is no evidence that observed effects would occur at exposures below the National Ambient Air Quality Standards. There also remain uncertainties associated with extrapolating the results to humans.

Finally, studies that evaluated pulmonary inflammation, injury, and oxidative stress are not informative regarding respiratory risks from long-term ozone exposure; epidemiology studies do not evaluate risks of ozone specifically, and animal bioassays use very high exposures and did not evaluate exposure-response. Two new epidemiology studies evaluated the effects of ozone on allergic responses and host defense, but inherent limitations of these studies make the interpretation of their results difficult.

Taken as a whole, the new evidence in the ISA does not support a likely causal association between long-term ozone exposure and respiratory morbidity.

1 Introduction

In the 2006 ozone *Air Quality Criteria Document* (AQCD) (US EPA, 2006), EPA concluded that evidence was "suggestive but inconclusive for respiratory health effects from long-term [ozone] exposure." EPA noted that animal toxicity data suggested ozone could cause biochemical and morphological changes, but epidemiology studies that evaluated lung function declines, inflammation, and new asthma development were inconclusive. In the *Integrated Science Assessment for Ozone and Related Photochemical Oxidants – Final Report* (ISA) (US EPA, 2013), EPA upgraded its causality determination based largely on what it considered coherent new epidemiology evidence, concluding there is "likely to be a causal relationship" between long-term ozone exposure and respiratory morbidity.

The key long-term ozone exposure epidemiology studies EPA highlighted in the ISA include those examining asthma incidence (new onset asthma), asthma prevalence and symptoms, asthma hospital admissions (HAs) and emergency department (ED) visits, pulmonary structure and function, and pulmonary inflammation, injury, and oxidative stress. In its discussion of biological mechanisms, EPA emphasized new epidemiology studies that evaluated combined effects of variants of genes in inflammation and oxidative stress pathways and long-term ozone exposure on asthma, respiratory symptoms in asthmatics, medication use in asthmatics, and first asthma hospitalizations. The ISA also discussed a few new studies in animals, primarily monkeys, that evaluated structural pulmonary changes after exposure to high concentrations of ozone.

Below, and in Tables 1 to 6, we summarize the evidence from the studies that EPA highlighted in the ISA regarding an association between long-term ozone exposure and respiratory morbidity. We demonstrate that, overall, these studies do not indicate that long-term ozone exposure below the current National Ambient Air Quality Standard (NAAQS) of 75 parts per billion (ppb) is likely causal of respiratory effects.

2 Asthma

In the AQCD, EPA concluded that there was little evidence from epidemiology studies regarding respiratory effects from long-term ozone exposure because no associations with asthma-related symptoms, asthma prevalence, or allergy in children were reported. In the ISA, EPA stated that recent epidemiology studies provide compelling evidence for associations between long-term ozone exposure and respiratory health effects. Many of these studies evaluated asthma endpoints, including evidence of new onset asthma, asthma prevalence and symptoms, and asthma HA and ED visits.

Both cross-sectional and longitudinal studies have been conducted, mostly of children; some evaluate asthma effects of ozone alone while others evaluate effects of ozone in combination with certain polymorphisms (*i.e.*, gene variants) (Table 1). A working hypothesis regarding the relationship between asthma and ozone exposure is that inflammation and oxidative stress play a role (US EPA, 2013), therefore studies have focused primarily on genes in these pathways. Variants in several of these genes that have been investigated in conjunction with ozone exposures include those that code for tumor necrosis factor alpha (TNF-alpha), glutathione-S-transferase MI and PI (GSTM1, GSTP1), NADPH:quinone oxidoreductase 1 (NQO1), catalase (CAT), heme oxygenase (HMOX-1), manganese superoxide dismutase (MnSOD), and arginases (ARG1 and 2).

Below, we discuss the key studies highlighted in the ISA that evaluate ozone exposure and asthma incidence, asthma prevalence, and asthma HA and ED visits, including several that evaluate the interaction between ozone and polymorphisms of genes in inflammatory and oxidative stress pathways. The studies are also summarized in Tables 1-3.

2.1 New Onset Asthma

Most of the new onset asthma evaluations in the ISA were conducted as part of the Children's Health Study (CHS) (Table 1). The CHS is a prospective study that evaluates chronic effects of air pollution on the health of children living in 12 communities in Southern California (Peters *et al.*, 2004). Approximately 10,000 children were enrolled in the study, and data on their health, exposures to air pollutants, and other factors were collected annually in a consistent manner until the children completed high school. Specifically, in 1993, the CHS enrolled about 3,600 non-asthmatic children from fourth, seventh, and tenth grades. In 1996, an additional cohort was enrolled of about 2,000 fourth graders. In 2002, about 5,300 children in kindergarten and first grade were enrolled. Ozone, nitrogen dioxide (NO₂), particulate matter [PM, including coarse (PM₁₀), fine (PM_{2.5}), and various constituents of PM], and acid aerosol exposures were estimated from central air monitors. Health outcomes were measured annually by pulmonary function tests (*via* spirometry), questionnaires on respiratory conditions and symptoms, and reviews of school absences. Questionnaires were also used to collect demographic, housing, time-activity, and tobacco smoke exposure information. Only about 10% of study subjects were lost to follow-up, and there was no evidence that attrition was associated with exposure or outcomes. The results from this large epidemiology study have been reported in several published papers (*e.g.*, Peters *et al.*, 1999; Gauderman *et al.*, 2000, 2002, 2004; McConnell *et al.*, 2002, 2010; Berhane *et al.*, 2004).

A recent analysis of the CHS by McConnell *et al.* (2010) specifically investigated new onset asthma in the most recent cohort of kindergarten and first graders that were followed for three years. Only children free of physician-diagnosed asthma at entry into the study were included, and new onset asthma during

follow-up was determined by questionnaire. McConnell *et al.* (2010) reported no new onset asthma in children living in communities with the highest ozone concentrations (8-hour, 10 am to 6 pm annual average maximum, 59.8 ppb) *vs.* the lowest ozone concentration (29.5 ppb), over the range of ozone concentrations across the California communities studied (30.3 ppb) [hazard ratio (HR) = 0.76, 95% confidence interval (CI): 0.38, 1.54]. Similarly, no ozone effects were reported when estimates were adjusted for exposures to modeled traffic-related air pollutants (HR = 1.01, 95% CI: 0.49, 2.11).

These results are consistent with previous CHS findings. For example, McConnell *et al.* (2002) analyzed data from the initial 1993 CHS cohort of more than 3,500 non-asthmatic children with five years of follow-up. In that time, 265 new cases of asthma were identified. The authors stratified children according to 4-year annual average air pollution concentrations and identified six communities with high ozone levels [annual mean of 1-hour max ozone 75.4 ppb, standard deviation (SD) 6.8] and low ozone levels (50.1 ppb, SD 11.0). Other pollutants, including PM₁₀, PM_{2.5}, and NO₂, were elevated in the communities with elevated ozone. Overall, no elevated risks of developing asthma were found for the communities with higher air pollution levels. In fact, a statistically significant *decreased* risk of developing asthma was reported for communities with higher annual average 1-hour maximum ozone [relative risk (RR) = 0.7, 95% CI: 0.6, 0.9]. The authors also reported that children who played three or more team sports had elevated asthma risks (RR = 1.8, 95% CI: 1.2, 2.8). When evaluated separately in high and low air pollution communities, the authors reported statistically significant asthma risks in children playing at least three team sports in communities with high PM levels (RR = 2.0, 95% CI: 1.1, 3.6) and high ozone levels (RR = 3.3, 95% CI: 1.9, 5.8) but not in low air pollution communities. The study was limited, however, by the small number of children (29) who played three or more team sports. In addition, the authors noted that confounding effects by other pollutants (such as diesel exhaust) or allergens could not be ruled out. Exposure misclassification is also a probable source of bias, especially given that exposures were based on a crude measurement of ozone (*i.e.*, based on stratified analysis of "low" and "high" ozone communities).

In another analysis of the CHS study, Islam *et al.* (2007) evaluated whether (1) children who had better lung function at study entry had a lower risk of new onset asthma, and (2) this protective effect was attenuated after exposures to air pollutants. The authors reported that better lung function had protective effects for new onset asthma; these effects were significantly attenuated in children who lived in communities with higher PM and NO₂, but not in children living in high or low ozone exposure communities. This study suggests that ozone does not impact the protective effects that good lung function confers on development of asthma in children.

Several studies of the CHS investigated the association between ozone exposure, polymorphisms of genes in inflammatory and oxidative stress pathways, and asthma incidence. For example, Li *et al.* (2006) evaluated polymorphisms in the gene for TNF- α , which plays a role in the initiation of airway inflammation. The authors found that the TNF-308 GG genotype was protective against asthma and wheezing compared to the less common GA and AA genotypes; these genotypes are associated with increased inflammation and airway hyper-reactivity, but only in children living in low ozone-exposure communities (as defined above). Although the authors concluded that the protective effects of the TNF 308 GG variant depend on the level of oxidant exposure, as well as available antioxidant defenses, one would expect to see this association in high-ozone communities if this were the case. Even in communities with high ozone exposure, and in populations with the less protective inflammatory and antioxidant gene variants, no direct associations between ozone and asthma or wheeze were observed.

Islam *et al.* (2008) evaluated polymorphisms of the HMOX-1 gene, which codes for an inducible form of the antioxidant enzyme heme oxygenase (HO), a first line of defense against oxidative stress. The "short" variants of the HMOX-1 gene are associated with higher expression of HO. The authors reported protective effects from new onset asthma in children with a short variant of HMOX-1 and who live in low

ozone exposure communities, but not for those in high ozone exposure communities. When the authors compared children with high exposure to ozone to those with lower exposure (for all children without the protective HMOX-1 variant), there was no difference in risk of new onset asthma (HR = 0.94, 95% CI: 0.36, 2.43).

Islam *et al.* (2009) expanded on the findings of McConnell *et al.* (2002) with regard to interactions between children playing sports, exposures in high and low air pollution communities of the CHS, and genetic variability. The authors examined variants in the gene encoding GSTP1, an enzyme that metabolizes reactive oxygen species and is involved in modulating inflammatory responses. They reported an increased risk of new onset asthma in children with the codon 105 Ile/Ile variant of GSTP1 compared to the Ile/Val or Val/Val genotypes in children participating in two or more sports and living in high-ozone communities. A significant limitation of these findings, however, is the small number of children in these stratifications. In addition, as noted by EPA, the findings for the role of GSTP1 gene variants in asthma incidence have been inconsistent, with some studies reporting increased risks for the GSTP1 Ile/Ile variant and others for the GSTP1 Val/Val variant (US EPA, 2013). Further, the authors did not report findings for other air pollutants (PM, NO₂, and acid aerosols); therefore, confounding effects cannot be ruled out.

Lastly, Salam *et al.* (2009) investigated interactions between ozone exposure and variants of the genes encoding arginase in a CHS cohort. Arginase is an enzyme that competes with nitric oxide synthases to catalyze the conversion of L-arginine to urea instead of to nitric oxide. Although nitric oxide can contribute to oxidative stress, the role of arginase in asthma is unclear. The authors examined differences in the risk of asthma depending on genetic variants of two arginase genes (ARG1 and ARG2). They reported protective effects of ARG1 variants that were statistically significant for children in high-ozone communities, but not for those in low-ozone communities. No significant effects of asthma were observed in either high- or low-ozone communities for the ARG2 variants. As noted by EPA, the implications of these study results are unclear, because the functional relevance of the ARG1 and ARG2 genetic variants is not known.

The results of the CHS analyses are supported by a case-control study conducted in British Columbia in a population of 3-4 year old children (Clark *et al.*, 2010). The authors evaluated associations between incidence of asthma and exposures to air pollutants (CO, NO, NO₂, PM₁₀ and PM_{2.5}, SO₂, BC, wood smoke, and ozone). Exposures were determined for gestational period and first-year of life from high-resolution modeled concentrations based on monitor data, as well as land use regression models to account for temporal variability in pollutant concentrations. The authors found that ozone was not associated with an elevated ozone exposures either *in utero* (OR=0.83, 95% CI: 0.77-0.89) or in the first year (OR = 0.81, 95% CI: 0.74,0.87). The authors noted several limitations with their study including confounding and measurement error (especially for the *in utero* exposures). The outcome determination also lacked clinical details and any indication of asthma severity, which could result in outcome misclassification, but the authors noted that the estimated asthma incidence was consistent with previous findings. Lastly, the young age of the child was noted as an important limitation, as wheeze, which can lead to an asthma diagnosis, is common in young children and this tends to resolve with age. Authors restricted their analysis, however, to children with reported hospital admission or with at least two outpatient diagnoses of asthma.

In conclusion, while one CHS analysis reported an association between playing three or more sports in a high-ozone exposure community and increased risk of developing asthma, it is unclear whether the effect is from ozone because of the limited sample size and crude stratification by "high" and "low" ozone exposure communities. In addition, while some polymorphisms in certain genes associated with inflammation and oxidative stress pathways have been demonstrated to impact asthma risk, there is no evidence that ozone plays a role in children with higher-risk genotypes. Overall, the CHS does not

provide evidence that exposure to ozone is associated with new onset asthma, and are supported by findings in an additional case-control study.

2.2 Prevalence of Asthma and Asthma Symptoms

In the 2006 AQCD, EPA noted that evidence from cross-sectional studies of ozone and the prevalence of asthma and asthma symptoms was mixed, with some studies showing associations and others reporting none (US EPA, 2013). In the ISA, EPA cited recent cross-sectional studies as providing more support for an association between ozone and asthma prevalence or symptoms (Hwang *et al.*, 2005, 2013; Akinbami *et al.*, 2010; Sousa *et al.*, 2011; Rage *et al.*, 2009a; Jacquemin *et al.*, 2012; Meng *et al.*, 2007; Lee *et al.*, 2009). We summarize key studies below and in Table 2. Results from these studies are not consistent, however, and EPA did not consider important limitations associated with these studies (*e.g.*, selection bias, residual confounding, and exposure measurement error¹).

Asthma symptoms were investigated in the CHS. In the first cross-sectional analysis of the cohort, McConnell *et al.* (1999) evaluated the association between ozone exposures and chronic lower respiratory tract symptoms. In asthmatics, the authors reported associations between bronchitis, phlegm, and cough and PM, NO₂, and acid aerosols, but not with ozone. Similarly, in a longitudinal analysis, McConnell *et al.* (2003) reported no associations between ozone and bronchitic symptoms in CHS children with asthma when effects were evaluated across 12 communities. An analysis across time, but comparing effects within the community, resulted in a small but not significant increase in symptoms (RR = 1.06, 95% CI: 1.00, 3.21), but these effects were reduced in two pollutant models.

Hwang *et al.* (2005) evaluated asthma risk in a population of 3,825 Taiwanese children. Children were enrolled from schools that were within 1 km of air quality monitors that measured ozone, PM₁₀, nitrogen oxides, sulfur dioxide (SO₂), and carbon monoxide (CO). The authors reported a marginally significant association between asthma and ozone exposure [odds ratio (OR) = 1.138, 95% CI: 1.001, 1.293], which remained in two- and three-pollutant models. There were several limitations that may have impacted results, including selection bias, confounding, and exposure measurement error. Selection bias is a common limitation of cross-sectional studies because these studies capture only a snapshot in time; it is not always possible to determine a subject's residential history and the corresponding exposures over time. Poor control for confounding is also an issue. Although Hwang *et al.* (2005) reported controlling for many potential confounders (*e.g.*, age, sex, parental education and atopy, environmental tobacco smoke, and mold), residual confounding still remains a possible explanation for the findings. Exposure measurement error from the use of central monitors is another potential source of bias.

In the same population of Taiwanese children, Hwang *et al.* (2013) assessed the interactions between exposures to air pollutants and genetic variations in the GSTP1 gene on the risk of asthma and wheezing. The authors reported a negative association between ozone exposure and asthma (OR = 0.74, 95% CI: 0.06, 0.90) in children with the GSTP1 Ile/Ile gene variant and a non-significant OR of 1.19 (95% CI: 0.91, 1.57) in children with the Ile/Val or Val/Val genotypes. None of the effect estimates for wheeze achieved statistical significance. The authors concluded that the GSTP1 Ile/Ile variant is protective for risk of asthma in children exposed to ozone and PM_{2.5}. It is noteworthy, however, that these results are inconsistent with the findings by Islam *et al.* (2009, discussed above), who did not observe the same protective effects of the GSTP1 Ile/Ile gene variant. Given the inconsistencies in the findings of potential

¹ Selection bias occurs when enrollment criteria are not the same for comparison groups (*e.g.*, cases and controls are recruited in a different manner). A confounder is a factor associated with both the exposure and the health outcome that is not in the causal pathway of interest; residual confounding occurs when confounders are only partially accounted for in a study. Exposure measurement error results when measured or estimated exposures differ from true exposures; this can occur from the use of central fixed-site monitors to estimate individual exposure. All of these factors can bias results.

susceptibility of children with specific genetic variants, and how this modifies any effects from ozone, it is difficult to interpret the findings of Hwang *et al.* (2013).

In another cross-sectional study, Akinbami *et al.* (2010) evaluated the prevalence of asthma or asthma attacks in the 12 months prior to the study in children 3-17 years old across the US. Asthma prevalence was determined from the National Health Interview Survey (NHIS). Annual average concentrations of five criteria pollutants (PM₁₀, PM_{2.5}, SO₂, NO₂, and CO) were obtained for each US county based on measured concentrations from the EPA Aerometric Information Retrieval System, the nationwide network of monitors. Only children with matching exposure data were included in the analysis for each pollutant, and only 202 counties had valid ozone monitor data linked to children in the study (compared to 399 for PM_{2.5}). Akinbami *et al.* (2010) reported no association between ozone and asthma or asthma attacks in unadjusted models, but the authors observed a small increase in current asthma (OR = 1.08, 95% CI: 1.02, 1.14) in models adjusted for multiple co-variates (*e.g.*, sex, ethnicity, age). The risk of asthma attacks was not statistically significant in the adjusted models (OR = 1.07, 95% CI: 1.00, 1.13). Increases in current asthma and asthma attacks were also observed for exposures to PM_{2.5}, but the increases were not statistically significant. The authors noted differences in many potential confounding factors across the sub-samples of matched county data to child data, including ethnicity, exposures to smoking in the house, parental education, poverty status, and region. Other potential confounders, including other home exposures or unaccounted for tobacco smoke exposures, parental history of asthma, genetic makeup, use of medication, and exposure to allergens, were not evaluated; this may have resulted in residual confounding. The authors also noted exposure measurement error as a potential source of bias, as exposures were estimated based on county-level measured concentrations. This also could have occurred for children who did not live at their residences for the full 12 months prior to the evaluation.

In a much smaller cross-sectional study, Sousa *et al.* (2011) evaluated asthma prevalence in children living in two rural areas of Portugal with elevated ozone concentrations compared to children living in a community with low ozone concentrations. To determine the presence of asthma, the authors used a questionnaire for the full cohort and, for a subset of the children, three measurements of lung function: forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and forced expiratory flow 25-75% (FEF_{25%-75%}). Average ozone concentrations were determined from passive monitoring conducted at two time points in the study areas. The authors reported a greater asthma risk in children living in the high-ozone communities compared to the low-ozone community (RR = 2.84, 95% CI: 1.82, 4.43). The primary limitations with this study include confounding and exposure measurement error. The authors reported no adjustment for any potential confounders (*e.g.*, allergen exposures). Exposure assessment of ozone and other pollutants was also limited, which likely resulted in significant exposure measurement error.

In another cross-sectional study of five French cities, the French Epidemiology study on Genetics and Environment of Asthma (EGEA), Rage *et al.* (2009a) assessed the relationship between ambient air pollution (ozone, NO₂, and SO₂) and asthma severity in the 12 months prior to the study. Asthma severity was determined by a severity score, which integrated clinical events asthma treatment, and an asthma score based only a symptoms. Exposures were determined two different ways: one based on measured data from the closest monitor within 10 km of a subject's residence, and the other based on a spatial geostatistical model with interpolated concentrations for each residence. The modeled grid area was large (4 km x 4 km). The authors reported significantly increased symptoms scores for ozone in single- and multi-pollutant models (single-pollutant model OR = 2.56, 95% CI: 1.58, 4.14 per interquartile range, IQR). These effect estimates differed by city, however, with statistically significant results observed only in one city (Lyon). The authors noted that other environmental or population factors may have accounted for the associations observed. In addition, they noted that ozone may be a marker for other pollutants, and this may account for the observed heterogeneity in the results across cities. No PM measurements were available for evaluation. Exposure measurement error is likely also an important source of bias.

Even though the authors evaluated exposure two ways, both relied on central monitors to estimate personal exposures. In addition, exposures were measured over very large areas. As with other cross-sectional studies, selection bias presents additional uncertainty.

In a follow-up to this study, Jacquemin *et al.* (2012) evaluated associations between geospatially modeled estimates of NO₂, ozone, and PM₁₀ and asthma symptoms, asthma exacerbations, and lung function in those with controlled, partially controlled, or uncontrolled asthma. In models adjusted for sex, age, body mass index, education, smoking, and medication use, only summer-time ozone was increased for partly controlled (OR = 1.53, 95% CI: 1.01, 2.33) and uncontrolled asthmatics (OR = 2.14, 95% CI: 1.34, 3.43). However, summer ozone was significantly associated with asthma symptoms only (OR = 1.59, 95% CI: 1.10, 2.30), not with lung function or asthma exacerbations. As with the study by Rage *et al.* (2009a), several limitations apply to this study. The authors noted potential confounding by stress and allergens or exposures to other asthmogens, none of which were adjusted for in the study.

Meng *et al.* (2007) evaluated poorly controlled asthma in a cohort of adults with physician-diagnosed asthma living in Los Angeles and San Diego. Poorly controlled asthma was defined by the authors as having daily or weekly asthma symptoms and by at least one HA or ED visit in the 12 months prior to the interview. Annual average ozone concentrations were determined based on monitored data within five miles of the subject's residence. Ozone was marginally significantly associated with uncontrolled asthma only in elderly individuals exposed to ozone concentrations above an annual average of 28.7 ppb (OR = 3.34, 95% CI: 1.01, 11.09) and in men with continuous exposures per 10 ppb ozone (OR = 1.76, 95% CI: 1.05, 2.94). Associations were not significant for all adults, for non-elderly adults (18-64 yrs old), or for women (evaluated separately). No significant associations were found among all adults or in other subgroups. More consistent results were observed for measures of traffic density, with significant associations across all groups. The use of central monitors could have led to exposure measurement error; selection bias and confounding are additional sources of uncertainty.

In another study of CHS data, Lee *et al.* (2009) evaluated interactions between polymorphisms in TNF- α and long-term ozone exposure in the occurrence of bronchitic symptoms in asthmatic children. Children living in low ozone exposure communities that carried the TNF-308 GG genotype (which is associated with reduced inflammation) had reduced bronchitic symptoms (OR = 0.53, 95% CI: 0.31, 0.91). In high ozone communities, however, bronchitic symptoms were not altered in children with the same genotype (OR = 1.42, 95% CI: 0.75, 2.70). As noted above, confounding effects and measurement error introduced from stratification of exposures by rudimentary "high" and "low" pollutant level communities likely introduced bias, making it unclear if observed effects were due to ozone exposure or other factors. In addition, the authors did not demonstrate that children with less-protective TNF- α genotypes have an increased risk of bronchitic symptoms with increasing ozone exposure.

Cross-sectional studies do not consistently show long-term ozone exposure affects asthma prevalence or symptoms. The most robust analyses were conducted as part of the CHS, and these do not indicate increased risks. Although most of the studies accounted for some potential confounders and evaluated effects in multi-pollutant models, residual confounding is still a potential limitation. For example, none of the studies controlled for exposures to allergens or other asthmogens. Evidence for confounding by co-pollutants was mixed, with some studies reporting confounding effects and others not. Each of the studies used estimates of exposures based on central site monitors, modeled concentrations over large geographic areas, and/or reported results based on crude stratification of "low" and "high" air pollution area, all of which could have led to exposure measurement error or exposure misclassification. Overall, the evidence is not supportive of an association between long-term ozone exposures and asthma prevalence or symptoms.

2.3 Asthma Hospital Admissions and Emergency Department Visits

In the 2006 AQCD, the only available studies of asthma-related HA and ED visits estimated effects of short-term ozone exposure. Since the AQCD was released, several studies have evaluated the association between long-term ozone exposure and asthma HA and ED visits (Karr *et al.*, 2007; Meng *et al.*, 2007; Lin *et al.*, 2008; Moore *et al.*, 2008; Meng *et al.*, 2010). These studies were reviewed in the ISA, and they are discussed below and summarized in Table 3.

Four studies reviewed in the ISA involved populations living in Southern California (Karr *et al.*, 2007; Meng *et al.*, 2007, 2010; Moore *et al.*, 2008). In a case-control study, Karr *et al.* (2007) investigated the risk of HA for bronchiolitis (inflammation of the bronchioles) in infants living in the South Coast Air Basin of California. The authors assessed the association for exposures one month prior to hospitalization and for the lifespan from birth up until hospitalization. The authors found a significantly *decreased* risk of bronchiolitis hospitalization in infants exposed to ozone for any exposure period (OR = 0.92, 95% CI: 0.88, 0.97, per 10 ppb). In multi-pollutant models adjusted for PM_{2.5} or CO and NO₂, risks remained statistically significantly lowered, but risks were not significant in the model adjusting for all three pollutants.

Moore *et al.* (2008) conducted an ecologic study of asthma hospital discharges in California's South Coast Air Basin (SoCAB) during the summer, when ozone levels are particularly high, to assess the time trends. Exposure was determined based on quarterly average ozone levels (of daily 1-hour maximums) for 195 spatial grids (10 x 10 km) across the SoCAB. Hospital discharge data for asthma were obtained from the State of California for the period 1980-2000. The authors also included discharges for acute sinusitis and pneumonia if asthma was listed as a secondary diagnosis. The authors reported that a 10 ppb increase in average quarterly ozone concentrations were associated with 1.4 discharges per 100,000 population (95% CI: 0.71, 2.09 per 100,000 population). In addition, the authors found that the proportion of discharges over all grids and quarters increased by 4.6% with 10 ppb increases in ozone. The authors asserted that their analysis confirms a causal association between long-term ozone exposure and asthma hospitalizations. It is not clear whether the model is correctly specified or whether unmeasured confounders could have affected results. Also, ecological bias is common with this type of study design and may have affected results.

In a cross-sectional study, Meng *et al.* (2010) investigated the relationship between exposure to ozone and asthma-related HA or ED visits over the year prior to the study. Study subjects (children and adults) resided in the San Joaquin Valley of California and were part of the California Health Interview Survey (CHIS) cohort. Data on hospitalizations and annual average ozone concentrations were collected for 2000-2001. The authors reported ORs (adjusted for age, gender, race, poverty, and insurance status) for the full period and by quartiles of annual average ozone exposure: < 27 ppb, 27.1-30.2 ppb, 30.3-33.9 ppb, and ≥ 34.0 ppb. In single-pollutant analyses, the risk of HA or ED visits was significantly increased for the entire study period (OR = 1.49, 95% CI: 1.05, 2.11 per 10 ppb), but estimates for increasing quartiles of ozone concentrations indicated no trend of increasing HA or ED visits with increasing ozone concentrations. Furthermore, when the analysis was stratified by age, the ORs per 10 ppb for children aged 1-17 and adults 18 years and older were not statistically significant (OR = 1.63, 95% CI: 0.95, 2.81 and OR = 1.43, 95% CI: 0.87, 2.34, respectively), although the authors noted that sample size may be an issue. No information on duration of residence was available and exposures were estimated based on central monitors within 5 miles of the resident home, which can result in exposure measurement error. Asthma outcomes were also self-reported, potentially leading to outcome misclassification.

In a retrospective cohort study, Lin *et al.* (2008) investigated the effect of long-term exposure to ozone on asthma HA in infants between 1995 and 1999 in New York. Births and asthma HA data were obtained

using the New York State Integrated Health Information System, and 8-hour maximum ozone concentration data were collected from the Department of Environmental Conservation. The authors reported an increased odds of asthma HA per 1 ppb increase in ozone, both throughout the entire period and in the ozone season (OR = 1.16, 95% CI: 1.15, 1.17; OR = 1.22, 95% CI: 1.21, 1.23, respectively). When stratified by ozone exposure level, there was a statistically significant concentration-response relationship for both New York City (NYC) and other regions in New York State evaluated separately. In NYC, the mid-exposure group (37.3-38.11 ppb) had an OR of 1.43 (95% CI: 1.29, 1.58), while the high-exposure group (38.12-50.13 ppb) had an OR of 1.69 (95% CI: 1.52, 1.80) compared with the low-exposure group. All estimates were adjusted for co-exposures to PM_{2.5}, PM₁₀, NO₂, and SO₂. Potential limitations of this study included the lack of information on individual exposures (which can result in exposure measurement error) and confounding by unmeasured factors.

In conclusion, the evidence regarding long-term exposure to ozone and asthma HA and ED visits is mixed. Of the four California studies available, only one (Meng *et al.*, 2010) reported any statistically significant association between ozone and asthma HA/ED visits, but there was no trend of increased HA/ED visits with increased ozone exposure, indicating the association was not indicative of causation. Only the study of New York State infants reported a consistent statistically significant increased risk of asthma HA. There were potential limitations of all of these studies that may impact their interpretation, including uncontrolled confounding and exposure measurement error. Overall, the evidence does not indicate that the association between long-term ozone exposure and asthma HA and ED visits is likely causal.

3 Pulmonary Structure and Function

Evidence regarding long-term ozone effects on pulmonary function comes primarily from epidemiology studies, of which the longitudinal CHS is the largest and most comprehensive. Evidence regarding effects of ozone exposure on pulmonary structure comes primarily from animal bioassays. Although there are some recent rodent studies, EPA highlighted findings from non-human primates in the ISA because their respiratory systems most closely resemble that of humans. As discussed below, overall, there is little new evidence to indicate that long-term ozone exposure at levels below the current NAAQS are associated with lung function deficits or pulmonary structural changes. Study summaries are provided in Table 4 (epidemiology studies) and 6 (animal studies).

3.1 Epidemiology Studies

The CHS analyses included several evaluations of lung function based on FVC, FEV₁, maximal mid-expiratory flow rate (MMEF), forced expiratory flow at 75% FVC (FEF75), and peak expiratory flow rate (PEFR).² Effects of air pollutants on lung function growth were also evaluated in this cohort. In the initial cross-sectional analysis of the first year of the study, Peters *et al.* (1999) found no consistent associations between lung function deficits and exposure to ozone. In the longitudinal analysis (which included the first four years of follow-up), Gauderman *et al.* (2000, 2002) found no significant association between long-term ozone exposure and lung function growth impairment. The analysis of the eight-year follow-up of this cohort confirmed the findings of the previous analysis (Gauderman *et al.*, 2004). Taken together, these analyses do not support effects on lung function or lung function growth from ozone.

Three studies of prenatal exposures to ozone and effects on pulmonary function have been published recently, two of the same cohort (Mortimer *et al.*, 2008a,b; Latzin *et al.*, 2009). Mortimer *et al.* (2008a,b) evaluated the association between prenatal and postnatal exposures to ozone and pulmonary function and allergen sensitization in asthmatic children (ages 6-11). In the first study, Mortimer *et al.* (2008a) found no adverse effects of ozone exposure on pulmonary function. In the second study, Mortimer *et al.* (2008b) reported that exposure to *lower* prenatal ozone concentrations were associated with increased allergy sensitization in children. In a cohort of newborns, Latzin *et al.* (2009) reported that pulmonary function parameters (*e.g.*, tidal breathing, lung volume, and other pulmonary function parameters) were not associated with prenatal exposures to ozone.

In a more limited cross-sectional study of approximately 42,000 adults (16 years or older) that participated in the Health Survey of England (1995-1997, and 2001), Forbes *et al.* (2009) evaluated whether exposures to ozone and other outdoor pollutants accelerated adult decline in lung function. No associations were observed with exposure to ozone.

In a prospective cohort study of school-aged, non-asthmatic children in Mexico City, Rojas-Martinez *et al.* (2007) evaluated the association between long-term exposure to ozone, PM₁₀, and NO₂ and lung function growth. Exposures were determined based on the closest central-site monitors from the child's home. The authors reported significant deficits in lung function growth in single- and multi-pollutant models. An annual decrease of 12 mL (for girls) and 4 mL (for boys) in FEV₁ was reported per IQR of ozone exposure. The interpretation of the results is limited, however, because of potential confounding

² MMEF and FEF75 measure small airway function, while PEFR measures upper airway function.

effects that may not have been properly controlled for or included in the model. Exposure measurement error is another source of bias, as exposures were based on central-site monitors.

In conclusion, only one study from Mexico City reported statistically significant effects of long-term ozone exposure in children (Rojas-Martinez *et al.*, 2007). In contrast, in the much larger CHS study of US children, as well as several other studies highlighted in the ISA, no associations with ozone were observed. Although all of these studies suffer from similar limitations as other epidemiology studies, overall, the evidence suggests that ozone is not associated with long-term respiratory effects.

3.2 Animal Studies

In the ISA, EPA focused on studies conducted in infant rhesus macaque monkeys (Fanucchi *et al.*, 2006; Carey *et al.*, 2007; Plopper *et al.*, 2007; Miller *et al.*, 2009; van Winkle *et al.*, 2010; Maniar-Hew *et al.*, 2011; see Table 6). As noted above, the respiratory system of non-human primates most closely resembles the human respiratory system, and these animals have been shown to be the most appropriate for studying potential effects in human asthmatics because they exhibit similar characteristics (*e.g.*, impaired air flow, increased immune cells in airways, and airway hyper-responsiveness) (US EPA, 2013; Plopper *et al.*, 2007). Except for some minor variations (*e.g.*, 6-hour/day *vs.* 8-hour/day exposures), each study had a similar design: several cycles of 5 days of exposure to 500 ppb ozone followed by 9 days of exposure to filtered air. This design was developed to mimic the intermittent human exposure to clean and polluted air (Maniar-Hew *et al.*, 2011). Although EPA discussed pulmonary structure and function studies in adult monkeys exposed to ozone in the 2006 AQCD (US EPA, 2006), the focus of recent studies has shifted to infant primate models to better characterize the effect of early life exposure to ozone – the subject of several recent epidemiology studies. EPA (2013) reported that similar respiratory effects have been found in both adult and infant rhesus monkeys chronically exposed to high levels of ozone, but the infant monkey model better represents airway development observed in children.

Fanucchi *et al.* (2006) examined the effect of 500 ppb ozone exposures on the development of the distal airway in infant (30 days old) male monkeys. The authors measured the length and diameter of both the terminal and respiratory bronchioles and counted the number of airway branches in the left cranial, right cranial, and right middle lobe of the lung. The left cranial lobe was also separated into the cranial and caudal segments, and the number of airway branches were presented for each individual segment. Animals exposed to ozone had significant reductions in respiratory bronchiole diameter and the number of airway branches in the right cranial lobe, as well as both the cranial and caudal segments of the left cranial lobe. The authors noted that these structural alterations may contribute to increased airway resistance associated with asthma, but the clinical significance of these changes is unclear (particularly for the small changes in the number of airway branches).

Similar to Fanucchi *et al.* (2006), Plopper *et al.* (2007) investigated the effect of ozone on the number of airway branches in developing monkeys (30 days old). In addition, the authors investigated the effect of house dust mite allergen (HDMA; in this case, *Dermatophagoides farinae*) alone and in combination with ozone on airway branching and several other measures of immune and asthmatic responses. The authors reported that 500 ppb ozone exposures resulted in significant decreases in the number of respiratory bronchiole branches in the right middle lobe and right cranial lobe at both 6 months and 1 year. The mass of mucous goblet cells was also significantly increased at 6 months after ozone-only and ozone-HDMA co-exposure. The volume of epithelial and interstitial eosinophils were also increased, but the increase was only significant for the ozone and HDMA combination exposure.

Carey *et al.* (2007) conducted a 70-day study of the effect of ozone exposures (500 ppb) on the tissue of the nasal cavity of 180-day old monkeys. The authors reported significant decreases in nasal epithelial

thickness, ciliary volume density, and cytoplasmic volume density. Nuclear volume density was slightly decreased, but this effect was not statistically significant. These changes were consistent with ozone-induced rhinitis and epithelial necrosis; however, the characteristics, severity, and distribution of these lesions were similar to those seen in acutely exposed monkeys in the same study, indicating that long-term exposures are no more harmful than short-term. Studies have also shown adaptive responses (US EPA, 2013). Therefore, the long-term consequences of these nasal injuries are unknown.

Miller *et al.* (2009) investigated the effects of ozone alone (500 ppb) and in combination with HDMA on the number of immune cells in airway mucosa and bronchoalveolar lavage (BAL) fluid of infant male monkeys. All monkeys that received HDMA were sensitized to this allergen *via* subcutaneous injection prior to the study. While some airway immune cell counts were increased, others were decreased and none were statistically significantly different from controls. The only significant increases were found in BAL, where there was an increase in the percentage in several of the immune cell counts in animals exposed to ozone combined with HDMA, but not ozone alone.

Van Winkle *et al.* (2010) examined the effect of cyclic ozone exposures (500 ppb) and HDMA exposure, alone and in combination with ozone, on the abundance of tryptase- and chymase-positive cells in the trachea and intrapulmonary bronchi. The authors reported small elevations in tracheal and intrapulmonary tryptase- and chymase-positive mast cells, but the results were not statistically significant. Further, the combination of ozone and HDMA did not produce statistically significant alterations in mast cells. According to the authors, mast cells are "key players" in characteristic asthma-related changes in mucous production, the organization of smooth muscle, and lung physiology.

Maniar-Hew *et al.* (2011) exposed infant male monkeys to either filtered air or 11 cycles of ozone followed by filtered air. The authors performed necropsies on some animals at 6 months of age (179-183 days old), while a second set of animals was necropsied at the age of 1 year. The animals in the latter group remained in filtered air housing for 6 months after ozone exposure, after which they were given a lipopolysaccharides (LPS) challenge at 1 year. After exposure to 500 ppb of ozone for 5 months, the number of lymphocytes in BAL was significantly reduced, while the number of eosinophils was significantly increased compared with filtered air controls. However, the number of total cells, polymorphonuclear leukocytes, monocytes, and macrophages were not significantly increased in exposed monkeys. Furthermore, in the animals exposed to filtered air for 6 months after ozone exposure, only the monocyte levels remained significantly elevated after recovery. The LPS challenge was predicted to invoke a strong immune response because ozone-exposed animals had increased eosinophil counts and, thus, more cells with the receptor for LPS. Both blood and lavage cell responses following the LPS challenge, however, were significantly decreased compared to controls.

While the available animal studies suggest that exposure to high levels of ozone may cause some structural changes in the airways of infant monkeys, the overall significance of these results is not clear. An important question that remains is whether the respiratory and immune cell changes seen in these studies are clinically relevant. Several authors posited that ozone may promote the development of allergic airways disease during early life by increasing blood and pulmonary immune cells; however, the studies do not extend beyond 1 year of life (and in most cases, only 6 months). It is unknown whether these changes would persist beyond the time points evaluated in the studies and, ultimately, lead to allergic airway disease or other respiratory conditions later in life (Maniar-Hew *et al.*, 2011). As observed by Maniar-Hew *et al.* (2011), for example, the changes in several immune cell levels in the BAL were reversed after a recovery period of 6 months. In addition, although this is considered a good model for human asthma, there is always uncertainty introduced when extrapolating results from laboratory animals to humans. Furthermore, all of these studies tested only one high exposure concentration (well above the current NAAQS and actual human exposures in the US), and there is no information on either exposure-response or whether any of the effects reported would occur at ozone exposures below the

NAAQS. Because these effects all likely have a threshold mode of action, studies with multiple exposure concentrations – including concentrations closer to the NAAQS – are needed to determine whether these results have any relevance to humans.

4 Other Respiratory Effects

In addition to studies of asthma and lung function, EPA highlighted a few studies that evaluated pulmonary inflammation, injury, and oxidative stress; allergic responses; and host defense in the ISA. These are discussed below and summarized in Table 5.

4.1 Pulmonary Inflammation, Injury, and Oxidative Stress

In the ISA, EPA noted that there is limited new epidemiology evidence of pulmonary inflammation, injury, and oxidative stress from long-term exposure to ozone, but the large majority of studies evaluated short-term exposures. Two long-term ozone exposure studies were evaluated in the ISA, one in Italy and one in Mexico, but the individual impacts from ozone could not be determined in either. Renzetti *et al.* (2009) suggested a reduced inflammatory response in a small number (37) of children living in an urban area of Italy with elevated pollutant levels (PM₁₀, ozone, and NO₂) seven days after relocation to a rural area, but they did not report pollutant-specific results (Renzetti *et al.*, 2009). Similarly, abnormal chest radiographs suggestive of inflammation in healthy children were associated with elevated levels of air pollutants (including PM_{2.5} and ozone) in a study from Mexico City, but effects from ozone exposure alone could not be assessed (Calderón-Garcidueñas *et al.*, 2006).

EPA also noted some evidence from laboratory animal studies suggesting inflammation occurs after very high ozone exposure (300 or 500 ppb) (US EPA, 2013). In some studies, the inflammatory response was attenuated with daily exposures, suggesting that animals adapted to ozone. It is unclear if adaptation to repeated ozone exposures indicates that adverse effects (*e.g.*, frank disease) are unlikely. Some researchers have found evidence that cellular damage might continue even if inflammatory indicators are reduced after repeated exposure to ozone. Another explanation is that homeostatic processes may have countered the effects of ozone exposures (*e.g.*, increased antioxidant capacity) to prevent injury that would result in an adverse effect. None of these studies evaluated exposure-response, and, because of the high-exposure regimens, these studies do not provide information regarding risks at lower (more typical) exposure levels. There is also uncertainty associated with extrapolating risks from laboratory animals to humans.

Overall, studies that evaluated pulmonary inflammation, injury, and oxidative stress are not informative regarding respiratory risks from long-term ozone exposure.

4.2 Allergic Responses and Host Defense

Only two epidemiology studies published since the AQCD evaluated the effects of ozone on allergic responses and host defense (Parker *et al.*, 2009; Rage *et al.*, 2009b). In a study of respiratory allergies using the 1999-2005 NHIS of 70,000 children across the US and ozone measurements at monitors within 20 miles of each child's residential block for each year, Parker *et al.* (2009) reported significant associations between respiratory allergy/hay fever and increased summertime ozone levels per IQR (OR = 1.2, 95% CI: 1.15, 1.26). Similar results were reported for PM. In multi-pollutant models with SO₂, NO₂, and PM, ozone effects were reduced compared to single-pollutant model estimates, but remained statistically significant. Although the study was based on a large number of diverse children using a carefully conducted NHIS survey, it had several limitations. Both selection bias from the cross-sectional

design and recall bias (is a systematic error caused by differences in the accuracy or completeness of the recalled past events or experiences by study participants) based on parental reported allergies in the previous 12 months likely affected risk estimates. The authors also noted the difficulty in defining allergic disease and bias that may have been introduced from the parental self-reported allergies *vs.* biomarkers of disease that are commonly used. Allergen levels were not measured in the study, and other confounding factors (*e.g.*, exposure to tobacco smoke) may have been either poorly controlled for or not included in the analysis. Lastly, because exposure was estimated from data that may not represent the exact recall period for the study and exposure was defined over a very large area (20-mile radius), exposure measurement error likely occurred.

Rage *et al.* (2009b) measured levels of total immunoglobulin E (IgE) and associations with air pollution in 369 adult asthmatics in five French centers as part of the EGEA study. IgE is an antibody that plays a key role in immunity, but has also been associated with allergic diseases such as allergic asthma. Ozone exposures were modeled using geostatistical models on 4 x 4 km grids. Results were adjusted for various potential confounders, including age, sex, living in the country, and family history of asthma. Total IgE was increased by 19.1% (95% CI: 2.4, 38.6) in single-pollutant models, but it *decreased* in two-pollutant models with NO₂ (-6.3%, CI: -24.2, 15.7). The authors noted that the study strengths included well-characterized asthmatics, which minimized misclassification, but exposure misclassification was an important limitation, as exposures were estimated for a very large area. There was also evidence of potential confounding by NO₂. Additional confounders, such as known allergens (*e.g.*, pollen), were not evaluated .

As part of the CHS, Wenten *et al.* (2009) evaluated interactions between gene variants associated with oxidative stress and respiratory-related school absences in a subset of Hispanic and non-Hispanic school children. The genes that were investigated include those that encode CAT and myeloperoxidase (MPO), both of which modulate the oxidative environment in the lungs. There is evidence that single nucleotide polymorphisms (SNPs) in the genetic sequence of the promoter region of the CAT gene (-330 G/A or A/A) increase catalase activity and reduce oxidative stress. Similarly, an A allele in the promoter region of MPO gene (-463 GA or AA) leads to lower enzyme activity and could result in a lower oxidative state, depending on CAT activity. The authors found that the combination of the CAT-330 GG and MPO-463 GA or AA alleles was associated with increased respiratory-related school absences, but the effects of these gene variants on school absences were not statistically significantly different when comparing areas with high and low ozone concentrations. Therefore, these results suggest that the susceptibility from the combined effects of having the two gene variants is unrelated to ozone levels.

The limitations of these studies make interpreting their ozone results difficult. In addition, as noted by EPA in the ISA, two other studies published prior to the AQCD found no associations between allergic rhinitis/hay fever and long-term ozone exposures (Ramadour *et al.*, 2000; Hwang *et al.*, 2006). Taken together, these studies do not provide compelling evidence that long-term ozone exposure causes allergic responses or affects host defense.

5 Conclusions

EPA changed its causality determination from "suggestive but inconclusive for respiratory health effects from long-term [ozone] exposure" to "likely to be a causal relationship" in the ISA, but evidence from recent epidemiology studies does not support such a change. New onset asthma studies have been conducted as part of the CHS, and these studies do not provide consistent evidence to support an association with ozone exposures. Similarly, recent cross-sectional studies reported inconsistent results for associations between ozone and asthma prevalence or ER and HA admissions. Although most studies accounted for some potential confounders, they are limited by residual confounding and exposure measurement error or misclassification. These limitations impact the interpretation of study results. There is also little evidence to support chronic effects on pulmonary function. With regards to pulmonary structure, evidence is primarily from studies of non-human primates, and these studies used very high ozone concentrations and extrapolation to humans is questionable. Lastly, studies that evaluated pulmonary inflammation, injury, and oxidative stress are not informative regarding respiratory risks from long-term ozone exposure, as epidemiology studies do not evaluate risks of ozone specifically, and animal bioassays were conducted only at high exposures. Taken as a whole, the new evidence presented in the ISA does not support a likely causal association between long-term ozone exposure and respiratory morbidity.

References

- Akinbami, LJ; Lynch, CD; Parker, JD; Woodruff, TJ. 2010. "The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004." *Environ. Res.* 110(3):294-301.
- Berhane, K; Gauderman, WJ; Stram, DO; Thomas, DC. 2004. "Statistical issues in studies of the long-term effects of air pollution: The Southern California Children's Health Study." *Stat. Sci.* 19(3):414-449.
- Breton, CV; Salam, MT; Vora, H; Gauderman, WJ; Gilliland, FD. 2011. "Genetic variation in the glutathione synthesis pathway, air pollution, and children's lung function growth." *Am. J. Respir. Crit. Care Med.* 183(2):243-248.
- Calderón-Garcidueñas, L; Mora-Tiscareno, A; Fordham, LA; Chung, CJ; Valencia-Salazar, G; Flores-Gomez, S; Solt, AC; Gomez-del Campo, A; Jardon-Torres, R; Henriquez-Roldan, C; Hazucha, MJ; Reed, W. 2006. "Lung radiology and pulmonary function of children chronically exposed to air pollution." *Environ Health Perspect* 114:1432-1437.
- Carey, SA; Minard, KR; Trease, LL; Wagner, JG; Garcia, GJ; Ballinger, CA; Kimbell, JS; Plopper, CG; Corley, RA; Postlethwait, EM; Harkema, JR; Einstein, DR. 2007. "Three-dimensional mapping of ozone-induced injury in the nasal airways of monkeys using magnetic resonance imaging and morphometric techniques." *Toxicol. Pathol.* 35(1):27-40.
- Clark, NA; Demers, PA; Karr, CJ; Koehoorn, M; Lencar, C; Tamburic, L; Brauer, M. 2010. "Effect of early life exposure to air pollution on development of childhood asthma." *Environ. Health Perspect.* 118(2):284-290.
- Fanucchi, MV; Plopper, CG; Evans, MJ; Hyde, DM; Van Winkle, LS; Gershwin, LJ; Schelegle, ES. 2006. "Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys." *Am. J. Physiol. Lung Cell. Mol. Physiol.* 291(4):L644-L650.
- Forbes, LJ; Kapetanakis, V; Rudnicka, AR; Cook, DG; Bush, T; Stedman, JR; Whincup, PH; Strachan, DP; Anderson, HR. 2009. "Chronic exposure to outdoor air pollution and lung function in adults." *Thorax* 64(8):657-663.
- Gauderman, WJ; Avol, E; Gilliland, F; Vora, H; Thomas, D; Berhane, K; McConnell, R; Kuenzli, N; Lurmann, F; Rappaport, E; Margolis, H; Bates, D; Peters, J. 2004. "The effect of air pollution on lung development from 10 to 18 years of age." *N. Engl. J. Med.* 351(11):1057-1067.
- Gauderman, WJ; Gilliland, GF; Vora, H; Avol, E; Stram, D; McConnell, R; Thomas, D; Lurmann, F; Margolis, HG; Rappaport, EB; Berhane, K; Peters, JM. 2002. "Association between air pollution and lung function growth in Southern California children: Results from a second cohort." *Am. J. Respir. Crit. Care Med.* 166:76-84.

- Gauderman, WJ; McConnell, R; Gilliland, F; London, S; Thomas, D; Avol, E; Vora, H; Berhane, K; Rappaport, EB; Lurmann, F; Margolis, HG; Peters, J. 2000. "Association between air pollution and lung function growth in Southern California children." *Am. J. Respir. Crit. Care Med.* 162:1383-1390.
- Hwang, BF; Jaakkola, JJK; Lee, YL; Lin, YC; Y-LL, G. 2006. "Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren." *Respir Res* 7:23.
- Hwang, BF; Lee, YL; Yin, YC; Jaakkola, JJ; Guo, YL. 2005. "Traffic related air pollution as a determinant of asthma among Taiwanese school children." *Thorax* 60(6):467-473.
- Hwang, BF; Young, LH; Tsai, CH; Tung, KY; Wang, PC; Su, MW; Lee, YL. 2013. "Fine particle, ozone exposure, and asthma/wheezing: Effect modification by glutathione S-transferase P1 polymorphisms." *PLoS ONE* 8(1):e52715.
- Islam, T; Berhane, K; McConnell, R; Gauderman, WJ; Avol, E; Peters, JM; Gilliland, FD. 2009. "Glutathione-S-transferase(GST) P1, GSTM1, exercise, ozone and asthma incidence in school children." *Thorax* 64(3):197-202.
- Islam, T; McConnell, R; Gauderman, WJ; Avol, E; Peters, JM; Gilliland, FD. 2008. "Ozone, oxidant defense genes, and risk of asthma during adolescence." *Am. J. Respir. Crit. Care Med.* 177(4):388-395.
- Islam, T; Gauderman, WJ; Berhane, K; McConnell, R; Avol, E; Peters, JM; Gilliland, FD. 2007. "Relationship between air pollution, lung function and asthma in adolescents." *Thorax* 62(11):957-963.
- Jacquemin, B; Kauffmann, F; Pin, I; Le Moual, N; Bousquet, J; Gormand, F; Just, J; Nadif, R; Pison, C; Vervloet, D; Kunzli, N; Siroux, V. 2012. "Air pollution and asthma control in the Epidemiological Study on the Genetics and Environment of Asthma." *J. Epidemiol. Community Health* 66(9):796-802.
- Karr, C; Lumley, T; Schreuder, A; Davis, R; Larson, T; Ritz, B; Kaufman, J. 2007. "Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis." *Am. J. Epidemiol.* 165(5):553-560.
- Latzin, P; Roosli, M; Huss, A; Kuehni, CE; Frey, U. 2009. "Air pollution during pregnancy and lung function in newborns: A birth cohort study." *Eur. Respir. J.* 33(3):594-603.
- Lee, YL; McConnell, R; Berhane, K; Gilliland, FD. 2009. "Ambient ozone modifies the effect of tumor necrosis factor G-308A on bronchitic symptoms among children with asthma." *Allergy* 64(9):1342-1348.
- Li, Y; Gauderman, WJ; Avol, E; Dubeau, L; Gilliland, FD. 2006. "Associations of Tumor Necrosis Factor G-308A with Childhood Asthma and Wheezing." *Am J Respir Crit Care Med* 173:970-976.
- Lin, S; Liu, X; Le, LH; Hwang, SA. 2008. "Chronic exposure to ambient ozone and asthma hospital admissions among children." *Environ. Health Perspect.* 116(12):1725-1730.
- Maniar-Hew, K; Postlethwait, EM; Fanucchi, MV; Ballinger, CA; Evans, MJ; Harkema, JR; Carey, SA; McDonald, RJ; Bartolucci, AA; Miller, LA. 2011. "Postnatal episodic ozone results in persistent attenuation of pulmonary and peripheral blood responses to LPS challenge." *Am. J. Physiol. Lung Cell. Mol. Physiol.* 300(3):L462-L471.

- McConnell, R; Berhane, K; Gilliland, F; London, SJ; Islam, T; Gauderman, WJ; Avol, E; Margolis, HG; Peters, JM. 2002. "Asthma in exercising children exposed to ozone: A cohort study." *Lancet* 359(9304):386-391.
- McConnell, R; Berhane, K; Gilliland, F; London, SJ; Vora, H; Avol, E; Gauderman, WJ; Margolis, HG; Lurmann, F; Thomas, DC; Peters, JM. 1999. "Air pollution and bronchitic symptoms in Southern California children with asthma." *Environ. Health Perspect.* 107(9):757-760.
- McConnell, R; Berhane, K; Gilliland, F; Molitor, J; Thomas, D; Lurmann, F; Avol, E; Gauderman, WJ; Peters, JM. 2003. "Prospective study of air pollution and bronchitic symptoms in children with asthma." *Am. J. Respir. Crit. Care Med.* 168:790-797.
- McConnell, R; Islam, T; Shankardass, K; Jerrett, M; Lurmann, F; Gilliland, F; Gauderman, J; Avol, E; Kunzli, N; Yao, L; Peters, J; Berhane, K. 2010. "Childhood incident asthma and traffic-related air pollution at home and school." *Environ. Health Perspect.* 118(7):1021-1026.
- Meng YY; Rull, RP; Wilhelm, M; Lombardi, C; Balmes, J; Ritz, B. 2010. "Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California." *J. Epidemiol. Community Health* 64(2):142-147.
- Meng, YY; Wilhelm, M; Rull, RP; English, P; Ritz, B. 2007. "Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults." *Ann. Allergy Asthma Immunol.* 98(5):455-463.
- Miller, LA; Gerriets, JE; Tyler, NK; Abel, K; Schelegle, ES; Plopper, CG; Hyde, DM. 2009. "Ozone and allergen exposure during postnatal development alters the frequency and airway distribution of CD25+ cells in infant rhesus monkeys." *Toxicol. Appl. Pharmacol.* 236(1):39-48.
- Moore, K; Neugebauer, R; Lurmann, F; Hall, J; Brajer, V; Alcorn, S; Tager, I. 2008. "Ambient ozone concentrations cause increased hospitalizations for asthma in children: An 18-year study in Southern California." *Environ. Health Perspect.* 116(8):1063-1070.
- Mortimer, K; Neugebauer, R; Lurmann, F; Alcorn, S; Balmes, J; Tager, I. 2008a. "Air pollution and pulmonary function in asthmatic children: Effects of prenatal and lifetime exposures." *Epidemiology* 19(4):550-557.
- Mortimer, K; Neugebauer, R; Lurmann, F; Alcorn, S; Balmes, J; Tager, I. 2008b. "Early-lifetime exposure to air pollution and allergic sensitization in children with asthma." *J. Asthma* 45(10):874-881.
- Parker, JD; Akinbami, LJ; Woodruff, TJ. 2009. "Air pollution and childhood respiratory allergies in the United States." *Environ. Health Perspect.* 117(1):140-147.
- Peters, JM; Avol, E; Gauderman, WJ; Linn, WS; Navidi, W; London, SJ; Margolis, H; Rappaport, E; Vora, H; Gong, H Jr.; Thomas, DC. 1999. "A study of twelve Southern California communities with differing levels and types of air pollution: II. Effects on pulmonary function." *Am. J. Respir. Crit. Care Med.* 159:768-775.
- Peters, JM. 2004. "Epidemiologic Investigation to Identify Chronic Effects of Ambient Air Pollutants in Southern California." Submitted to California Environmental Protection Agency(CalEPA); California Air Resources Board (CARB). 310p., May 14.

- Plopper, CG; Smiley-Jewell, SM; Miller, LA; Fanucchi, MV; Evans, MJ; Buckpitt, AR; Avdalovic, M; Gershwin, LJ; Joad, JP; Kajekar, R; Larson, S; Pinkerton, KE; Van Winkle, LS; Schelegle, ES; Pieczarka, EM; Wu, R; Hyde, DM. 2007. "Asthma/allergic airways disease: Does postnatal exposure to environmental toxicants promote airway pathobiology?" *Toxicol. Pathol.* 35(1):97-110.
- Rage, E; Jacquemin, B; Nadif, R; Oryszczyn, MP; Siroux, V; Aguilera, I; Kauffmann, F; Kunzli, N. 2009a. "Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults." *Allergy* 64(1):40-46.
- Rage, E; Siroux, V; Kunzli, N; Pin, I; Kauffmann, F. 2009b. "Air pollution and asthma severity in adults." *Occup. Environ. Med.* 66(3):182-188.
- Ramadour, M; Burel, C; Lanteaume, A; Vervloet, D; Charpin, D; Brisse, F; Dutau, H; Charpin, D. 2000. "Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous air pollutants." *Allergy* 55(12):1163-1169.
- Renzetti, G; Silvestre, G; D'Amario, C; Bottini, E; Gloria-Bottini, F; Bottini, N; Auais, A; Perez, MK; Piedimonte, G. 2009. "Less air pollution leads to rapid reduction of airway inflammation and improved airway function in asthmatic children." *Am. J. Respir. Crit. Care Med.* 176 (4) : 377-384.
- Rojas-Martinez, R; Perez-Padilla, R; Olaiz-Fernandez, G; Mendoza-Alvarado, L; Moreno-Macias, H; Fortoul, T; McDonnell, W; Loomis, D; Romieu, I. 2007. "Lung function growth in children with long-term exposure to air pollutants in Mexico City." *Am. J. Respir. Crit. Care Med.* 176(4):377-384.
- Salam, MT; Islam, T; Gauderman, WJ; Gilliland, FD. 2009. "Roles of arginase variants, atopy, and ozone in childhood asthma." *J. Allergy Clin. Immunol.* 123(3):596-602.
- Sousa, SI; Ferraz, C; Alvim-Ferraz, MC; Martins, FG; Vaz, LG; Pereira, MC. 2011. "Spirometric tests to assess the prevalence of childhood asthma at Portuguese rural areas: Influence of exposure to high ozone levels." *Environ. Int.* 37(2):474-478.
- US EPA. 2006. "Air Quality Criteria for Ozone and Related Photochemical Oxidants (Volume I of III)." National Center for Environmental Assessment-RTP Division, EPA 600/R-05/004aF.
- US EPA. 2013. "Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Final)." National Center for Environmental Assessment (NCEA). EPA/600/R-10/076F, 1,251p., February.
- Van Winkle, LS; Baker, GL; Chan, JK; Schelegle, ES; Plopper, CG. 2010. "Airway mast cells in a rhesus model of childhood allergic airways disease." *Toxicol. Sci.* 116(1):313-322.
- Wenten, M; Gauderman, WJ; Berhane, K; Lin, PC; Peters, J; Gilliland, FD. 2009. "Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: An example of epistasis in gene-environment interactions." *Am. J. Epidemiol.* 170(12):1494-1501.

Tables

Table 1 Epidemiology Studies of Long-term Ozone Exposure and New Onset Asthma

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/ Co-variates	Subject Group (Genotype)	Effect Measure	Estimate	95% CI	p-value					
McConnell <i>et al.</i> (2010)	CHS; 13 California communities	2,497	44.6	29.5-59.8	New onset asthma	10 am-6 pm	None	N/A	HR per 30.3 ppb	0.76	0.38, 1.54	NR					
										1.01	0.49, 2.11	NR					
										1.50	1.20, 1.86	< 0.01					
										1.54	1.10, 2.14	< 0.01					
Li <i>et al.</i> (2006)	CHS; 12 California communities	2,727	37.5 (Low)	NR	Ever asthma	10 am-6 pm (8-hr daytime average)	None	TNF-GG	OR compared to GA/AA alleles	0.8	0.5-1.1	NR					
			57.8 (High)							0.9	0.7-1.2	NR					
			37.5 (Low)							0.5	0.4-0.7	NR					
										0.5	0.3-0.8	NR					
										0.5	0.4-0.8	NR					
			57.8 (High)							1.0	0.8-1.3	NR					
										1.1	0.7-1.5	NR					
										0.9	0.6-1.2	NR					
Islam <i>et al.</i> (2008)	CHS; 12 California communities	1,125 (Non-Hispanic) 576 (Hispanic)	38.4-55.2	28.6-64.9	New onset asthma	10 am-6 pm avg.	PM ₁₀	Non-Hispanic, HMOX-1 + Hispanic, HMOX-1	HR	0.64	0.41, 0.99	< 0.01					
										1.25	0.64, 2.47	> 0.05					
										0.90	0.61, 1.31	> 0.05					
										1.93	1.05, 3.55	< 0.05					
			Low O ₃ 38.4							28.6-45.5	1.00 (ref)	N/A	N/A				
			High O ₃ 55.2							46.5-64.9	0.44	0.23, 0.83	0.003				
										0.94	0.36, 2.43	NR					
										0.88	0.33, 2.34	NR					
Islam <i>et al.</i> (2009)	CHS; 12 California communities	1,610	38.4-55.2	28.6-64.9	New onset asthma	Ann. avg.	None ^a	SNP1 (A)	HR	1.45	1.12, 1.94	0.007					
										0.61	0.43, 0.82						
										1.52	1.12, 2.14						
										1.42	1.09, 2.15	NR					
										0.62	0.45, 0.85	NR					
										1.53	1.09, 2.15	NR					
			Low O ₃ 38.4				Low (28.6-45.5)	No sports	Ile/Ile	HR	1.00 (ref)	N/A	N/A				
											1-2 sports	1.37	0.6, 3.0	NR			
											> 2 sports	1.06	0.30, 4.0	NR			
											High O ₃ 55.2	High (46.5-64.9)	No sports	Ile/Ile	1.00 (ref)	N/A	N/A
											1-2 sports	1.37	0.6, 3.1	NR			
											> 2 sports	6.15	2.2, 7.4	< 0.05			
Clark <i>et al.</i> (2010)	British Columbia	37,401	<i>In utero</i> exposure 15.7-15.9	IQR: 13.2-18.2	New onset asthma	24-hr avg	None	N/A	OR per 10 µg/m ³	0.83	0.77, 0.89	NR					
			First year exposure 14.4-14.6							IQR: 12.7-16.4	N/A	0.81	0.74, 0.87	NR			

Ann. = annual; CHS = Children's Health Study; CHIS = California Health Interview Survey; CI = confidence interval; GSTM1 = glutathione S-transferase Mu 1 gene; HR = hazard ratio; N/A = not applicable; NR = not reported; OR = odds ratio; ref = referent group; SNP = single-nucleotide polymorphism; SW = Southwestern; TRP = traffic related pollution (mixture of pollutants that are highly correlated; including carbon monoxide, nitrogen dioxide, total oxides of nitrogen, elemental and organic carbon and PM₁₀ and PM_{2.5}).

(a) Joint GSTM1 and GSTP1 base model. Islam *et al.* (2009) also calculated HRs for by genotype/haplotype for the GSTP-1 (glutathione S-transferase pi gene) only model, but these are not presented. According to authors, the SNP model involving the variations rs6591255 (SNP1) and Ile105Va (SNP3) best captured the association between GSTP1 and asthma.

Statistically significant results are bold.

Table 2 Epidemiology Studies of Long-term Ozone Exposure and Asthma Prevalence and Asthma Symptoms

Study	Cohort/ Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/ Co-variates	Subject Group (Genotype)	Effect Measure	Estimate	95% C.I.	p-value						
Hwang <i>et al.</i> (2005)	6-15 yr olds in 22 munis. in Taiwan	32,672	23.14	18.65-31.17	Asthma Prevalence	Monthly avg.	None	N/A	OR (per 10 ppb)	1.138	1.001, 1.293	NR						
							NOx			1.208	1.037, 1.408							
							CO			1.274	1.100, 1.474							
							SO ₂			1.166	1.022, 1.331							
							PM ₁₀			1.253	1.089, 1.442							
							NO _x + SO ₂			1.360	1.152, 1.604							
							NO _x + PM ₁₀			1.501	1.274, 1.768							
							CO + SO ₂			1.500	1.273, 1.767							
Sousa <i>et al.</i> (2011)	Portugal	95	Low-O ₃ neighborhood: 21.3	NR	Asthma Prevalence	8-hr average	None	High O ₃ neighborhood	RR	2.84	1.82, 4.43	NR						
			High: 63.6						OR	3.02	1.88, 4.86							
Akinbami <i>et al.</i> (2010)	3-17 yr. olds in NHIS	18,746	39.8 (median)	21.2-59.5 (1 st -4 th quartile)	Current asthma	8-hr max	None	N/A	OR	1.08	1.02, 1.14	NR						
					Recent asthma attack						1.07		1.00, 1.13					
					NR					SO ₂ , NO ₂ , PM _{2.5} , + PM ₁₀	N/A		OR	0.99	0.78, 1.26			
														1.09	0.85, 1.41			
														1.56	1.15, 2.10			
														0.89	0.67, 1.17			
0.98	0.73, 1.32																	
1.38	0.99, 1.91																	
Lee <i>et al.</i> (2009)	CHS, 12 southern California communities	3,593	39.2 (low); 56.5 (high)	NR	Bronchitic symptoms	Ann. avg. of 8-hr avg (10 am-6 pm)	None	All children with TNF-308 GG genotype	OR	0.81	0.55, 1.21	NR						
								Children with TNF-308 GG genotype in low-ozone communities (avg < 50 ppb)		0.53	0.31, 0.91							
								Children with TNF-308 GG genotype in high-ozone communities (avg > 50 ppb)		1.42	0.75, 2.70							
Rage <i>et al.</i> (2009a)	France, EGEA; summer-only	328	31.5 (median)	IQR: 21.9-38.0	Adult asthma severity	6-mo. 8-hr avg	None	N/A	OR per IQR	2.56	1.58, 4.14	NR						
			> 57.3	NR		Days w/ 8-hr avg > 57.3 ppb				2.53	1.69, 3.79							
			31.5 (median)	IQR: 21.9-38.0		6-mo. 8-hr avg				2.74	1.68, 4.48							
Jacquemin <i>et al.</i> (2011)	EGEA2	481	Summer: 35.04	27.3-45.0	Asthma control	Monthly avg.	None	Partly controlled asthma	OR	1.53	1.01, 2.33	< 0.05						
								Uncontrolled asthma		2.14	1.34, 3.43							
								Ordinal (loss of control)		1.69	1.22, 2.34							
								PM ₁₀ Ordinal (loss of control)		1.50	1.07, 2.11							
								None		N/A	OR		1.35	0.80, 2.28	> 0.05			
								Lung function (FEV ₁)		N/A	1.59		1.10, 2.30	< 0.05				
								Symptoms		N/A	1.58		0.97, 2.59	> 0.05				
								Exacerbations		N/A	1.33		0.96, 1.84	> 0.05				
								All-year: 24.6		18.6-38.6	Asthma control		None	Partly controlled asthma	OR	1.19	0.83, 1.70	> 0.05
								Lung function (FEV ₁)		N/A	1.07		0.73, 1.58	> 0.05				
								Symptoms		N/A	1.29		0.98, 1.72	> 0.05				
Exacerbations	N/A	0.94	0.65, 1.37	> 0.06														

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/Co-variates	Subject Group (Genotype)	Effect Measure	Estimate	95% C.I.	p-value		
Meng <i>et al.</i> (2007)	Los Angeles and San Diego adults; CHIS	1,609	NR	NR	Poorly controlled asthma	Ann. avg. of 1-hr avg	None ^a	All adults	OR per 1 pphm	1.08	0.84, 1.39	NR		
									OR > 2.87 pphm	1.03	0.65, 1.64			
									OR per 1 pphm	1.70	0.91, 3.18			
									OR > 2.87 pphm	3.34	1.01, 11.09			
Meng <i>et al.</i> (2010)	CHIS; San Joaquin Valley CA	1,502	30.3	IQR: 27.1-34.0	Asthma symptoms	Ann. avg.	None	N/A	OR (per 10 ppb)	1.23	0.94, 1.60	NR		
			N/A	27.1-30.2						1.54	0.91, 2.61			
				30.3-33.9						2.18	1.30, 3.68			
				34.0 +						1.62	0.95, 2.67			
Hwang <i>et al.</i> (2013)	Taiwan Children Health Study	3,816	44.64	30.34-59.12	Asthma	3-yr avg from 8-hr avgs	None	GSTP-1 Ile-Ile	OR per 8.77 ppb	0.74	0.60, 0.90	0.03		
										GSTP-1 Ile-Val or Val-Val	1.19	0.91, 1.57		
					Wheezing					GSTP-1 Ile-Ile	0.82	0.69, 0.96	0.049	
										GSTP Ile-Val or Val-Val	1.09	0.88, 1.82		
					Asthma					CO	GSTP-1 Ile-Ile	0.72	0.58, 0.88	NR
										GSTP Ile-Val or Val-Val	1.30	0.96, 1.77		
										NO ₂	GSTP-1 Ile-Ile	0.72	0.59, 0.88	NR
										GSTP Ile-Val or Val-Val	1.24	0.92, 1.66		
										SO ₂	GSTP-1 Ile-Ile	0.76	0.62, 0.94	NR
										GSTP Ile-Val or Val-Val	1.18	0.89, 1.57		
					Wheezing					CO	GSTP-1 Ile-Ile	0.83	0.69, 0.98	NR
										GSTP Ile-Val or Val-Val	1.14	0.90-1.45		
	NO ₂	GSTP-1 Ile-Ile	0.81	0.69, 0.96	NR									
	GSTP Ile-Val or Val-Val	1.10	0.88-1.38											
	SO ₂	GSTP-1 Ile-Ile	0.84	0.71, 0.99	NR									
	GSTP Ile-Val or Val-Val	1.11	0.88, 1.40											

Notes:

Ann. = annual; ARG1 = arginase gene; ARG2 = arginase 2 gene; CHS = Children's Health Study; CHIS = California Health Interview Survey; CI = confidence interval; EGEE = Epidemiological study on Genetics and Environment of Asthma; GSTP = glutathione S-transferase pi gene; HR = hazard ratio; ICHIS = NY State Integrated Child Health Information System; munis = municipalities; N/A = not applicable; NHIS = National Health Interview Survey; NR = not reported; OR = odds ratio.

(a) The authors did not specify the level of ozone present in low-ozone communities; it is assumed to be < 50 ppb, but it is unclear what the minimum ozone values were.

(b) Ozone concentrations were obtained from US EPA (2013); actual concentrations were not noted in the study report by Raga *et al.* (2009a).

(c) CAT (rs1001179): G-330A.; MPO (rs2333227): G-463A.

Table 3 Epidemiology Studies of Long-term Ozone Exposure and Asthma Hospital Admissions and Emergency Department Visits

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging time	Co-pollutants/ Co-variates	Subject Group (Genotype)	Effect Measure	Estimate	95% CI	p-value				
Moore <i>et al.</i> (2008)	CA South Coast Air Basin	13.2 mil	87.7 (median)	28.6-199.9	Proportion of asthma hospitalization	Quarterly 1-hr max	None	N/A	Percent increase (per 10 ppb)	4.6	NR	NR				
Karr <i>et al.</i> (2007)	CA South Coast Air Basin	18,595 cases; 169,472 controls	23	2-96	Bronchiolitis hospital admission	Mean 8-hr max 1-mo prior	None	N/A	OR per 10 ppb	0.92	0.88, 0.97	NR				
													From birth		0.92	0.88, 0.96
													1-mo prior	PM _{2.5}	0.98	0.91, 1.07
													From birth		1.02	0.94, 1.10
													1-mo prior	CO + NO ₂	0.90	0.84, 0.96
													From birth		0.89	0.84, 0.95
													1-mo prior	PM _{2.5} , CO + NO ₂	0.96	0.86, 1.08
From birth		1.00	0.90, 1.11													
Meng <i>et al.</i> (2010)	CHIS; San Joaquin Valley CA	1,502	30.3	IQR: 27.1-34.0	ER/ hospital visits	Ann avg.	None	N/A	OR (per 10 ppb)	1.49	1.05, 2.11	NR				
			N/A	27.1-30.2						2.35	1.12, 4.95					
				30.3-33.9						1.80	0.82, 3.95					
				34.0 +						2.65	1.26, 5.57					
Lin <i>et al.</i> (2008)	ICHIS, New York State	1.2 mil	37.51-47.78	NR	Asthma hospitalization	8-hr max	PM ₁₀ , PM _{2.5} , NO ₂ , SO ₂	Mean ozone level (per 1 ppb increase/day)	OR	1.16	1.15, 1.17	NR				
										Mean concentration during ozone season (per 1 ppb increase/day)	1.22	1.21, 1.23	NR			
										Exceedance proportion (%) > 70 ppb per 2.51% increase in ozone	1.68	1.64, 1.73	NR			
										Low exposure (31.46-37.29)	1.00 (ref)	N/A	N/A			
										Medium exposure in NYC (37.30-38.11)	1.43	1.29, 1.58	NR			
										High exposure in NYC (38.12-50.13)	1.69	1.52, 1.80	NR			
										High exposure in other NYS regions (33.50-42.57)	1.00 (ref)	N/A	N/A			
										Medium exposure in other NYS regions (42.58-45.06)	1.64	1.48, 1.82	NR			
High exposure in other NYS regions (45.07-55.19)	2.06	1.87, 2.27	NR													

Notes:
 Ann. = annual; CHIS = California Health Interview Survey; CI = confidence interval; ER = emergency room; mo = month; N/A = not applicable; NR = not reported; OR = odds ratio; ref = referent group.

(a) The authors noted that they performed analyses using multipollutant models, but results did not differ significant so they did not present those data.

Statistically significant results are bold.

Table 4 Epidemiology Studies of Long-term Ozone Exposure and Pulmonary Structure and Function

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/ Co-variates	Subject Group	Effect Measure	Estimate	95% CI	p-value	
Islam <i>et al.</i> (2007)	CHS, 12 southern California communities	2,057	28.5 ^a	NR	New onset asthma	10 am- 6 pm avg. over 8 yrs	None	LM	HR over 10 th -90 th percentile range of FEF ₂₅₋₇₅	0.35 ^a	NR	0.64	
			30.0 ^a					SM		0.49 ^a			
			37.0 ^a					LG		0.63 ^a			
			41.2 ^a					AT		0.55 ^a			
			44.7 ^a					AL		1.26 ^a			
			45.3 ^a					LN		0.20 ^a			
			46.4 ^a					LE		0.90 ^a			
			51.7 ^a					RV		1.15 ^a			
			54.5 ^a					SD		0.27 ^a			
			54.8 ^a					UP		0.66 ^a			
			56.7 ^a					LB		0.74 ^a			
			65.0 ^a					ML		0.21 ^a			
Breton <i>et al.</i> (2011) ^b	CHS, 12 southern California communities	2,106	28.7 (least polluted) ^a	NA	FEV ₁	Ann. 10 am-6 pm avg.	None ^b	Haplotype 0100000	Change per 36.3 ppb	25.9	-102.4, 154.3	0.69	
			Other Haplotypes					-76.6		-224.3, 71.1			0.31
			Haplotype 0100000					14.0		-79.7, 107.8			0.77
			Other Haplotypes					-86.5		-239.1, 66.2			0.27
			FVC		Ann. 10 am-6 pm avg.	None ^b	Haplotype 0100000	Change per 36.3 ppb	0.1	-130.0, 130.1	1.00		
							Other Haplotypes		-17.2			-174.6, 140.3	0.83
							Haplotype 0100000		-10.9			-119.9, 98.0	0.84
							Other Haplotypes		-37.0			-198.8, 124.9	0.65
			MMEF		Ann. 10 am-6 pm avg.	None ^b	Haplotype 0100000	Change per 36.3 ppb	136.5	-80.7, 353.7	0.22		
							Other Haplotypes		-200.3			-466.9, 66.2	0.14
							Haplotype 0100000		118.5			-54.8, 291.8	0.18
							Other Haplotypes		-202.5			-478.5, 73.6	0.15

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/ Co-variables	Subject Group	Effect Measure	Estimate	95% CI	p-value
Latzin <i>et al.</i> , 2009	Newborns in Bern, Switzerland	241	Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	Minute ventilation (mL/min)	9 mos.	None ^d	All newborns	Change per 1 µg/m ³	0.7	-2.8, 4.2	0.696
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.2	-5.0, 4.6	0.929
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	Mean tidal expiratory flow (mL/sec)		None ^d			0.2	-0.9, 1.3	0.749
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			2.4	0.27, 4.6	0.028
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	Mean tidal inspiratory flow (mL/sec)		None ^d			0.05	-0.08, 0.19	0.448
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.04	-0.22, 0.14	0.560
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	Respiratory rate (breaths/min)		None ^d			-0.01	-0.05, 0.03	0.601
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			0.09	0.005, 0.17	0.038
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	Tidal volume (mL)		None ^d			-0.007	-0.13, 0.12	0.909
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			0.05	-0.12, 0.22	0.560
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	FRC _{ao} (mL/kg)		None ^d			0.03	-0.01, 0.07	0.145
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			0.07	-0.004, 0.15	0.063
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	LCI		None ^d			0.08	-0.07, 0.22	0.297
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.005	-0.20, 0.19	0.961
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	eNO (ppb)		None ^d			-0.01	-0.06, 0.04	0.629
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			0.09	0.007, 0.18	0.035
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)		None ^d			-0.02	-0.09, 0.06	0.629
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			0.01	-0.09, 0.11	0.830
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)		None ^d			0.01	-0.02, 0.03	0.611
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.01	-0.06, 0.03	0.573
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)		None ^d			0.01	-0.04, 0.07	0.635
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			0.03	-0.06, 0.11	0.537
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)		None ^d			-0.002	-0.02, 0.02	0.780
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.008	-0.05, 0.03	0.649
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)		None ^d			-0.001	-0.01, 0.01	0.825
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.006	-0.02, 0.01	0.368
			Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)		None ^d			0.001	-0.006, 0.01	0.819
			Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c			None ^e			-0.02	-0.11, 0.06	0.608
Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)	None ^d	0.01	-0.09, 0.11	0.856						
Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c		None ^e	0.01	-0.02, 0.04	0.418						
Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)	None ^d	0.02	-0.02, 0.07	0.302						
Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c		None ^e	-0.21	-3.7, 3.3	0.905						
Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)	None ^d	-0.13	-4.7, 4.5	0.956						
Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c		None ^e	0.17	-0.93, 1.28	0.758						
Prenatal O ₃ : 45.2 ^c	38.6-58.2 ^c	NO output (pL/sec)	None ^d	0.97	-1.09, 3.03	0.356						
Postnatal O ₃ : 45.6 ^c	13.0-81.4 ^c		None ^e									

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/ Co-variables	Subject Group	Effect Measure	Estimate	95% CI	p-value	
Forbes <i>et al.</i> 2009	The Health Survey for England	NR	NR	NR	FEV ₁ (mL)	NR	None ^f	Model A	Difference per 10 µg/m ³	22	3, 40	NR	
		11,400	27.8 ^c (median)	IQR: 25.2-30.4 ^c			None ^g	Model B: 1995 cohort		-48	-82, -15	NR	
		11,963	27.0 ^c (median)	IQR: 24.7-29.2 ^c			None ^g	Model B: 1996 cohort		39	-4, 82	NR	
		6,359	26.4 ^c (median)	IQR: 24.4-28.4 ^c			None ^g	Model B: 1997 cohort		57	-10, 123	NR	
		10,607	27.0 ^c (median)	IQR: 23.9-30.1 ^c			None ^g	Model B: 2001 cohort		5	-50, 60	NR	
		40,329	NR	NR			None ^g	Model B: combined		-4	-26, 19	NR	
		20,545	NR	NR			None ^g	NR		Ages 16-44	-21	-51, 9	NR
		19,082								Ages 45-75	3	-26, 32	NR
		3,348								Ages 75+	19	-45, 82	NR
		NR	NR	NR						Never smokers	-22	-51, 7	NR
		NR			Ex-smokers	17			-19, 53	NR			
		NR			Current smokers	-9			-48, 30	NR			
		NR	NR	NR	None ^f	NR			Model C	0.0	-0.4, 0.3	NR	
		11,400	27.8 ^c (median)	IQR: 25.2-30.4 ^c			None ^g	Model D: 1995 cohort	-0.2	-0.9, 0.6	NR		
		11,963	27.0 ^c (median)	IQR: 24.7-29.2 ^c				Model D: 1996 cohort	-0.2	-1.0, 0.7	NR		
		6,359	26.4 ^c (median)	IQR: 24.4-28.4 ^c				Model D: 1997 cohort	1.3	0.0, 2.7	NR		
		10,607	27.0 ^c (median)	IQR: 23.9-30.1 ^c				Model D: 2001 cohort	-0.6	-1.7, 0.5	NR		
		40,329	NR	NR		Model D: combined	-0.1	-0.5, 0.4	NR				

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging Time	Co-pollutants/ Co-variables	Subject Group	Effect Measure	Estimate	95% CI	p-value	
Rojas-Martinez <i>et al.</i> , 2007	Mexico	3,170	69.8	54.5 (10 th percentile) 85.4 (90 th percentile)	FVC (mL)	Ann. 10 am-6 pm avg.	None ^h	Girls	Change per 11.3 ppb	-35	-41, -29	< 0.0001	
							PM ₁₀			-25	-32, -19	< 0.0001	
							NO ₂			-22	-29, -16	< 0.0001	
							PM ₁₀ + NO ₂			-19	-25, -12	< 0.0001	
							None ^h	Boys		-25	-31, -19	< 0.0001	
							PM ₁₀			-18	-24, -11	< 0.0001	
							NO ₂			-13	-20, -7	< 0.0001	
							PM ₁₀ + NO ₂			-9	-16, -2	< 0.0001	
							FEV ₁ (mL)	None ^h		Girls	-24	-30, -19	< 0.0001
								PM ₁₀			-17	-23, -12	< 0.0001
								NO ₂			-16	-22, -10	< 0.0001
								PM ₁₀ + NO ₂			-12	-18, -6	< 0.0001
					None ^h	Boys		-16	-21, -11	< 0.0001			
					PM ₁₀			-11	-16, -5	< 0.0001			
					NO ₂			-8	-14, -2	< 0.0001			
					PM ₁₀ + NO ₂			-4	-10, 2	NR			
					FEF ₂₅₋₇₅ (mL)	None ^h		Girls	-20	-32, -8	< 0.005		
						PM ₁₀			-18	-30, -6	< 0.005		
						NO ₂			-19	-31, -8	< 0.005		
						PM ₁₀ + NO ₂			-18	-30, -5	< 0.05		
						None ^h	Boys	-8	-19, 4	NR			
						PM ₁₀		-6	-18, 5	NR			
						NO ₂		-6	-18, 5	NR			
						PM ₁₀ + NO ₂		-4	-16, 8	NR			
						FEV ₁ /FVC (%)	None ^h	Girls	0.29	0.17, 0.40	< 0.0001		
							PM ₁₀		0.21	0.11, 0.32	< 0.0001		
							NO ₂		0.22	0.09, 0.34	< 0.005		
							PM ₁₀ + NO ₂		0.18	0.07, 0.29	< 0.005		
					None ^h		Boys	0.26	0.16, 0.37	< 0.0001			
					PM ₁₀			0.24	0.13, 0.34	< 0.0001			
					NO ₂			0.22	0.09, 0.34	< 0.005			
					PM ₁₀ + NO ₂			0.21	0.08, 0.33	< 0.005			
					FVC (%)		None ^h	Girls	-1.07	-1.28, -0.86	< 0.0001		
							PM ₁₀		-0.81	-1.02, -0.60	< 0.0001		
							NO ₂		-0.74	-0.96, -0.52	< 0.0001		
							PM ₁₀ + NO ₂		-0.62	-0.85, -0.39	< 0.0001		
						None ^h	Boys	-0.76	-0.94, -0.58	< 0.0001			
						PM ₁₀		-0.62	-0.81, -0.44	< 0.0001			
						NO ₂		-0.50	-0.70, -0.29	< 0.0001			
						PM ₁₀ + NO ₂		-0.36	-0.58, -0.14	< 0.005			
						FEV ₁ (%)	None ^h	Girls	-0.68	-0.89, -0.48	< 0.0001		
							PM ₁₀		-0.55	-0.76, -0.34	< 0.0001		
							NO ₂		-0.51	-0.73, -0.28	< 0.0001		
							PM ₁₀ + NO ₂		-0.40	-0.63, -0.16	< 0.005		
					None ^h		Boys	-0.46	-0.65, -0.27	< 0.0001			
					PM ₁₀			-0.34	-0.54, -0.15	< 0.005			
					NO ₂			-0.28	-0.49, -0.07	< 0.05			
					PM ₁₀ + NO ₂			-0.18	-0.40, 0.04	> 0.05			

Notes:

Ann. = annual; CHS = Children's Health Study; CI = confidence interval; eNO = exhaled nitric oxide; FEF₂₅₋₇₅ = forced expiratory flow over the mid-range of expiration; FEV₁ = forced expiratory volume in one second; FRC_{ao} = functional residual capacity at airway opening; FVC = forced vital capacity; HR = hazard ratio; LCI = lung clearance index; MMEF = maximal mid-expiratory flow rate; NA = not applicable; NR = not reported; O₃ = ozone; PM_{2.5} = particulate matter with an aerodynamic diameter no greater than 2.5 µm.

(a) Ozone concentrations estimated from a digitized graph using GetData Graph Digitizer.

(b) The ozone concentration estimates for the most and least polluted cities are associated with an estimation error, as the difference in concentrations between these two communities should equal 36.3. Models are also adjusted for height, sex, BMI, ever having asthma, respiratory illness at time of testing, exercise, smoking, ethnicity, cohort, town, field technician, GSTM1, and ancestry indicators (q factors).

(c) Units were converted from µg/m³ to ppb using a conversion factor of 0.521 (value in µg/m³ * 0.521 = value in ppb, per US EPA (2013)).

(d) Models are adjusted for sex, post-natal age, season of birth, outdoor temperature on measurement day, and maternal smoking in pregnancy.

(e) Models are adjusted for sex, post-natal age, season of birth, outdoor temperature on measurement day, maternal smoking in pregnancy, and minute ventilation.

(f) Models are adjusted for age, sex, height, and all their two-way interactions.

(g) Models are adjusted for age, sex, height, all their two-way interactions, pack-years of active smoking, passive smoking in non-smokers, social class, region, and season.

(h) Models are adjusted for age, BMI, height, height by age, weekday time spent in outdoor activities, environmental tobacco smoke exposure, previous-day mean air pollution concentration, and time since first test.

Table 5 Epidemiology Studies of Long-term Ozone Exposure and Allergic Responses and Host Defense

Study	Cohort/Region	n	Mean Ozone Conc. (ppb)	Ozone Range (ppb)	Outcome	Averaging time	Co-pollutants/Co-variables	Subject Group (Genotype)	Effect Measure	Estimate	95% CI	p-value	
Parker <i>et al.</i> (2009) [NHIS	58,147	31.5 (median)	IQR: 27.6 to 35.1	Childhood respiratory allergy/hay fever	5 mos. (summer) 8-hr avg.	None	NA	OR per 10 ppb	1.18	1.13-1.23	NR	
							None ^a			1.15	1.11-1.20	NR	
							None ^b			1.20	1.15-1.26	NR	
							None			1.24	1.15-1.34	NR	
SO ₂ , NO ₂ , PM _{2.5} , + PM _{2.5-10}	OR per 10 ppb ^c	1.18	1.09-1.27	NR									
Wenten <i>et al.</i> (2009)	CHS,	1,136	46.9 ^b	27.6-65.3	Respiratory-related school absence	10 am-6 pm avg	None	CAT G/A or A/A and MPO G/G ^c	RR	1.15	0.87, 1.53	NR	
								" genes; low-ozone community		1.07	0.73, 1.56		
								" genes; high-ozone		1.23	0.80, 1.88		
								CAT G/G and MPO G/A or A/A ^c		1.35	1.03, 1.77		
								" genes; low-ozone community		1.21	0.83, 1.75		
								" genes; high-ozone		1.45	0.99, 2.14		
								CAT G/A or A/A and MPO G/A or A/A ^c		0.81	0.55, 1.19		
								" genes; low-ozone community		1.04	0.66, 1.65		
" genes; high-ozone	0.42	0.20, 0.89											
Rage <i>et al.</i> (2009b)	EGEA	367	23.4 ^d	IQR: 20.5-25.1 ^d	IgE	NR	None	NA	% Change per 10 µg/m ³ increase	19.1	2.4-38.6	NR	
			32.5 ^d (summer-only)							NO ₂	13.8	-7.9-40.6	NR
										None	16.9	2.5-33.2	NR
										NO ₂	-6.2	-23.4-15.0	NR

Notes:

AOR = adjusted odds ratio; CI = confidence interval; NA = not applicable; NHIS = National Health Interview Survey; NR = not reported; OR = odds ratio.

(a) Model adjusted for year, poverty, race, family structure, insurance, usual source of care, age, and education of adult.

(b) Model adjusted for year, poverty, race, family structure, insurance, usual source of care, age, education of adult, urban status, region, and median income of county.

(c) Adjusted odds ratio.

(d) Units were converted from µg/m³ to ppb using a conversion factor of 0.521 (value in µg/m³ * 0.521 = value in ppb, per US EPA, 2013).

Table 6 Animal Studies of Long-term Ozone Exposure and Respiratory Effects in Infant Monkeys

Study	n	Exposure Duration	Outcome	Results (Average ± SD)			p-value	
				Exposure Level (ppb)				
				0	500	500 + HDMA		
Fanucchi <i>et al.</i> (2006)	12 (M)	5 mos. (11 cycles of 5 d of O ₃ 8 hr/d followed by 9 d of FA)	Terminal bronchiole diameter, μm	1,010 ± 226	630 ± 153	N/A	0.073	
			Terminal bronchiole length, μm	882 ± 239	480 ± 92.7	N/A	0.053	
			Respiratory bronchiole diameter, μm	958 ± 43.3	568 ± 192	N/A	0.026	
			Respiratory bronchiole length, μm	1,088 ± 357	693 ± 288	N/A	0.210	
			No. airway branches, right cranial ^a	13.29 ± 0.96	10.23 ± 0.38	N/A	< 0.05	
			No. airway branches, right middle ^a	13.04 ± 1.66	10.56 ± 2.36	N/A	> 0.05	
			No. airway branches, left cranial: cranial segment ^a	13.95 ± 2.23	10.45 ± 1.34	N/A	< 0.05	
			No. airway branches, left cranial: caudal segment ^a	14.47 ± 1.66	11.29 ± 1.85	N/A	< 0.05	
Carey <i>et al.</i> (2007) ^a	NR	70 days (cycles of 5 d of O ₃ 8 hr/d followed by 9 d of FA)	Epithelial thickness (μm)	58.9 ± 6.50	30.6 ± 6.89	N/A	< 0.05	
			Ciliary volume density (μm ³ /μm ²)	7.53 ± 0.98	2.72 ± 1.36	N/A	< 0.05	
			Cytoplasmic volume density (μm ³ /μm ²)	30.8 ± 4.99	14.8 ± 3.04	N/A	< 0.05	
			Nuclear volume density (μm ³ /μm ²)	17.4 ± 1.52	11.4 ± 2.76	N/A	> 0.05	
Plopper <i>et al.</i> (2007) ^a	NR	5 mos. (11 cycles of 5 d of O ₃ for 8 hr/d followed by 9 d of FA; or 11 cycles of 2 hr/d of HDMA allergen + O ₃)	No. respiratory bronchiole branches, right cranial after 6 mos	15.1 ± 1.02	11.4 ± 0.61	9.37 ± 0.61	< 0.05	
			No. respiratory bronchiole branches, right middle after 6 mos.	16.4 ± 0.61	11.88 ± 0.61	11.17 ± 1.02	< 0.05	
			No. respiratory bronchiole branches, right cranial after 1 yr	16.29 ± 1.23	12.81 ± 0.92	11.89 ± 0.92	< 0.05	
			No. respiratory bronchiole branches, right middle after 1 yr	17.53 ± 1.74	14.04 ± 0.82	15.06 ± 1.43	< 0.05	
			Mucous goblet cells mass (μm ³ /μm ²) at 6 mos.	0.77 ± 0.75	2.17 ± 1.28	3.21 ± 1.14	< 0.05	
			Epithelial eosinophil volume (x 10 ⁻⁵ mm ³ /mm ²)	13.95 ± 4.65	18.60 ± 13.95	204.65 ± 60.5	> 0.05 ^b < 0.001^c	
			Interstitial eosinophil volume (x 10 ⁻⁵ mm ³ /mm ²)	176.7 ± 65.1	279.1 ± 116.3	507.0 ± 83.7	> 0.05 ^b < 0.001^c	
Miller <i>et al.</i> (2009) ^a	24 (M)	5 mos. (11 cycles of 5 d of O ₃ for 8 hr/d followed by 9 d of FA; or 11 cycles of 2 hr/d of HDMA allergen + O ₃)	Airway epithelial CD25+ cells (x 10 ⁵ mm ³ /mm ²)	0.6 ± 5.53	0.55 ± 1.11	60.28 ± 23	> 0.05 ^b < 0.01^c	
			Airway interstitial CD25+ cells (x 10 ⁵ mm ³ /mm ²)	2.34 ± 4.41	8.12 ± 7.71	53.84 ± 20.9	> 0.05 ^b < 0.01^c	
			Airway epithelial CD4+ cells (x 10 ⁵ mm ³ /mm ²)	151.0 ± 52.46	154.7 ± 32.8	224.4 ± 62.3	> 0.05	
			Airway interstitial CD4+ cells (x 10 ⁵ mm ³ /mm ²)	1346.9 ± 359	1265.4 ± 303	1411.5 ± 163	> 0.05	
			BAL CD4+ cells, % CD25+ positive	3.54 ± 0.58	6.57 ± 1.74	18.7 ± 2.60	> 0.05 ^b < 0.05^c	
			BAL CD8+ cells, % CD25+ positive	1.27 ± 0.58	11.08 ± 2.04	16.75 ± 1.16	> 0.05 ^b < 0.01^c	
			Van Winkle <i>et al.</i> (2010) ^a	24 (M)	5 mos. (11 cycles of 5 d of O ₃ for 6 hr/d followed by 9 d of FA; or 11 cycles of 2 hr/d of HDMA allergen + O ₃)	Tracheal MC _T volume (μm ³ /μm ²)	7.46 ± 2.59	8.41 ± 3.24
Tracheal MC _{TC} volume (μm ³ /μm ²)	1.78 ± 0.43	3.74 ± 0.50				4.07 ± 0.50	> 0.05	
Intrapulmonary MC _T volume (μm ³ /μm ²)	2.93 ± 0.56	2.83 ± 0.59				4.82 ± 0.70	> 0.05	
Intrapulmonary MC _{TC} volume (μm ³ /μm ²)	0.22 ± 0.08	0.88 ± 0.19				1.44 ± 0.32	> 0.05	
Maniar-Hew <i>et al.</i> (2011) ^d	4-9/group	5 mos. (11 cycles of 5 d of O ₃ for 8 hr/d followed by 9 d of FA)				BAL, total cells (x 10 ⁵)	115 ± 25	115 ± 60
			BAL, No. PMN (x 10 ⁵)	6.0 ± 6.5	0.5 ± 0.5	N/A	> 0.05	
			BAL, No lymphocytes (x 10 ⁵)	16 ± 4.0	2.0 ± 1.0	N/A	< 0.05	
			BAL, No. monocytes (x 10 ⁵)	1.0 ± 0.5	0.05 ± 0.01	N/A	> 0.05	
			BAL, No. eosinophils (x 10 ⁵)	2.5 ± 1.5	12.6 ± 6.4	N/A	< 0.05	
			BAL, No. macrophages (x 10 ⁵)	99 ± 12	105 ± 50	N/A	> 0.05	
			Post-exposure, 6 mos. FA; LPS challenge at 1 yr	BAL, total cells 6 hrs after LPS ^a	16.81 ± 5.32	8.65 ± 0.76	N/A	< 0.05
			BAL, total cells 24 hrs after LPS ^a	21.4 ± 4.41	10.96 ± 1.83	N/A	< 0.05	

Notes:

BAL = bronchoalveolar lavage; FA = filtered air; HDMA = house dust mite (*Dermatophagoides farinae*) allergen; LPS = lipopolysaccharides; MC_T = tryptase; MC_{TC} = chymase; N/A = not available; No. = number; PMN = polymorphonuclear leukocytes.

(a) Data estimated from figures in the original report using GetData Graph Digitizer.

(b) p-value refers to results from 500 ppb exposure level.

(c) p-value refers to results from 500 + HDMA exposure level

(d) All values were estimated manually using bar charts in Maniar-Hew *et al.* (2011); digitizer software could not be used due to breaks in the scale, except where noted.

Long-Term Ozone Exposure and Mortality

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Table 1 Epidemiology Studies of Long-term Ozone Exposure and Mortality

Abbreviations

ACS	American Cancer Society
AHSMOG	Adventist Health Study of Smog
AQCD	Air Quality Criteria Document
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
EPA	United States Environmental Protection Agency
HR	Hazard Ratio
IHD	Ischemic Heart Disease
ISA	Integrated Science Assessment
MI	Myocardial Infarction
MSA	Metropolitan Statistical Area
PPB	Parts Per Billion
PM	Particulate matter
PM _{2.5}	Particulate matter with an aerodynamic diameter less than or equal to 2.5 micrometers
RR	Relative Risk
SLA	Statistical Local Area
UARG	Utility Air Regulatory Group

1 Overview

Gradient was asked by the Utility Air Regulatory Group (UARG) to review and prepare comments on the evidence regarding long-term exposures to ozone and mortality. Specifically, Gradient was asked to critically review the new studies that the United States Environmental Protection Agency (EPA) considered in the *Integrated Science Assessment for Ozone and Related Photochemical Oxidants – Final Report* (ISA) (US EPA, 2013) to support upgrading the relationship between long-term ozone exposure and mortality from "little evidence to suggest a causal relationship" to "suggestive of a causal relationship." These studies included those by Jerrett *et al.* (2009), Smith *et al.* (2009), Wang *et al.* (2009), and Zanobetti and Schwartz (2011). The studies by Jerrett *et al.* (2009) and Smith *et al.* (2009) are both re-analyses of the American Cancer Society's (ACS) Cancer Prevention Study II cohort. An additional re-analysis was conducted by Krewski *et al.* (2009), but results from this study are only discussed in the ISA in the context of lung cancer mortality.

In the ISA, EPA appears to base its upgraded causality determination primarily on the positive findings associated with respiratory mortality reported by Jerrett *et al.* (2009), despite many issues with this study, and more limited support from Smith (2009) and Zanobetti and Schwartz (2011). An additional study by Wang *et al.* (2009), conducted in Brisbane, Australia, was also discussed by EPA, but the null findings from this study were generally dismissed.

We critically review these key studies and also discuss key findings that were evaluated by EPA in the 2006 ozone Air Quality Criteria Document (AQCD) (US EPA, 2006). In addition, we evaluate two recent studies that were not included in the ISA. We conclude that the overall body of epidemiology studies that have evaluated long-term exposures to ozone and mortality remains limited, with results that are inconsistent and uncertain (Table 1). The evidence from the most recent studies, including those reviewed in the ISA, does not support upgrading the causality determination for mortality from long-term ozone exposures.

2 Long-term Ozone Exposure and Mortality Studies Evaluated in the ISA

2.1 American Cancer Prevention Study II Cohort Re-analyses

Of the studies of long-term ozone exposure and mortality discussed in the ISA, the Krewski *et al.* (2009), Smith *et al.* (2009), and Jerrett *et al.* (2009) studies are all re-analyses of the ACS Cancer Prevention Study II cohort. Although it is difficult to compare the reported mortality estimates across these studies because each study used a different exposure metric (*e.g.*, 1-hour or 8-hour maximum), all the mortality estimates were small [relative risks (RRs) range from 1.001 to 1.03] and there were differences in the reported statistical significance of the mortality effects both within and among studies. For example, in an extended follow-up of the ACS cohort (1982-2000), Krewski *et al.* (2009) evaluated the association between annual average ozone and summer-only concentrations in 1980 and all-cause, cardiopulmonary, ischemic heart disease (IHD), lung cancer, and all-other-cause mortality. For all-cause and cardiopulmonary mortality, Krewski *et al.* (2009) reported a significant association for summer-only ozone exposures [RR = 1.02, 95% confidence interval (CI): 1.01-1.02 for all-cause and RR = 1.03, 95% CI: 1.02-1.04 for cardiopulmonary per 10 parts per billion (ppb) ozone], but not for annual average ozone exposure. Relying on only one year/season of ozone data (1980) and the lack of adjustment for co-pollutants may have impacted effect estimates.

In another follow-up study, Smith *et al.* (2009) examined data from 66 Metropolitan Statistical Areas (MSAs) to determine the association between ozone concentrations during the warm season and all-cause and cardiopulmonary mortality. This study utilized data that included 18 years of follow-up (Smith *et al.*, 2009). Mortality was evaluated in single-pollutant models and in models adjusted for two particulate matter (PM) constituents, sulfate and elemental carbon. Smith *et al.* (2009) reported no significant associations for all-cause mortality, but found an association for cardiopulmonary mortality (RR = 1.025, 95% CI: 1.01-1.04 per 10 ppb ozone) in their summer-only analysis. These results were attenuated and no longer statistically significant after adjustment for elemental carbon (RR = 1.016, 95% CI: 0.996-1.037 per 10 ppb ozone).

Jerrett *et al.* (2009) evaluated the mortality risks associated with long-term ozone exposure in single- and two-pollutant models with particulate matter less than or equal to 2.5 micrometers in diameter (PM_{2.5}). The authors evaluated the ACS cohort data from 1977 through 2000 in 96 and 86 cities, for single- and two-pollutant models, respectively. They included separate evaluations for respiratory and cardiovascular-related mortality, as well as for the combined cardiopulmonary endpoint (including conditions of the heart and/or lungs) that had been previously evaluated by Pope *et al.* (2002) and others. Jerrett *et al.* (2009) reported some small increases in mortality, but the results were inconsistent across the mortality endpoints evaluated, including all-cause, cardiopulmonary, respiratory, cardiovascular, and IHD mortality. Specifically, in single-pollutant models, exposure to ozone was not associated with all-cause mortality, but was correlated with a small, but statistically significant, increase in the risk of cardiopulmonary death per 10 ppb ozone (RR = 1.016, 95% CI: 1.01-1.02) in the two-pollutant model. In addition, small and statistically significant effects were observed for cause-specific deaths, including cardiovascular (RR = 1.014, 95% CI: 1.01-1.02), IHD (RR = 1.017, 95% CI: 1.01-1.03), and respiratory (RR = 1.027, 95% CI: 1.01-1.05) mortality, in the same analysis of 86 cities (see Table 3 in Jerrett *et al.*,

2009). All of these estimates, with the exception of respiratory mortality, were null in two-pollutant models (Table 1).

As reviewed by Taubes (1995), epidemiologists generally consider risk estimates greater than 3 or 4 to reflect strong associations and to be supportive of a causal link, while smaller risk estimates (1.5 to 3) are considered to be weak and require other lines of evidence to demonstrate causality. As discussed by Boffetta *et al.* (2008) and Fewell *et al.* (2007), it is plausible that risk estimates on the order of 1.5 to 2.0 and below can be explained by confounding variables. This is likely the case with the studies by Krewski *et al.* (2009), Smith *et al.* (2009), and Jerrett *et al.* (2009). As noted above, Krewski *et al.* (2009) did not report results from multi-pollutant models, but both Smith *et al.* (2009) and Jerrett *et al.* (2009) showed mortality effects that were attenuated or null when co-pollutants were included in the model. As noted by Jerrett *et al.* (2009), the association of ozone with cardiovascular endpoints was particularly sensitive to adjustment for PM_{2.5}, such that it was difficult to determine the independent contributions of ozone and PM_{2.5} to statistical associations. While small statistical associations between ozone and respiratory mortality could be attributable to a number of factors (*e.g.*, chance, unmeasured confounding), the fact that ozone and PM_{2.5} were highly correlated indicates any association with ozone could just as likely be attributable to PM_{2.5}.

EPA highlights results from the study by Jerrett *et al.* (2009) as demonstrating an increased risk of respiratory mortality from long-term ozone exposure, but does not adequately consider a number of findings in this study that call the respiratory mortality findings into question. This is particularly important because this is the only study discussed in the ISA that reported a significant association for respiratory deaths independently from cardiopulmonary effects. As discussed in more detail below, no statistical associations between long-term ozone exposures and non-malignant respiratory deaths have been reported in other studies (Abbey *et al.*, 1999; Lipsett *et al.*, 2011).

EPA acknowledges that environmental temperature and region of the country are significant modifiers of the association between ozone concentration and respiratory mortality in the Jerrett *et al.* (2009) study. Jerrett *et al.* (2009) did not observe statistically significant associations between ozone concentration and respiratory deaths in two of the US regions with the largest number of respiratory deaths (the Northeast and Industrial Midwest regions), or in the Southern California region, which has some of the highest ozone concentrations in the US. In addition, these regional patterns in associations between ozone and respiratory mortality are opposite to those observed by Bell and Dominici (2008) for short-term ozone exposure and all-cause, total non-accidental mortality, where the highest ozone-mortality risk estimates were observed in the Northeast and Industrial Midwest regions, and no statistically significant associations were observed in the Southwest and Urban Midwest [*i.e.*, the locations observed by Jerrett *et al.* (2009) to have the greatest risk estimates for ozone-related deaths from respiratory causes]. Moreover, the ozone association with respiratory mortality was only statistically significant for external temperatures in excess of 28 degrees Celsius, suggesting a potential confounding role of temperature.

Controlling for confounding is much more complicated in long-term cohort studies, such as the ACS studies, than in short-term exposure time-series studies. Inferences from long-term studies are based on differences in pollution levels between cities, as opposed to day-to-day differences in pollution levels in a single city. Thus, any factor that varies from city to city could be a potential confounder, including socioeconomic and lifestyle factors. Controlling for these factors is difficult, and residual confounding is likely present even after including confounders in statistical models. Jerrett *et al.* (2009) featured analyses that controlled for individual-level covariates that were taken from a 1982 enrollment questionnaire and additional neighborhood-level socioeconomic covariates (*e.g.*, education, poverty levels, and unemployment) based on 1980 census data. Although Jerrett *et al.* (2009) reported that effect estimates were fairly robust to adjustment for socioeconomic factors, because these factors were only

measured at a single time point (in 1982), they may not be representative of the complete time period studied.

EPA also did not account for several uncertainties in the approach used by Jerrett *et al.* (2009) to estimate exposures, including the use of ozone data from 1977 to 2000, but PM_{2.5} data from only 1999 to 2000, in their two-pollutant models. In addition, Jerrett *et al.* (2009) averaged the second and third quarterly averages to form a single time series of air pollution measurements for each metropolitan area. Tong *et al.* (2009) previously commented on the uncertainties associated with the use of a single ozone value, averaged over both space and time, to represent ozone exposures of the entire population within a metropolitan area. Thus, Jerrett's approach could have resulted in significant exposure measurement error. The same issues apply to the study re-analyses by Smith *et al.* (2009). Because Krewski *et al.* (2009) only used one year of ozone data, their estimates are likely to be even more uncertain. As discussed in more detail below, the Wang *et al.* (2009) study of long-term air pollution exposures and cardiorespiratory mortality in Brisbane, Australia used a more refined geospatial approach to estimate ozone concentrations at the statistical local area (SLA) level.

Furthermore, in EPA's discussion of Jerrett *et al.* (2009), little attention is given to the question of whether there is a threshold in the ozone-mortality relationship. Jerrett *et al.* (2009) observed a flattening of the ozone exposure-response curve for long-term average exposures to daily maximum ozone levels below 60 ppb. Based on a formal analysis that compared the model fit for a standard threshold model with that of a nonthreshold linear model, Jerrett *et al.* (2009) concluded that "There was limited evidence that a threshold model specification improved model fit as compared with a nonthreshold linear model ($p = 0.06$)." In the ISA, EPA downplayed these findings because they are not statistically significant. The statistical significance of a comparative model fit should not be considered in the absence of a consideration of a potential mode of action. Also, the distinct flattening of the concentration-response function provides at least some evidence of a threshold.

Jerrett *et al.* (2009), Smith *et al.* (2009), and Krewski *et al.* (2009) used the Cox proportional hazards model. Issues have been raised concerning the use of this model for analysis of long-term exposure studies. For example, Moolgavkar (2006) discussed limitations of analyses in long-term cohort studies. This model is based on two fundamental assumptions: (1) that the impact of exposures and potential confounders on hazard are constant over time, and (2) that the exposure and other covariates contribute linearly to the natural log of the hazard ratios.

With regard to the first assumption, it is unlikely that the associations between ozone exposures and potential confounders are constant over time. For example, Moolgavkar (2006) noted that cigarette smoking, a potential confounder of the associations between health effects and PM_{2.5} and ozone, has a time-varying effect on cardiovascular mortality. Furthermore, the risk for lung cancer is strongly dependent on the smoking duration and varies with age (Rachet *et al.*, 2004; Burns *et al.*, 1996, both as cited in Reiss *et al.*, 2007). In addition, Lipfert *et al.* (2000) reported decreasing ozone-mortality associations with increased follow-up time. Similarly, for PM_{2.5}, which tends to be highly correlated with ozone, researchers have shown that the risks of mortality have decreased over time (Laden *et al.*, 2006; Enstrom, 2005).

In terms of the second assumption, EPA and others have reported that the effects of air pollution may not contribute proportionately to health effects, as has been shown in the varied severity of health effects experienced between people of different ages exposed to the same level of air pollution. Abrahamowicz *et al.* (2003) tested whether the second assumption held for a subset of the ACS Cancer Prevention Study II cohort. They found that there was a statistically significant deviation from the traditional, low-dose linearity assumption that underlies the conventional Cox proportional hazard model for fine and sulfate particles. It is likely that this would be true for ozone as well.

2.2 The Medicare Cohort

EPA also stated that the recent study of a cohort of Medicare recipients by Zanobetti and Schwartz (2011) provides additional evidence of mortality from long-term ozone exposures. The authors compared the association between year-to-year variations in 8-hour mean daily ozone concentrations for the summer (May-September) and for transitional months (spring and autumn) with year-to-year variations in mortality among Medicare participants with chronic conditions that may have predisposed them to the effects of ozone, such as chronic obstructive pulmonary disease (COPD), diabetes, congestive heart failure (CHF), and myocardial infarction (MI). The analysis was conducted for 105 cities using data from 1985 through 2006; the results were combined using a random effects meta-regression analysis. Statistically significant results were reported for all cohorts, but only for the summer months; hazard ratios (HR, per 10 ppb increment) were reported to be 1.12 (95% CI: 1.06-1.17) for the CHF cohort, 1.19 (95% CI: 1.12-1.25) for the MI cohort, 1.14 (95% CI: 1.10-1.21) for the diabetes cohort, and 1.14 (95% CI: 1.08-1.19) for the COPD cohort. These associations were not significant for the spring and autumn ozone exposure data. A major limitation in this study was that PM_{2.5} and other co-pollutant data were unavailable and, hence, not adjusted for. As discussed above, most studies have reported associations that were null or attenuated and no longer statistically significant when co-pollutants were included in the model.

Furthermore, when the authors grouped cities into six regions with similar climates and controlled for temperature, none of the regional HRs were significant for any of the pre-existing conditions. This is contrary to what might be expected, given that certain regions, for example, US cities in the Southwest and West Coast that had higher mean summer ozone concentrations (48.6-71.4 ppb) compared to other regions, such as some cities in the southeastern US (Zanobetti and Schwartz, 2011, Figure 1). This may be indicative of confounding by temperature, and is consistent with the effect modification reported by Jerrett *et al.* (2009). Zanobetti and Schwartz (2011) also did not have information on important subject-specific confounders such as smoking, body mass index, and medication use.

2.3 Wang *et al.* (2009)

Wang *et al.* (2009) evaluated the association between long-term exposures to gaseous air pollutants (nitrogen dioxide, ozone, sulfur dioxide) and cardiorespiratory mortality in Brisbane, Australia for the period 1996 to 2004. A particular strength of this study was the use of geographical information system techniques to map the spatial patterns of the gas concentrations and to assign long-term exposure estimates at the SLA level. The authors then used a generalized estimating equations model to investigate the relationship between long-term exposures to these gases and cardiorespiratory mortality. For ozone, daily 1-hour maximum ozone concentrations were used in single- and multi-pollutant models. Wang *et al.* (2009) did not observe an association between long-term averages and mortality in either model. The lack of associations reported by Wang *et al.* (2009), who reported low ozone exposures (23.7-35.6 ppb), is consistent with the Jerrett *et al.* (2009) findings of a possible threshold for long-term average exposures to daily maximum ozone levels below 50 to 60 ppb. EPA acknowledged that the range of ozone exposure estimates across the Brisbane communities was low and of limited variability, but concluded that the low concentrations contributed to decreased study power for detecting an association between ozone exposure and health effects. Maximum 1-hour ozone concentrations in these Brisbane communities were well within the flat region of the Jerrett *et al.* (2009) exposure-response curve, indicating that a threshold is a possible alternative explanation for the lack of an ozone association in the Wang *et al.* (2009) study. EPA also dismissed these findings by emphasizing that Wang *et al.* (2009) is an ecologic study lacking information for individuals on potential confounders such as smoking. This is a major limitation that

applies to all of the ozone cohort studies, where this information was either not available (Zanobetti and Schwartz, 2011) or was poorly controlled for because of lack of follow-up (Jerrett *et al.*, 2009; Smith *et al.*, 2009; Krewski *et al.*, 2009) and thus does not mean the Wang *et al.* (2009) study should be given less weight in the analysis. As noted earlier, however, a particular strength of the Wang *et al.* (2009) study involved its use of a geospatial approach to estimate ozone concentrations for SLAs, rather than relying on exposure from a few monitor locations, potentially reducing exposure measurement error.

2.4 Conclusion

In the ISA, EPA discussed two recent re-analyses of the ACS cohort (Jerrett *et al.*, 2009; Smith *et al.*, 2009); another re-analyses conducted by Krewski *et al.* (2009) was discussed but only in the context of lung cancer mortality. EPA also briefly mentioned the study by Wang *et al.* (2009), but dismissed the null findings from this study, and instead highlighted the positive finding reported for respiratory mortality by Jerrett *et al.* (2009). In addition to the numerous uncertainties associated with all of these studies (*e.g.*, confounding effects and limitations of the statistical models), the lack of consistency in positive and statistically significant effects across the mortality endpoints calls into question EPA placing undue weight on a single finding from a single study.

3 Long-term Ozone Exposure and Mortality Studies Evaluated in the 2006 AQCD

EPA's focus in the ozone ISA is on studies published since the ozone AQCD, but one must consider the evidence from all relevant epidemiology analyses of long-term ozone exposures and mortality to evaluate whether the weight of evidence indicates there is likely to be an association. EPA provides a brief review of some of the key findings from prior epidemiology analyses of long-term ozone exposure and mortality in Section 7.7 of the ISA, highlighting the general lack of consistently positive associations for several studies of large cohorts, including the Harvard Six Cities, ACS, Adventist Health Study of Smog (AHSMOG), and US Veterans cohorts. While still relatively limited, the overall body of evidence from available studies shows a trend indicative of a lack of association between long-term ozone exposure and all-cause and cause-specific mortality. For historical studies, most report a lack of association between mortality and long-term ozone exposures. Specifically, all-cause mortality was not significantly associated with long-term ozone in Dockery *et al.* (1993); non-malignant lung disease, cardiopulmonary, and all-cause (natural) mortality were not significant in Abbey *et al.* (1999); and all-cause mortality was not associated with prior long-term ozone exposure in Lipfert *et al.* (2000).

One of the seminal studies reviewed in the AQCD of air pollution effects on mortality is the Harvard Six Cities Study (Dockery *et al.*, 1993). This prospective cohort study was comprised of a random sample of adults (25-74 years of age) from six US cities (Watertown, MA; Harriman, TN; Steubenville, OH; Portage, WI; St. Louis, MO; and Topeka, KS). Ozone data were collected from centrally located monitors in each community between 1977 and 1985. Mortality data were collected for the years 1974 to 1989. Dockery *et al.* (1993) calculated all-cause mortality rate ratios based on a comparison of the most and least polluted cities. The estimated rate ratios from Figure 3 in Dockery *et al.* (1993) are as follows: Portage and Topeka, 1.0; Watertown, 1.08; St. Louis, 1.14; Harriman, 1.17; and Steubenville, 1.26. No CIs were provided and no combined-city rate ratios were calculated for ozone. Based on Figure 3, there appears to be no relationship between ozone levels in any city and mortality. In fact, Steubenville and Topeka, the two cities with the highest reported ozone levels, had the lowest all-cause mortality estimates. One limitation of this study is the lack of analysis of ozone data collected prior to the study period; this may have biased results.

The original ACS cohort analysis is not supportive of associations between long-term ozone exposures and mortality (Pope *et al.*, 2002). This study consisted of about 500,000 adults in 134 metropolitan areas that were enrolled in the ACS cohort. The authors used daily one-hour maximum ozone concentrations from 1982 to 1998, and mortality data were collected between 1982 and 1998. The authors reported no significant associations between long-term ozone exposure and all-cause, cardiopulmonary, lung cancer, or "all other cause" mortality in either all-year or summer-only (July-September) analyses. The authors did not evaluate multi-pollutant models to account for possible confounding by co-pollutants, but adjusted for individual effects of sex, age, race, education level, occupational exposures, consumption of fats and fruits/vegetables/whole grains, body mass index, alcohol use, and smoking status (information collected in questionnaires at the beginning of the study). As noted previously, due to the lack of follow-up, residual confounding is still likely. A particular strength of this study is the inclusion of a large sample of residents across the entire US, as well as the use of a spatial random-effects component in the Cox proportional hazards model, which accounted for some of the regional heterogeneity. The limitations of this study, however, are the same as those discussed previously in Section 2 for the Jerrett *et al.* (2009), Smith *et al.* (2009), and Krewski *et al.* (2009) studies.

Another key study was conducted by Abbey *et al.* (1999), who evaluated mortality in the AHSMOG cohort of 6,338 non-smoking Seventh-day Adventists living in the areas of San Francisco, Los Angeles, or San Diego, CA. Monthly averages of ozone were collected from fixed-site monitors from 1973 through 1992, and mortality data were collected for the period 1977 to 1981. The authors reported that non-malignant lung disease, cardiopulmonary, and all-cause (natural) mortality were not significantly increased with each 12 ppb increase in ozone above 100 ppb in single-pollutant models. The only significant increase was reported for lung cancer mortality in males (RR = 4.19, 95% CI: 1.81-9.69), but not females (RR = 1.39, 95% CI: 0.52-3.67). Abbey *et al.* (1999) noted that, when they analyzed the mortality by exposure cutoffs, the association between lung cancer in males and ozone was only significant for cutoffs of 60-150 ppb. It is noteworthy that Abbey *et al.* (1999), like Jerrett *et al.* (2009), evaluated respiratory mortality, but found no association. No co-pollutants were included in the analyses; however, the authors adjusted for a large number of other covariates, including sex, age, years of education, past smoking, history of high blood pressure, alcohol use, exposure to second-hand smoke, exercise, occupational exposure, and body mass index.

Lipfert *et al.* (2000) investigated all-cause mortality associated with peak ozone (95th percentile of hourly measurements) in the US Veterans cohort of 50,000 middle-aged men. The authors analyzed results based on four exposure periods, including concurrent exposure and several historical exposure periods. For concurrent measures of peak exposure, the authors reported an increase of 9.4% (95% CI: 0.4-8.4) in all-cause mortality for each 1000 ppb increase in ozone. While EPA highlighted this positive association, it is inconsistent with the finding of no significant associations for prior exposure and current all-cause mortality (% excess risk = -0.2, 95% CI: -12.5-12.1). The authors pointed out that the approach of examining temporal coherence between exposure and mortality provided important insights. Specifically, the authors noted that "the general decline of mortality responses to air pollution with increasing follow-up time...could suggest depletion of the cohort of its most susceptible subjects, a concentration-response threshold, increasing uncertainty about the exposures and characteristics of the cohort, or all of these" (Lipfert *et al.*, 2000). The authors also commented that, in previous studies, significant associations have been found only for peak ozone concentrations, noting that "when 1975–1981 [ozone] was tested for linearity, a clear threshold was seen slightly above the previous federal 1-h standard [120 ppb]...[this] suggests that the present standard may be protective of public health from the standpoint of premature mortality" (Lipfert *et al.*, 2000).

In its discussion of the available studies in the AQCD, EPA did not include the study by Jerrett *et al.* (2005), which reported no association between long-term ozone exposure and mortality, even though EPA cited and placed high reliance on this study in its recent review of PM. In the AQCD EPA states that "[t]he document mainly assesses pertinent literature published through 2004, but also includes assessment of a few additional important studies published or accepted for publication in 2005." (US EPA, 2006, p. I-iii). Therefore it is unclear why this study was not included in the AQCD, and was also not discussed in the ISA. This omission is especially notable because EPA highlights on p. 7-85 of the ISA (US EPA, 2013) a trend of increasing ozone mortality risk estimates for "more accurate exposure metrics" in the Pope *et al.* (2002) analyses of the ACS cohort. The Jerrett *et al.* (2005) study arguably relies upon more accurate exposure metrics than the Pope *et al.* (2002) analyses because it used small-scale exposure measures in an attempt to reduce exposure misclassification. While Jerrett *et al.* (2005) reported a larger association with PM_{2.5} than previous analyses of the ACS prospective cohort data, they reported a general absence of elevated risks for ozone despite the frequent, elevated ozone concentrations characteristic of Los Angeles. Jerrett *et al.* (2005) concluded that their use of small-scale exposure measures likely reduced measurement error, and no ozone effects were observed.

Overall, much of the literature reviewed in the AQCD reported no association between long-term ozone exposures and mortality. These studies need to be included in the overall weight-of-evidence evaluation

for mortality effects. When considering all studies evaluated in the ISA and AQCD, the evidence is not sufficient to support a causal relationship between long-term ozone exposure and increased all-cause mortality or cause-specific mortality.

4 Long-term Ozone Exposure and Mortality Studies Not Included in the ISA

We identified two recent long-term ozone exposure and mortality epidemiology studies that were not included in the ISA, but should have been according to the criteria set forth by EPA in the ISA, that is: "[l]iterature searches have been conducted routinely since then to identify studies published since the last review, focusing on studies published from 2005 (closing date for the previous scientific assessment) through July 2011" (US EPA, 2013, p. 2-2). These studies are a recent analysis of the California Teachers Study by Lipsett *et al.* (2011) and a recent retrospective cohort study of kidney transplant recipients from across the US by Spencer-Hwang *et al.* (2011).

Lipsett *et al.* (2011) investigated the association between ozone and all-cause mortality and mortality from cardiovascular effects, non-malignant respiratory conditions, lung cancer, and IHD. The cohort included 101,784 female teachers residing in California. Mortality data were collected for the period 1997 through 2005 and ozone data for 1996 through 2005. In all-year, single-pollutant models, the authors found no associations between long-term ozone exposures and all-cause mortality nor any of the respiratory or cardiovascular mortality endpoints (Table 1). When analyzed for the summer season only, however, the association between ozone and IHD was marginally significant (HR = 1.09, 95% CI: 1.01-1.19) for each 22.96 ppb increase in ozone. In the all-year, two-pollutant model with PM_{2.5}, the ozone-mortality associations were attenuated. For example, for IHD, the authors reported a non-significant HR of 1.07 (95% CI: 0.97-1.07) that was reduced to 0.99 (95% CI: 0.88-1.11) per 10 ppb ozone with inclusion of PM_{2.5} in the model. For respiratory mortality, the authors reported a nonsignificant HR of 1.13 (95% CI: 1.00-1.29) that, unlike the findings by Jerret *et al.* (2009), was reduced with inclusion of PM_{2.5} (HR = 1.11, 95% CI: 0.95-1.30). Strengths of this study include estimates of pollutant exposures at individuals' homes, a low prevalence of active smokers, and the relatively uniform occupational status, all of which potentially reduced bias.

Spencer-Hwang *et al.* (2011) evaluated the risk of death from coronary heart disease and all-cause mortality in non-smoking patients who underwent transplants between 1997 and 2003 and lived within 50 km of an air pollutant monitor. Spencer-Hwang *et al.* (2011) reported marginally significant associations for a 10 ppb increase in ozone and CHF in one- and two-pollutant models that included PM₁₀ (RR = 1.35, 95% CI: 1.01-1.81 in the single-pollutant model; RR = 1.34, 95% CI: 1.01-1.79 in the two-pollutant model), but no significant associations for all-cause mortality in either one- or two-pollutant models (RR = 1.10, 95% CI: 0.96-1.25 in the single-pollutant model; RR = 1.09, 95% CI: 0.96-1.24 in the two-pollutant model). Although they controlled for medication use, immunosuppressive medication after transplant is a known and significant risk factor for cardiovascular disease and onset of diabetes after transplant. The authors noted that, "[m]ore research is needed to confirm these findings and determine whether patients with decreased kidney function in general have an increased risk of fatal CHD associated with ambient air pollution" (Spencer-Hwang *et al.*, 2011).

Overall, the most recent studies report findings are inconsistent with the findings in previous studies; therefore, the association between long-term ozone exposures and mortality effects remains highly uncertain. In particular, Lipsett *et al.* (2011) reported respiratory mortality impacts that were not statistically significant and were attenuated after inclusion of PM_{2.5} in the models, which contrasts with the finding by Jerrett *et al.* (2009). Although Spencer-Hwang *et al.* (2011) reported positive findings,

these were inconsistent with null findings from other studies, and confounding issues with this specific cohort of transplant patients cannot be ruled out.

5 Conclusion

As discussed by EPA throughout the ozone ISA, there remains a limited number of epidemiology studies that have reported findings bearing on the relationship between long-term exposure to ozone and mortality (Table 1). Of the few additional studies published since the 2006 AQCD, most reported no significant associations between long-term ozone exposures and all-cause or cause-specific mortality, including cardiopulmonary mortality. Only the study by Jerrett *et al.* (2009) reported a positive association between long-term ozone exposure and respiratory-related mortality that was unaffected in the two-pollutant analysis with PM_{2.5}. The recent study by Lipsett *et al.* (2011) did not find a significant association for respiratory mortality, which is consistent with the findings by Abbey *et al.* (1999). Given the limited number of studies, the limitations of these studies, and the inconsistent findings among them, the evidence linking long-term ozone exposure with mortality is insufficient to support a causal relationship between long-term exposure to ozone and mortality.

Table 1 Epidemiology Studies of Long-term Ozone Exposure and Mortality

Study	Cohort	n	Time Period of		Seasonal or All Year	Ozone Metric	Outcome	Copolutant(s) in Model	Risk Measure	Unit of Measure	Estimate	95% Confidence Interval
			Mortality Analysis	Ozone Data								
Dockery <i>et al.</i> (1993)	Harvard Six Cities cohort (US)	8.9 mil.	1974-1989	1977-1985	All year	NR	All-cause	None	Rate ratio	Varied	1.0-1.28 ^a	NR
Abbey <i>et al.</i> (1999)	AHSMOG cohort of non-smokers (CA)	6,338	1982-1998	1982-1998	All year	Monthly avg.	Lung cancer	None	RR (M)	Per 12 ppb; >100 ppb	4.19	1.81-9.69
									RR (F)		1.39	0.52-3.67
							NM lung		RR (M)		1.20	0.88-1.47
									RR (F)		1.01	0.77-1.33
							Cardiopulmonary		RR (M)		1.06	0.88-1.29
									RR (F)		0.88	0.75-1.02
Lipfert <i>et al.</i> (2000)	US veterans cohort, 31 cities	50,000	1975-1981	1975-1981	All year	Current peak ^b	All-cause mortality	None	RR	Per 1000 ppb	1.10 ^c	1.00-1.20
						Peak, delayed ^b					1.00 ^c	0.99-1.01
Pope <i>et al.</i> (2002)	ACS cohort, 134 metropolitan areas	500,000	1982-1998	1980-1998	All year	1-hr max	All other causes ^d	None	RR	N/A	0.98	0.90-1.05
					July-Sept						1.00	0.95-1.05
					All year						1.01	0.95-1.10
					July-Sept						1.05	0.98-1.11
					All year						1.10	0.95-1.21
					July-Sept						1.11	0.99-1.20
					All year						0.90	0.80-1.10
					July-Sept						0.95	0.85-1.10
Chen <i>et al.</i> (2005)	AHSMOG cohort (CA)	3,239	1973-1998	1977-1998	All year	Monthly avg.	Coronary heart disease	None	RR (M)	Per 10 ppb	0.89	0.60-1.30
									RR (F)		0.97	0.68-1.38
Jerrett <i>et al.</i> (2005)	ACS, 86 metropolitan areas (US)	22,905	1982-2000	1999-2001	All year	Peak	None	RR	N/A	0.98	0.96-1.01	
						Max 8-hr ^e				0.99	0.98-1.01	
						Peak				0.97	0.93-1.02	
						Max 8-hr ^e				0.98	0.95-1.02	
						Peak				0.97	0.94-0.99	
						Max 8-hr ^e				0.99	0.96-1.01	
						Peak				0.99	0.91-1.07	
						Max 8-hr ^e				0.97	0.91-1.03	
Lipfert <i>et al.</i> (2006a)	US Veterans cohort, 31 cities	70,000	1997-2001	1997-2001	All year	Peak	None	RR	Per 1 ppb	1.25	NR	
						24-hr avg.				0.82	NR	
						Peak				1.18	NR	
Lipfert <i>et al.</i> (2006b)	US Veterans cohort, 31 cities	70,000	1989-2001	1989-1996	All year	Peak	None	RR	Per 40 ppb	1.094	1.03-1.16	
			1997-2001	1999-2001	All year, counties with NO ₂ data					TD	1.080	1.02-1.15
										None	1.035	0.92-1.17
										TD	1.033	0.92-1.16

Study	Cohort	n	Time Period of		Seasonal or All Year	Ozone Metric	Outcome	Copolutant(s) in Model	Risk Measure	Unit of Measure	Estimate	95% Confidence Interval
			Mortality Analysis	Ozone Data								
Jerrett <i>et al.</i> (2009)	ACS cohort, 86 metropolitan areas (US)	448,850	1982-2000	1977-2000; 1999-2000 (PM)	Summer only (April-Sept)	1-hr max	All-cause	None	RR ^f	Per 10 ppb	1.001	1.00-1.01
								PM			0.989	0.98-1.00
								None			1.016	1.01-1.02
								PM			0.992	0.98-1.00
								None			1.027	1.01-1.05
								PM			1.040	1.01-1.07
								None			1.014	1.01-1.02
								PM			0.983	0.97-0.99
Krewski <i>et al.</i> (2009)	ACS cohort, 116 metropolitan areas	1.2 mil	1982-2000	1980	All year	8-hr max	All-cause	None	HR	Per 10 ppb	1.00	0.99-1.01
								PM _{2.5}			1.02	1.01-1.02
								None			0.99	0.98-1.01
								PM _{2.5}			1.01	1.00-1.03
								None			1.03	1.02-1.04
								PM _{2.5}			0.99	0.96-1.01
								None			1.01	0.98-1.03
								PM _{2.5}			1.01	0.99-1.02
								None			0.98	0.95-1.02
								PM _{2.5}			1.00	0.96-1.04
								None			0.99	0.96-1.02
								PM _{2.5}			0.97	0.91-1.03
								None			0.99	0.97-1.00
								PM _{2.5}			1.01	1.00-1.02
								PM _{2.5}			1.04	0.99-1.14
								Smith <i>et al.</i> (2009)			ACS cohort, 66 cities	352,000
2003-2005	Carbon and sulfate	1.00 ^c	0.99-1.01									
	Carbon	1.00 ^c	0.99-1.02									
Cardiopulmonary	None	1.03^c	1.01-1.05									
	Carbon and sulfate	1.02^c	1.01-1.04									
	Carbon	1.02 ^c	1.00-1.04									
Wang <i>et al.</i> (2009)	Cohort in Brisbane, Australia	887,955	1996-2004	1996-2004	All year	1-hr max	Cardiorespiratory	None	RR	Per 1 ppb	1.002	0.99-1.02
								NO ₂ and SO ₂			0.999	0.99-1.01

Study	Cohort	n	Time Period of		Seasonal or All Year	Ozone Metric	Outcome	Copolutant(s) in Model	Risk Measure	Unit of Measure	Estimate	95% Confidence Interval	
			Mortality Analysis	Ozone Data									
Lipsett <i>et al.</i> (2011)	California Teachers Study (F only)	101,784	1997-2005	1996-2005	All year ^g	Monthly avg.	All-cause	None	HR	Per 10 ppb	1.01	0.97-1.05	
								PM _{2.5}			1.00	0.95-1.05	
							CV	None			1.00	0.94-1.07	
								PM _{2.5}			0.97	0.90-1.05	
							IHD	None			1.07	0.97-1.17	
								PM _{2.5}			0.99	0.88-1.11	
							NM respiratory	None			1.13	1.00-1.29	
					PM _{2.5}			1.11			0.95-1.30		
					Lung cancer		None	0.95			0.80-1.13		
							PM _{2.5}	0.94			0.76-1.17		
					Cerebrovascular		None	1.02			0.89-1.16		
							PM _{2.5}	0.97			0.82-1.14		
					Summer-only		None	Per 22.96 ppb			All-cause	0.97	0.94-1.01
											CV	1.02	0.96-1.07
IHD	1.09	1.01-1.19											
NM respiratory	1.09	0.97-1.21											
Lung cancer	0.95	0.82-1.10											
Cerebrovascular	0.99	0.88-1.10											
Zanobetti and Schwartz (2011)	Four cohorts of Medicare patients ≥ 65 years old with chronic conditions, 105 cities (US)		1985-2006	1985-2006		Summer (May-Sept)			8-hr avg.	None	HR	Per 5 ppb	All cause; pre-existing:
					CHF		1.09	1.06-1.12					
					MI		1.07	1.05-1.10					
					Diabetes		1.07	1.04-1.09					
					COPD		1.02	0.99-1.05					
					Spring and Autumn	All cause; pre-existing:	1.04	1.00-1.08					
						CHF	1.03	1.00-1.07					
						MI	1.03	1.00-1.06					
						Diabetes	1.10	0.96-1.25					
						COPD	1.09	0.96-1.24					
Spencer-Hwang <i>et al.</i> (2011)	Cohort of kidney transplant recipients(US, 50 states)	32,239	1997-2003	1997-2003	All year	Monthly avg.	None	RR	Per 10 ppb	Natural all-cause	1.35	1.01-1.81	
										PM ₁₀	1.34	1.01-1.79	
										CHF	None		
											PM ₁₀		

Notes:

ACS = American Cancer Society; AHSMOG = Adventist Health Study of Smog; avg. = average; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; F = female; HR = hazard ratio; IHD = ischemic heart disease; M = male; max = maximum; MI = myocardial infarction; n = number of people; N/A = not available; NM = non-malignant; NR = not reported; Peak = 95% percentile of daily max; PM = particulate matter; ppb = parts per billion; RR = relative risk; TD = traffic density.

(a) Rate ratios are estimated from Figure 3 in Dockery *et al.* (1993). Range represents rate ratios across all six cities.

(b) Reported risks less estimated background ozone. "Concurrent" indicates mortality associated with current exposure levels; "delayed" indicates mortality associated with prior exposure periods.

(c) Converted from % excess risk to an RR using the equation "e^(% risk) = R."

(d) RR estimated based on Figure 5 in Pope *et al.* 2002.

(e) Average of the four highest 8-hr values.

(f) Results based on analysis of 86 cities for both single- and two-pollutant models.

(g) All-year data is from participants who had both ozone and PM_{2.5} data during the exposure time period.

Bolded values are statistically significant.

References

Abbey, DE; Nishino, N; McDonnell, WF; Burchette, RJ; Knutsen, SF; Lawrence Beeson, W; Yang, JX. 1999. "Long-term inhalable particles and other air pollutants related to mortality in nonsmokers." *Am. J. Respir. Crit. Care Med.* 159(2):373-382.

Abrahamowicz, M; Schopflocher, T; Leffondre, K; du Berger, R; Krewski, D. 2003. "Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study." *J. Toxicol. Environ. Health* 66(16-19):1625-1654.

Bell, ML; Dominici, F. 2008. "Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 US communities." *Am. J. Epidemiol.* 167:986-997.

Boffetta, P; McLaughlin, JK; La Vecchia, C; Tarone, RE; Lipworth, L; Blot, WJ. 2008. "False-positive results in cancer epidemiology: A plea for epistemological modesty." *J. Natl. Cancer Inst.* 100:988-995.

Chen, LH; Knutsen, SF; Shavlik, D; Beeson, WL; Petersen, F; Ghamsary, M; Abbey, D. 2005. "The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk?" *Environ. Health Perspect.* 113(12):1723-1729.

Dockery, DW; Pope, CA; Xu, X; Spengler, JD; Ware, JH; Fay, ME; Ferris, BG Jr.; Speizer, FE. 1993. "An association between air pollution and mortality in six U.S. cities." *N. Engl. J. Med.* 329(24):1753-1759.

Enstrom, J. 2005. "Fine particulate air pollution and total mortality among elderly Californians, 1973-2002." *Inhal. Toxicol.* 17(14):803-816.

Fewell, Z; Smith, GD; Sterne, JAC. 2007. "The impact of residual and unmeasured confounding in epidemiologic studies: A simulation study." *Am. J. Epidemiol.* 166(6):646-655.

Jerrett, M; Burnett, RT; Ma, R; Pope, CA; Krewski, D; Newbold, KB; Thurston, G; Shi, Y; Finkelstein, N; Calle, EE; Thun, MJ. 2005. "Spatial analysis of the air pollution and mortality in Los Angeles." *Epidemiol.* 16(6):727-736.

Jerrett, M; Burnett, RT; Pope, CA; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. 2009. "Long-term ozone exposure and mortality." *N. Engl. J. Med.* 360(11):1085-1095.

Krewski, D; Jerrett, M; Burnett, RT; Ma, R; Hughes, E; Shi, Y; Turner, MC; Pope, A; Thurston, G; Calle, EE; Thun, MJ. 2009. "Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality." HEI Research Report 140. 154p., May.

Laden, F; Schwartz, J; Speizer, FE; Dockery, DW. 2006. "Reduction in fine particulate air pollution and mortality: Extended follow-up to the Harvard Six Cities Study." *Am. J. Respir. Crit. Care Med.* 173(6):667-672.

- Lipfert, FW; Perry, HM; Miller, JP; Baty, JD; Wyzga, RE; Carmody, SE. 2000. "The Washington University-EPRI Veterans' Cohort Mortality Study: Preliminary results." *Inhal. Toxicol.* 12(Suppl. 4):41-73.
- Lipfert, FW; Baty, JD; Miller, JP; Wyzga, RE. 2006a. "PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans." *Inhal. Toxicol.* 18(9):645-657.
- Lipfert, FW; Wyzga, RE; Baty, JD; Miller, JP. 2006b. "Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: Long-term mortality in a cohort of US veterans." *Atmos. Environ.* 40(1):154-169.
- Lipsett, MJ; Ostro, BD; Reynolds, P; Goldberg, D; Hertz, A; Jerrett, M; Smith, DF; Garcia, C; Chang, ET; Bernstein, L. 2011. "Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort." *Am. J. Respir. Crit. Care Med.* 184(7):828-835.
- Moolgavkar, SH. 2006. "Fine particles and mortality." *Inhal. Toxicol.* 18(1):93-94.
- Pope, CA; Burnett, RT; Thun, MJ; Calle, EE; Krewski, D; Ito, K; Thurston, GD. 2002. "Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution." *JAMA* 287(9):1132-1141.
- Reiss, R; Anderson, EL; Cross, CE; Hidy, G; Hoel, D; McClellan, R; Moolgavkar, S. 2007. "Evidence of health impacts of sulfate-and nitrate-containing particles in ambient air." *Inhal. Toxicol.* 19:419-449.
- Smith, KR; Jerrett, M; Anderson, HR; Burnett, RT; Stone, V; Derwent, R; Atkinson, RW; Cohen, A; Shonkoff, SB; Krewski, D; Pope, CA III; Thun, MJ; Thurston, G. 2009. "Public health benefits of strategies to reduce greenhouse-gas emissions: Health implications of short-lived greenhouse pollutants." *Lancet* 374(9707):2091-2103.
- Spencer-Hwang, R; Knutsen, SF; Soret, S; Ghamsary, M; Beeson, WL; Oda, K; Shavlik, D; Jaipaul, N. 2011. "Ambient air pollutants and risk of fatal coronary heart disease among kidney transplant recipients." *Am. J. Kidney Dis.* 58(4):608-616.
- Taubes, G. 1995. "Epidemiology faces its limits." *Science* 269:164-169.
- Tong, DQ; Yu, S; Kan, H. 2009. "Ozone exposure and mortality." *N. Engl. J. Med.* 360(26):2788.
- US EPA. 2006. "Air Quality Criteria for Ozone and Related Photochemical Oxidants (Volume I of III)." National Center for Environmental Assessment-RTP Division. EPA 600/R-05/004aF. 821p., February.
- US EPA. 2013. "Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Final)." National Center for Environmental Assessment (NCEA). EPA/600/R-10/076F. 1251p., February.
- Wang, XY; Hu, W; Tong, S. 2009. "Long-term exposure to gaseous air pollutants and cardio-respiratory mortality in Brisbane, Australia." *Geospat. Health* 3(2):257-263.
- Zanobetti, A; Schwartz, J. 2011. "Ozone and survival in four cohorts with potentially predisposing diseases." *Am. J. Respir. Crit. Care Med.* 184(7):836-841.