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# Risk in Perspective

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## Ozone and Mortality — An Update

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Joel Schwartz

*“Evidence that ozone kills people is relatively new, and more controversial....While uncertainties remain, a significant fraction of the questions have been resolved..”*

While it has long been accepted that ozone can produce morbidity, as clearly demonstrated in chamber studies, the evidence that ozone kills people is relatively new, and more controversial. In particular, a number of questions have been raised that are central to translating that literature into risk assessment and benefit analyses. Is the ozone-associated mortality just short-term mortality displacement? Does risk vary by individual? If so, what characteristics define the at-risk individual? Are the associations confounded by temperature? By other secondary air pollutants? How are any early deaths associated with ozone exposure to be valued? Recent work by Harvard Center for Risk Analysis faculty and staff has addressed these questions, and is summarized below.

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### Background

While many studies have reported adverse responses to ozone, a highly oxidizing gas, reports that ozone exposure might hasten deaths have been more recent. The first large-scale report came from Europe, where seven cities were studied using identical methods and the results combined<sup>1</sup>. Studies from Europe during that period (the 1990's) have the advantage that use of air conditioning was quite low. Open windows ensure that day-to-day changes in outdoor ozone concentrations are more highly correlated with day-to-day changes in personal exposure, and hence reduce exposure error. This may limit generalizability to North America, however. Since then a number of studies have reported similar results, including three large meta-analyses commissioned by the US EPA<sup>2-4</sup>. Moreover, a large multicity study has found no evidence of a threshold down to very low levels<sup>5</sup>.

The implications of these findings for ozone risk assessment are enormous. In

cost-benefit analyses of air pollutants, mortality risks, when monetized, dominate the benefit calculation. Because of this, a National Academy of Sciences committee was commissioned to review the evidence. Its report, recently issued, concluded that the evidence for a mortality association is strong<sup>6</sup>. Among the questions raised to the committee are the ones above. These address the potential for confounding (i.e., that other exposures may actually be responsible for the observed association), as well as questions about who is being affected that have importance for health impact assessments and benefit analyses. Because of the critical role these might play in estimating an appropriate level for the standard, we have been active in addressing these issues. A recent RIP has focused on the valuation issue, which of course generalizes to other exposures<sup>7</sup>. This RIP will focus on results addressing the other questions.

### Are the ozone-associated deaths due to other exposures?

The major concern of observational epidemiology studies is that some other exposure, correlated with the exposure of interest, may explain the observed association, which is not causal but due to that correlation. To confound studies of short term changes in ozone and daily

*Are the ozone-associated deaths due to the association of ozone with high temperature?*

Ozone is not directly emitted by polluting sources. It is produced by chemical reactions in the atmosphere between nitrogen oxides and volatile organic compounds (VOCs), and those reactions are driven by sunlight and temperature. Hence ozone covaries with temperature. All studies of the effect of ozone on daily deaths have therefore controlled for temperature. However, the association of temperature with death is highly nonlinear, with heat wave conditions associated with much larger increases in deaths than temperatures just a few degrees cooler. How can we be sure that those studies correctly captured that relation, and that the ozone association is not due to ozone capturing the remaining effect of temperature?

I addressed this in an analysis of over one million deaths in 14 cities<sup>7</sup>. Rather than examine the correlation

*Are the ozone-associated deaths due to other secondary pollutants?*

The same processes, chemical reactions driven by light and heat, that produce ozone also produce other secondary pollutants (secondary because they are not directly emitted). Among these are sulfate particles, from the reaction of sulfur oxides with ammonia, nitrate particles, from the reaction of nitrogen oxides with ammonia, and organic particles, which like ozone derive from reactions of hydrocarbons. In addition, other gaseous pollutants, such as peroxyacetylnitrate (PAN), are produced by the same type of reactions that produce ozone. These pollutants are rarely measured, and hence previous studies have not controlled for them. To the extent that the control measures adopted to reduce ozone, such as reductions in emissions of nitrogen oxides and hydrocarbons, also reduce these other secondary pollutants, such as PAN, it may not be critical for policy analysis to distinguish among them. However, all strategies do not reduce these secondary

deaths, such confounders must co-vary with ozone over the same timescale. There are two obvious candidates for such a confounder—temperature and other secondary pollutants.

between daily ozone and daily deaths, I converted the analysis into a case-control study. Using a variant called case-crossover analysis, I matched each decedent with him or herself, on a control day in the same month of the same year that they died, which also had the same temperature (rounded to the same degree). This matching controlled for season and time trend, by choosing a control day in the same month and year as the date of death, and since the temperature was the same on the control day as the case day, it could not explain which day the death occurred on. I then compared the ozone levels on the two days to see if they predicted which day was the date of death. I found the same association with ozone that I found analyzing the data using the more traditional time-series analysis. This indicates that confounding by temperature is unlikely to explain the observed ozone-mortality association.

pollutants equally, and secondary sulfate particles would be reduced by a completely different strategy, the control of sulfur oxide emissions. Hence this is a key remaining uncertainty.

To address this, Franklin and Schwartz turned to the U.S. EPA's speciation monitoring network<sup>8</sup>. Unfortunately, this network has only been operating since 2000, usually monitors only 1 in 3 or 1 in 6 days, and only measures particles, and not other oxidant gases. Nevertheless, using data from 18 cities with speciated particle measurements, we showed that control for nitrate particles or organic carbon particles did not change the estimated effect of ozone on mortality. In contrast, control for sulfate particles reduced the estimated ozone effect by about 25%, although the confidence interval in that estimate was wide, and included the possibility of no change in the ozone effect. Hence some of the effect attributed by past studies to ozone may have been due to sulfate particles, but organic and nitrate particles do not appear to be confounders.

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### Are the ozone-associated deaths advanced by only a small amount?

One possible explanation of the observed associations is that they are causal, but that only extremely sensitive individuals, who are on the brink of death, are affected by this exposure. If ozone is merely bringing forward deaths

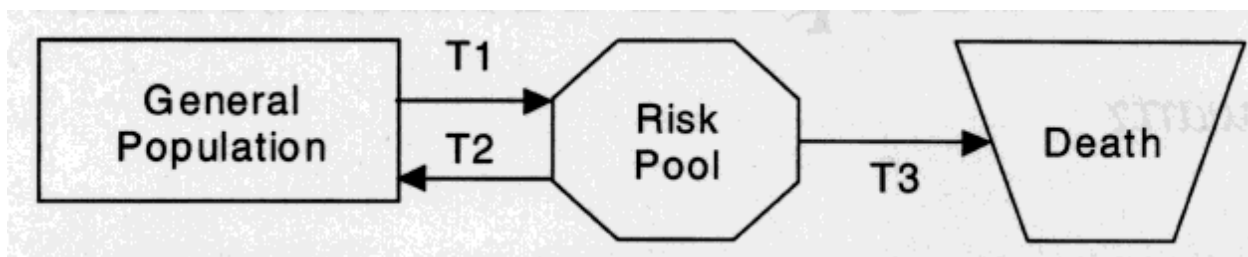
among people who would have died in the next week anyway, the public health impact of the observed ozone-mortality association is much reduced. Recently, we addressed this question in a large, multicity study.

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To understand this question, it is useful to consider the following schematic. In it, we imagine that there is a pool of persons who are highly susceptible to dying in the short run. This could, for example, include persons with severe pneumonia, or with acute inflammations that have decreased the stability of atherosclerotic plaques that are temporarily at much higher than normal risk of rupturing and producing a heart attack. Persons in this high-risk pool can recover and return to a more normal risk, or they can die. Each day some die, some recover, and some new people enter the high-risk pool. Conceptually, air pollution might affect all three transition rates. If air pollution only increased the rate of dying out of the pool, then we would expect the pool to be depleted by an ozone epi-

sode, resulting in fewer deaths in the next week. In this case, the deaths associated with ozone exposure are only being brought forward by a short period. However, if ozone affects the recruitment rate, the size of the pool could actually increase, and excess deaths could continue well after the ozone episode occurred.

If ozone's primary effect is on the death rate from the risk pool and deaths were only being brought forward by, e.g. seven days, then, *ceteris paribus*, we would expect a negative correlation between ozone exposure today and deaths a week from now. Zanobetti and Schwartz used this insight to look at the correlation between ozone levels and death counts in 48 U.S. cities for time periods up to 21 days after exposure<sup>9</sup>.



They found that there was no negative correlation between ozone and mortality up to 21 days later, and that the positive association persisted over several days but fell to zero within a few days. The overall effect of ozone over the period was an increase of 0.5% in daily deaths (95% C.I.: 0.05-0.96) per 10 ppb increase in 8 hour average ozone, compared with an increase of 0.3% (95% C.I.:

0.2-0.4) when deaths on only one day were considered. Hence the deaths associated with ozone are not just being brought forward by a few weeks, and previous studies may have underestimated the overall effect of ozone on mortality by just considering the effect of the ozone on deaths the same day.

## Who is Susceptible to the Effects of Ozone?

The question of who is dying on high-ozone days affects many areas of risk assessment and health policy analysis. The presence of chronic conditions or the age of the individuals at risk may affect the benefit values associated with delaying the ozone-associated deaths. In addition, since the age pyramid and prevalence of certain conditions are changing in the United States and elsewhere, understanding of the relative risks in different subpopulations will be important. To address this, we conducted a case-only study. A case-only study is focused on identifying factors that modify risk, and does not examine what the baseline risk is. It is based on the following idea. Suppose some personal characteristic, for example diabetes, modifies the risk of dying on a high air pollution day. Then one would expect, on average, more of the deaths on high-ozone days to be among diabetics than the deaths

on low-ozone days. Therefore, one can test this hypothesis (greater susceptibility of diabetics to ozone) by doing a regression on the people who died over a period of years, with the outcome whether or not they were diabetic, and the predictor the ozone concentrations on the day they died. This approach has the advantage that things that only predict whether or not a person died are not confounders in this analysis, since they don't predict the outcome (diabetes, not deaths)<sup>10, 11</sup>.

Our analysis examined 2.7 million deaths in 48 cities between 1989 and 2000<sup>12</sup>. We found, as expected, increased susceptibility among persons 65 and older (~2.7 fold higher percent increase in deaths per 10 ppb of ozone). More interestingly, Blacks had roughly 1.8 times the percent increase in deaths as non-Blacks, and women over the age of 60 had about 1.9 times the percent in-

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crease in death as men. Below age 60, however, there was no difference between the risk in men and women, suggesting some protection by hormonal status. Among chronic diseases, atrial fibrillation was associated with 1.7 times the percent increase in deaths per 10ppb of ozone. Previous studies have suggested that atrial fibrillation also increased the risk of dying on very hot days<sup>13</sup>, or as a result of particle exposure<sup>14</sup>.

Analyses of mortality data are limited to looking at modifying factors that are shown on the death certificate. Examination of other potential markers of susceptibility requires other techniques. One approach is to look at a

surrogate outcome. Lung function is a continuous outcome which is highly predictive of mortality rate. We examined the short term association between ozone and decrements in lung function (forced expiratory volume in 1 second, FEV1) in a cohort of elderly men in the Boston area. We found that ozone was associated with reduced FEV1, but that the effect was larger in obese subjects<sup>15</sup>. Since obesity is a growing problem all over the world, this suggests that in the absence of contravening changes in other risk modifiers, the susceptible pool may grow over time.

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## Conclusions

While uncertainties still remain, a significant fraction of the questions have been resolved. The ozone-associated deaths do not appear to be short-term mortality displacement and aggregate effects over several days may increase the risk estimates. There may be some confounding by sulfate particles, but not by other secondary particles. This may reduce the risk estimates. Most of the ozone-associated deaths are in the elderly, but the differences by race and sex may be important. Major chronic diseases such as COPD and diabetes that provide significant reductions in quality of life are not modifiers of the ozone association. However, while diabetes is not a modifier, obesity may be. Given trends in obesity over time, this will also be relevant for risk assessments.

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