Comments to the CASAC Ozone Review Panel from Mark Nicolich, Independent Consultant, Sponsored by the American Petroleum Institute

I thank the Panel for reading my submission for this meeting.

BACKGROUND

I am asking CASAC to consider in its deliberations the journal article "Cumulative effects and threshold levels in air pollution mortality: data analysis of nine large US cities using the NMMAPS dataset," by my co-author Mario Stylianou and me that was published in *Environmental Pollution* in 2009 (Stylianou and Nicolich, 2009). This paper relates to several points used to develop the current and proposed ozone standards, and points referred to in the EPA charge questions. The specific points are the assumption of a linear no threshold concentration-response (CR) model for ozone exposure, the assumption that cities can be combined because they have similar CR functions, and the modeling of ozone without consideration of other pollutants. I'll provide a brief overview of the paper, and then discuss the points of the paper in some detail to support the conclusions.

ABSTRACT OF JOURNAL PAPER

Briefly, in the journal article we examined the existence of thresholds, cumulative effects and the homogeneity of five air pollutants (simultaneously) on the relative risk of three mortality outcomes using data from nine major US cities using data from NMMAPS. Overall, PM_{10} (usually 200 day accumulation) and ozone (3 day accumulation) were the two important predictors of outcome but their effect was not the same across the nine cities. Many of the models for different cities and endpoints exhibited thresholds (25-45 $\mu g/m^3$ for PM_{10}, and 10-45 ppb for O_3). Our analyses suggested that the use of a linear, no threshold model for pollution studies is not consistent with the observed data. Also, the heterogeneity in the risk estimates across the nine cities suggested that the practice of combining individual city or location risk estimates to obtain a national risk estimate may not be justifiable and the resulting estimate is likely to be confounded.

DETAILS OF JOURNAL PAPER

Although most of the air pollution literature deals with the short-term effects of air pollutants on mortality, it seems reasonable to assume that pollutants may increase the risk for adverse events over longer duration of exposure because a narrow moving window may not adequately capture larger effect variations of pollutants under study. Several researchers have considered longer-term effects; Schwartz (2000) studied the effect of $PM_{2.5}$ and weather variables using moving averages of up to 60 days. Janes et al. (2007) considered mean monthly exposures over the previous 12 months with an approximate 30-day window. More recently, Schwartz (2008) explored the effect of $PM_{2.5}$ exposure to mortality for up to the previous five years. However, there is no consensus in the literature regarding the lag or cumulative time needed to evaluate the pollutants effect.

Another consideration in air pollution models is the combined effect of several pollutants. Bell et al. (2004) estimated same day non-accidental mortality using cumulative ozone exposure during the previous week considering PM_{10} and the usual confounders of weather, day of the week, and calendar time. They report that ozone is associated with daily non-accidental mortality (and the subsets of cardiovascular and respiratory mortality) and these results are independent of adjustment for PM_{10}, weather, seasonality and long-term trends. However, PM_{10} was considered only with a 1-day lag which is different from most published models and may explain why PM_{10}

had no effect in the model with ozone. Bell et al. (2005) replicated their results in a subsequent meta-analysis of ozone mortality studies, again with short lag times for exposures to ozone and PM_{10} or $PM_{2.5}$. It is possible that a PM effect on the death count may be more pronounced when it is cumulated over longer times.

Many of the models assessing the effect of several pollutants on death rates produce relatively poor fitting or biased estimates of exposure-response association (Zeka and Schwartz, 2004). One explanation is that these pollutants are usually correlated in the short term and the correlation leads to unstable estimates of the pollution effects. One approach to the problem of correlated short-term data is to use long-term average or cumulative pollution data so the effect of correlation among long-term cumulative pollutants in the modeling process would be minimized. We have based our models on the work of Xia and Tong (2006) who suggested a method to account for the cumulative effects of longer-term exposures to air pollution by using a weighted cumulative sum for each pollutant without the restriction of a linear dose-response function. The weights are derived by a restricted minimization method where the weights are non-increasing (or decreasing) the further we go into the past. Their analysis of data from Hong Kong, El Paso, Chicago, and Pittsburgh suggests that cardiovascular disease (CVD) mortality is affected by a cumulative effect of PM_{10} for about 200 days, with roughly uniform weights, and that thresholds exist for all pollutants, noticeably for PM_{10} and ozone. Importantly, their study suggests that different pollutants may require different cumulative periods.

The objective of our paper was to investigate the simultaneous cumulative effects of O_3 and PM on non-accidental mortality and the existence of thresholds for these pollutants. We considerd the assumption of monotonicity between the risk function and pollutant levels. We thought that a monotonic (but not necessarily linear) assumption for a pollutant effect was reasonable in the absence of plausible mechanisms for beneficial effects and their likelihood that these effects at low concentrations are possibly due to chance. In addition, we explored the cumulative effect of other pollutants, such as NO_2, SO_2, and CO on death outcomes. Finally we questioned the usefulness of combining the city specific risk estimates to form a national average.

This investigation was based on daily time-series data extracted from NMMAPS for 1987 to 2000 from nine major U.S. cities; Baltimore, Chicago, Dallas/Fort Worth, Los Angeles, Miami, New York, Philadelphia, Pittsburgh, and Seattle, which have a combined population of more than 35 million people. The response variables considered were total non-injury related mortality, cardiovascular disease (CVD) mortality and respiratory disease mortality.

The following is a brief outline of the statistical models used and the full statistical details are in the journal article. The models we used were based on the research of Xia and Tong (2006). For each cause of death and for each city we first fit a model that considers calendar variables (day, time) and meteorological variables (temperature, dewpoint). Only those variables that are significantly associated with the outcome (at $p \leq 0.05$) remained in the model to form the "basic model". We added each pollutant individually to assess its importance in predicting the number of events. Each pollutant associated with the response in the basic model would be further considered for a multivariate model. We modeled the effects of pollutants on each of the daily causes of death using the generalized additive model. For example, a "full" model in a multivariate setting with a basic model plus all five pollutants could be:

$$
\begin{aligned}
E(\log(Y_t)) = \mu + \sum_{k=1}^{6} \beta_k D_{k,t} + g_1\left(\sum_{\tau=0}^{29} \theta_{1,\tau} T_{t-\tau}\right) + g_2\left(\sum_{\tau=0}^{29} \theta_{2,\tau} DP_{t-\tau}\right) + g_3(Time_t) \\
+ g_4\left(\sum_{\tau=0}^{199} \theta_{4,\tau} PM_{t-\tau}\right) + g_5\left(\sum_{\tau=0}^{2} \theta_{5,\tau} O_{t-\tau}\right) + g_6\left(\sum_{\tau=0}^{2} \theta_{6,\tau} NO2_{t-\tau}\right) \\
+ g_7\left(\sum_{\tau=0}^{2} \theta_{7,\tau} SO2_{t-\tau}\right) + g_8\left(\sum_{\tau=0}^{2} \theta_{8,\tau} CO_{t-\tau}\right)
\end{aligned}
\tag{1}
$$

where μ is the intercept term, the subscript t represents study time, the summations are over the cumulative period of interest (τ), Y_t is the daily number of deaths at time t, $D_{k,t}$ is the indicator function for day of the week, β_k is the mortality adjustment for the kth day of the week, T_t is the average daily temperature, DP_t is the average daily dew point, and $Time_t$ is calendar time. PM_t and O_t are the PM_{10} and ozone levels at time t, while, NO_{2t}, SO_{2t} and CO_t are the corresponding pollutants at time t. $g_1(x), \cdots, g_8(x)$ are unknown smooth functions, $\theta_{k,\tau}$ is the weight for the kth term at τ days prior to the current day, $\sum_{\tau=0}^{L} \theta_{k,\tau} = 1$ and $0 \le \theta_{k,L} \le \theta_{k,L-1} \le \cdots \le \theta_{k,0}$. The model fit was assessed both quantitatively and graphically using residual and partial residuals plots. Autocorrelation and partial autocorrelation plots were used to assess the existence of any autocorrelation remaining in the residuals.

Estimates of the RR were derived using the final model. The RR at exposure x is the risk from being exposed at level x relative to the risk at the base level. When the effect-function is linear any base can be used because the effect change is the same at all points along the line. We have chosen to report risk relative to the lowest observed exposure as do Leitenstorfer and Tutz (2007):

$$
RR(t) = \frac{E(event \mid P(t))}{E(event \mid P(\min))} = \frac{\exp(g\ (P(t))}{\exp(g\ (P(\min))} \tag{2}
$$

where $P(t)$ is the pollutant level at time t, $P(min)$ is the minimum pollutant level observed, and g is a smooth function.

In order to compare and contrast the individual city models with a model that is the same across cities, we have used a unified model that incorporated the same predictors for all cities. These predictors were time and meteorological variables and pollutants that are associated with death events across many cities.

Of the three types of deaths assessed (total, CVD, and respiratory), respiratory deaths have the weakest pollutant associations and total deaths outcome has the strongest associations. We found that 3-day cumulative ozone is the most likely pollutant to have a threshold with an average value of 32 ppb using the non restricted models for the six cities that appear to have a threshold with a total death outcome. Using a monotonic assumption we obtain an average threshold level at 21 ppb. Using CVD death as an outcome, the average threshold with a non-restricted and monotonic models is at 28 and 31ppb. With the 200-day cumulative $PM_{10,}$ a threshold is suggested only for Chicago using the unconstrained model, 29 and 30 $\mu g/m^3$ for total and CVD deaths. Under monotonic model the average threshold is 31 and 30 $\mu g/m^3$ for total and CVD deaths.
The basic model analyses suggest that PM_{10} and ozone are the most likely pollutants predictive of different accountings of mortality. We evaluated the consistency of the pollutant effect across the different cities using a model that adjusts for the same variables, that is, the basic model plus

PM_{10} and ozone. Figure 1 graphically displays the statistical significance levels of PM_{10} and ozone in the above model. Neither PM_{10} nor ozone is a predictor of total deaths in Miami; CVD deaths in Pittsburgh, Baltimore and Miami; or respiratory deaths in Pittsburgh, Miami and Dallas/Fort Worth. However, both PM_{10} and ozone are associated with the total deaths in Chicago, NY, Pittsburgh, and LA; CVD deaths in Chicago; and respiratory deaths in NY and LA. Please note that we use p-values not as a strict decision value, but in the sense of Weinberg (2001) and Poole (2001) to provide a useful scale to evaluate the relative usefulness of terms in the models of different cities.

The risk functions of PM_{10} on total deaths as shown in the journal article are mostly flat near a RR of 1, except Chicago where the RR for PM_{10} increases and flattens around 35 $\mu g/m^3$. Some risk estimates are not increasing with the PM_{10} level, such as NY or LA. Some even inexplicably decrease, as in Pittsburgh or Baltimore. This behavior could justify the monotonic (non-decreasing) assumption for the effect or risk function. The association and shape of the adjusted PM_{10} RR function (adjusted for ozone, day, time, temperature, and dp) are inconsistent across the nine cities; the only risk function significantly larger than one is for Chicago at 29 $\mu g/m^3$. Over half the functions appear linear but are either flat or declining. Chicago clearly appears to be nonlinear. The observed range of PM_{10} average cumulative levels and variability differ considerably between cities. Likewise, the shape of the ozone risk function is also inconsistent; thresholds appear to occur in the range of 20 to 40 ppb for all cities but Miami and LA. The estimated ozone risk function is not always a non-decreasing function (LA, Philadelphia, Pittsburgh, and Seattle).

Overall, our analyses suggest the effect of these pollutants across the nine cities studied is inconsistent. Associations are more likely for CVD or total death in older large industrialized cities such as Chicago and NY. A possible reason as to why PM10 and ozone were not as strongly associated with respiratory deaths could be the low daily events. While high levels of ozone and PM_{10} are associated with increased non-accidental mortality, our analyses suggest that these effects are not uniform across the U.S., that dose-response relationships are not necessarily linear, and that some relationship shapes are suggestive of no-effect thresholds. We believe that a monotonic (but not necessarily linear) assumption for a pollutant effect is reasonable in the absence of plausible mechanisms for beneficial effects and the likelihood that effects at low concentrations are likely due to chance.

The RR is often assumed or reported to be linear (Bell et a. 2004; Schwartz et al. 2001), implying that a specific increase of a given pollutant has a fixed risk. In contrast, our cumulative pollutant community-specific analyses indicate that the pollutant RR is often non-linear and the rate of risk increase is not constant. Bell et al.(2006) have explored the possibility of non-linearity or thresholds but they only reported the combined national average, leaving the reader wondering about the shape of the community-specific risk estimates. Even with the combined risk estimate they did find the possibility of thresholds at low levels of ozone. However, they dismissed the threshold models because the improvement in the model AIC was minimal (<1%). We have demonstrated that the inclusion of statistically significant PM10 or ozone in the basic model does not provide a considerable model improvement either (<0.4%).

Our analyses suggest that thresholds exist for some of the cities. We found that PM_{10} risk-function for Chicago tends to increase and then flatten at about a 200-day mean of 30 $\mu g/m^3$ in contrast to ozone risk-functions for most cities where the risk is flat at low levels and then starts to increase at about a 3-day mean of 20 to 30 ppb. These conclusions remain the same, even when we run the same basic model plus both PM_{10} and ozone. In another sensitivity analysis, we have compared the model R^2_{adj} and AIC with an ozone term as either linear or with a threshold at

30ppb. For most cities, the threshold model performs slightly better than the model using the linear ozone term.

Many authors attempted to combine city-specific RRs into a single national estimate (Bell et al 2004 and 2006; Dominici et al. 2002). This approach can increase the statistical power and give an overall RR perspective. However, several underlying assumptions must be true for the combined results to be valid. Since RR estimates are conditional on other predictors in the model, it is necessary to include the same variables in order to have the same risk interpretation. Our analyses suggest that even with the same variables in the model, the shapes of the risk-functions from such models are inconsistent across the different cities. This indicates that a rigorous examination of the results from each city is necessary before including specific cities into combined estimates of the RR. Similar conclusions regarding associations between 12-month $PM_{2.5}$ exposure and mortality were recently reached by Janes et al. (2007), that is, the association between trends in $PM_{2.5}$ and mortality at the national scale is more likely to be confounded. On the other hand our conclusions about linearity and thresholds are in contrast to those of Schwartz et al. (2008) using long term $PM_{2.5}$ exposure and mortality from the Harvard Six Cities Study.

CONCLUSION

EPA's ozone acute mortality risk assessment for the entire U.S. uses a fixed value based on a uniform linear no threshold model developed from 12 cities. Our work clearly shows that the assumption of a uniform linear no-threshold model across cities is inconsistent with the observed data. We have shown that each city has a different model form with different thresholds, and the threshold can change depending on the inclusion of other atmospheric pollutants in the model. In light of our results, ignoring location differences and combining the results into a single nation-wide standard result appears to be unjustified. We believe that continuing to estimate risks, specifically at lower exposures, based on a single pollutant linear no threshold model is not technically supported and will add greatly to the uncertainty of the resulting estimated risks.

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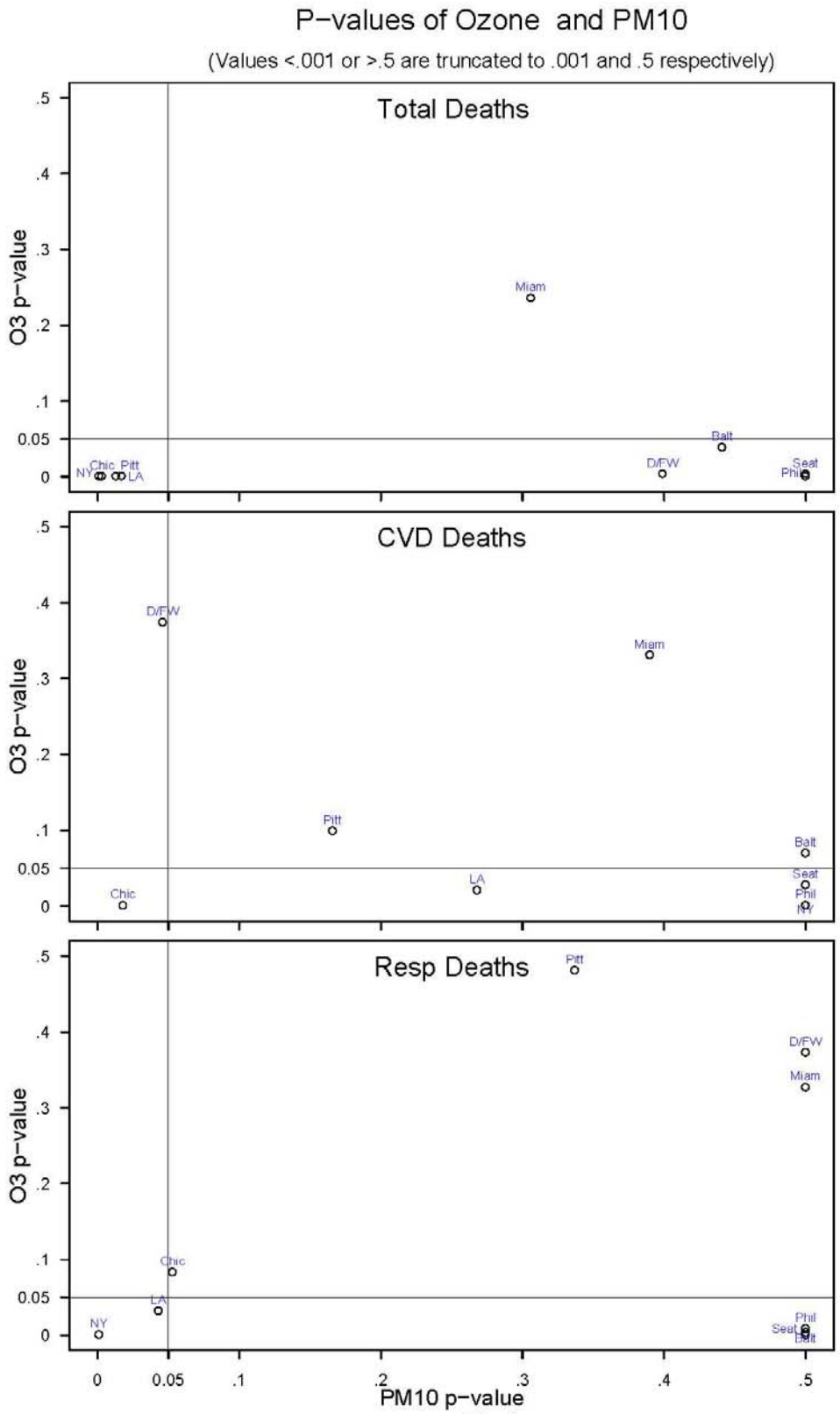
P−values of Ozone and PM10
(Values <.001 or >.5 are truncated to .001 and .5 respectively)
Total Deaths
CVD Deaths
Resp Deaths
O3 p−value
PM10 p−value
Miam
Balt
D/FW
Seat
Phil
NY
Chic
Pitt
LA
0
0.05
.1
.2
.3
.4
.5

Fig 1