

Comments Prepared for the
CASAC Review of the Second External Review Draft Integrated Science Assessment for
Ozone and Related Photochemical Oxidants

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Identification and Evaluation of a Dynamic Ozone- FEV_1 Exposure-Response Model
For Use in Conducting Risk Assessment in Support of the NAAQS for Ozone

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As noted in the Second Review Draft of the ISA for Ozone, we recently identified a dynamic exposure-response (E-R) model (McDonnell et al., 2007) for ozone-induced FEV_1 decrements that we believe would support a substantial improvement in EPA's risk assessment (RA) for ozone. The purpose of this comment is to suggest that the ISA should discuss the performance and benefits of this model as a basis for EPA updating its RA.

The foundation of the most recent version of EPA's ozone- FEV_1 RA is a five-point concentration-response (C-R) curve based upon responses measured at a single time point in several human controlled exposure studies to 0.04, 0.06, 0.08, 0.10, and 0.12 part per million (ppm) ozone. All studies were conducted using a similar pattern of rest and prolonged strenuous exercise, and the FEV_1 measures made at the end of a 6.6-hr exposure were used to estimate the effect of an 8-hr ozone exposure. The resulting RA is limited to estimating risk for the population experiencing a similar exposure pattern. The known effects of age and body mass index (BMI) upon ozone response are not accounted for in this model.

Exposure assessments indicate that the proportion of the general population that is exposed to ambient ozone under the conditions of these experimental exposures is small. Rather the majority of the population experiences diurnal variability in ambient ozone C as well as migration through microenvironments in which ozone concentrations may be less than 20% of the outdoor concentration. Similarly, few individuals undergo near continuous exercise at a single intensity for 8 hours. Rather most individuals experience multiple periods of various levels of activity surrounded by periods of rest. During the course of a day, it would not be unusual for an individual to experience a range of dose rates (concentration x minute ventilation) that varies by a factor of 10-20. It has also been demonstrated that the maximal FEV_1 responses to exposures with variable dose rates may be greater than predicted by using 8-hr average ozone concentrations and the responses measured at end exposure in the above studies (Hazucha et al., 1992). These factors combined with the restricted conditions (one time point and one activity pattern and level) under which the concentration-response function can be applied limit the applicability of the current RA to a small segment of the population.

As noted above, we have recently identified a dynamic E-R model that utilizes concentration (C) and minute ventilation (V_E) on a minute-to-minute basis as input and produces estimates of FEV₁ change as a function of time (t) across any range of exposure conditions. The model has the following characteristics:

1. FEV₁ response is a function of C(t), V_E (t), and t. Response increases monotonically with increases in any one of these factors if the other two are held constant. The effect of any one of these variables on magnitude of response is dependent upon the level of the other two variables. Ozone-induced FEV₁ responses are reversible, can decrease when dose-rate is reduced, and do decrease following cessation of exposure.

2. Responsiveness to ozone varies among individuals. A small proportion of this variability is explained by age and BMI with older individuals and those with smaller BMI experiencing smaller effects. The remaining between-individual variability is described by a log-normal distribution.

3. Minute ventilation is adjusted in the model for differences in body surface area (BSA).

4. Concentration is allowed to have a stronger effect on response than V_E .

The coefficients and other parameters of this model were originally estimated by fitting the model to E-R data from 15 human controlled exposure studies conducted over a wide range of conditions at the U.S. EPA Clinical Research Facility. Volunteers were 541 healthy, non-smoking white males ages 18-35 years. Ozone C ranged from 0.08 to 0.40 ppm, activity level varied within and between studies and ranged from rest to very heavy exercise, and most exposures were of 2.5- or 6.6-hr duration with FEV₁ measured hourly. Some measurements were made following cessation of exposure. The 541 volunteers participated in 864 separate exposures with FEV₁ decrement measured 3,485 times. The model described the data well over the entire range of exposures.

In order to evaluate the ability of this model to predict responses in independent data, we (McDonnell et al., 2010) conducted an internal n-fold cross validation using the original EPA data, and we also applied the model to the mean results of seven more recently published controlled exposure studies (six from UC-Davis and one from UNC/EPA). The agreement between observed and predicted values was excellent for the EPA data and was quite good (with a slight degree of overprediction of the observed data) for the seven independent studies as quantified by the slope and intercept of the best fit regression lines. The relationships between the observed and predicted values for the EPA cross validation and for the seven other studies, respectively, were described as:

$$\text{Observed}_{(\text{individuals})} = 0.98 * \text{Predicted}_{(\text{individuals})} - 0.20 \quad (\text{EPA data})$$

$$\text{Observed}_{(\text{mean})} = 0.96 * \text{Predicted}_{(\text{mean})} - 0.50. \quad (\text{Seven other studies})$$

Because much of the daily exposure of the population is to very low levels of ozone and because the lowest C in the EPA data was 0.08 ppm, it was desirable to re-estimate the parameters using data which included exposures at lower concentrations. Colleagues at UC-Davis and at EPA provided us with the individual data for eight published studies many of which included 6.6-hr exposures to 0.04 and 0.06 ppm, some of which included variable exposure C during the course of the study. We have fit the model to these data combined with the original EPA data and have found very good agreement between observed and predicted responses (manuscript in preparation). The relationship between mean observed and mean predicted responses for the combined data was as follows:

$$\text{Observed}_{(\text{mean})} = 0.97 * \text{Predicted}_{(\text{mean})} - 0.43.$$

The explicit modeling and estimation of the between-subject variability allows one to calculate other metrics of response for a given exposure such as the probability that an individual's response will exceed some value (e.g. a 10% decrement). From this one can estimate the proportion of individuals in a sample with responses exceeding this value, and we compared this predicted proportion with the observed proportion of volunteers with an FEV₁ decrement greater than 10% for each time point of each exposure. Again, good agreement was found with a slight underprediction of the observed response.

$$\text{Observed}_{(\text{proportion} > 10\%)} = 1.05 * \text{Predicted}_{(\text{proportion} > 10\%)} - 0.02$$

This latter metric of response (proportion with a greater than 10% FEV₁ decrement) which can be directly calculated from the model for any exposure is one that is used commonly in EPA's RA for ozone.

In addition to this previously identified model, Ed Schelegle (personal communication) has found evidence that a "threshold" level of exposure exists below which no FEV₁ response is observed. We have modified the original model to include a threshold and have fit the model to the combined data. We find evidence for a threshold that is significantly different from zero, and its inclusion improves the fit of the model to the data at the earliest time point of the low level exposures. Note that this threshold is not in fixed units of parts per million or micrograms of inhaled ozone, but is dependent upon rate of ozone exposure. The overall agreement between observed and predicted responses for this model is similar to that of the original model with the relationships given below:

$$\text{Observed}_{(\text{mean})} = 0.97 * \text{Predicted}_{(\text{mean})} - 0.34.$$

$$\text{Observed}_{(\text{proportion} > 10\%)} = 1.05 * \text{Predicted}_{(\text{proportion} > 10\%)} - 0.02$$

In summary, we have identified two similar models (with and without a threshold) that accurately predict the relationship between ozone exposure and FEV₁ response over

a wide range of exposure conditions for males and females, ages 18-35 yr. The models allow any pattern of exposure [$C(t)$ and $V_E(t)$] as input and provide predictions of population response as a function of time. These models integrate much of the information from individual studies that could previously not be compared because exposure conditions varied from study to study. Either model can serve as the basis for a health risk model that when combined with an exposure assessment model provides estimates of population risk under various regulatory and ambient concentration scenarios. Use of either model in place of the previous health risk model derived from data collected at one time point at one level and pattern of exposure will allow for calculation of risk for a much larger segment of the population. Although both of our earlier publications describing this model are referenced in Chapter 6 of the ISA, and although Figure 6.1A demonstrates the agreement between model predictions and observed data for the final time point of the 6.6-hr studies conducted at a single level of activity, there is no discussion of this model's ability to predict responses over a wide range of exposure conditions nor is there mention of its potential use in improving risk assessment for ozone-induced FEV₁ changes. We believe that this should be corrected with an added paragraph in the ISA.

References:

Hazucha, MJ, Folinsbee, LJ, Seal, E. Effects of steady state and variable ozone concentration profiles on pulmonary function. *Am Rev Respir Dis* 146:1487-1493, 1992.

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