Ozone-FEV_1 Dose-Response Analysis

Introduction. Clinical studies of human responses to ozone have been conducted for decades. These studies have investigated many health endpoints, including spirometric responses (i.e., lung function), symptoms, inflammation, airway hyper-responsiveness and changes in epithelial permeability (US EPA 2013, Chapter 5). The most studied endpoint has been forced expiratory volume in 1 second (FEV_1). FEV_1 is a measure of lung function that has been consistently and reliably measured in many ozone human clinical studies, and it shows a dose-response relationship with ozone. There is an expansive literature of human clinical exposures studies and ozone dose-response modeling, particular for ozone-FEV_1 dose-response. The following analysis goes beyond previous dose-response models and applies the results to real-world exposures. This allows decision makers to apply the exposures used in human clinical experiments to exposures expected in the general population. This document was written to inform the experts and participants in the Independent Workshop on Ozone NAAQS Science and Policy (April 7-9, 2015), and we will present a summary of this analysis at the workshop in the scientific discussion about human clinical studies.

The analysis conducted herein produces a dose-response model that fits both healthy young adults and other populations, such as children and asthmatics. We calculated ozone thresholds at which specific *group mean* FEV_1 decrements would be expected to occur, and also determined the number of people in the clinical experiments that experienced a greater-than-mean response to ozone at these thresholds. We compared these thresholds to the doses of ozone a person would be expected to attain during known exposure scenarios, given eight-hour maximum ambient ozone concentrations of 75, 70, or 65 parts per billion (ppb).

FEV_1-Ozone Dose Response Curves. In order to understand the dose-response relationship between ozone and FEV_1, we plotted total inhaled dose of ozone [which is calculated by multiplying ozone concentration in parts per million (ppm), duration of exposure in minutes, and ventilation rate in liters/minute (L/min)], and plotting this versus FEV_1 decrement. Because ventilation rate is dictated by exercise, these experiments were generally conducted while the participants were exercising to achieve significant doses of ozone. The main analysis used a dataset of 541 individuals (McDonnell 2007). To determine if the time it takes to achieve the dose affects the dose-response curve, the data were divided into two exposure duration categories: ≤ 3 hours and 6-8 hours. The zero ozone dose (called filtered air in the experiments) was also plotted on the graphs, but lung function at the zero dose was not subtracted from the ozone response data, as some investigators have done. Rather, all changes were determined in relationship to the pre-exposed FEV_1 value, which is the experimental control.

There were two distinct sigmoidal-shaped curves for the short and long exposure times (**Figure 1A, B**). There was a statistically significantly difference between the curves (regression analysis, $p < 0.001$). The difference between these curves might be attributable to the upregulation or replenishment of antioxidant molecules in the respiratory tract with longer exposure, which mitigates the physiological response to ozone (Mudway 1999).

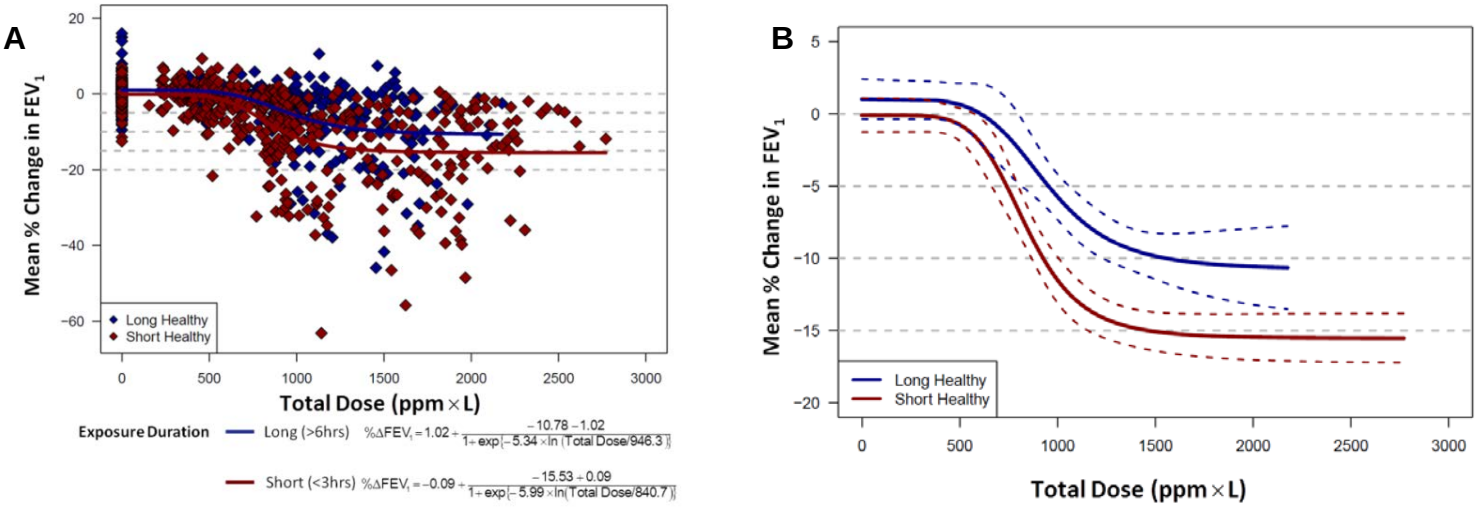

Figure 1. Ozone-FEV_1 dose-response curves. (A) Plot of total inhaled dose (in ppm x L) versus mean percent change in FEV_1 of healthy young adults exposed to ozone for ≤ 3 hours (short exposure, red diamonds and red trend line) or 6-8 hours (long exposure, blue diamonds and blue trend line) while exercising, with the equations associated with each curve below the graph; (**B**) The trend lines from A with 95% confidence intervals (dashed lines).

Ozone Threshold Doses. Using the best-fitting dose-response curves from Figure 1B, we calculated the doses at which 4 different mean FEV_1 decrements (5%, 10%, 15% and 20%) would be expected to occur, and the results are summarized in **Table 1**. We evaluated these specific decrements in part because the EPA considers the range of 10-20% FEV_1 decrements to be moderate (US EPA 1989), and has stated that a decrement of 10% might be adverse in a person with a pre-existing lung disease (US EPA 2014). Note that doses were not derived for a 15% or 20% FEV_1 decrement from the long-exposure curve, because the curve plateaued at a smaller decrement. Similarly, no 20% FEV_1 decrement dose was derived for the short-exposure curve, because that curve was never at or below 20%. Figure 1B also shows the presence of threshold doses at which no FEV_1 response would be expected to occur (the 0% FEV_1 threshold), at doses somewhere below 500 ppm x L. Such a threshold is consistent with the known ozone mode of action, in which antioxidants scavenge ozone in the epithelial lining fluid and prevent it from reacting and causing damage in the respiratory tract (see Chapter 5, US EPA 2013). Other groups that have modeled ozone-FEV_1 dose-response curves have also shown evidence of thresholds or doses of onset (McDonnell 2012, Schelegle 2012).

Table 1: Total ozone doses that produce a mean FEV_1 response

Mean % ΔFEV_1	Long Exposure Dose (ppm x L)	Short Exposure Dose (ppm x L)
- 5	953.5	740.2
- 10	1553.8	926.7
- 15	N/A	1467.4
- 20	N/A	N/A

We also estimated the percentage of individuals exposed to a given dose interval (the intervals were 250 ppm x L wide) who experienced an FEV_1 decrement ≥ 10% (**Figure 2**). For short exposures (≤ 3

hours), doses of 750-1000 ppm x L caused a more than five-fold increase in the number of people experiencing a 10% FEV_1 decrement, compared to doses of 500-750 ppm x L. For long exposures, a dose in the range of 1250-1500 ppm x L caused ~33% of people to experience an FEV_1 decrement of > 10%, whereas the range of 750-1000 ppm x L led to ~17% of people responding with an FEV_1 decrement of > 10%. The 5% FEV_1 thresholds (740 ppm x L for short exposure; 954 ppm x L for long exposure) correspond to the dose ranges that provide more protection against individuals experiencing 10% FEV_1 decrements (500-750 ppm x L for short exposures; 750-1000 ppm x L for long exposures). This shows that using 5% FEV_1 decrement thresholds would prevent not only group mean decrements of ≥10%, but would also prevent a significant number of more responsive individuals from experiencing a ≥10% FEV_1 decrement.

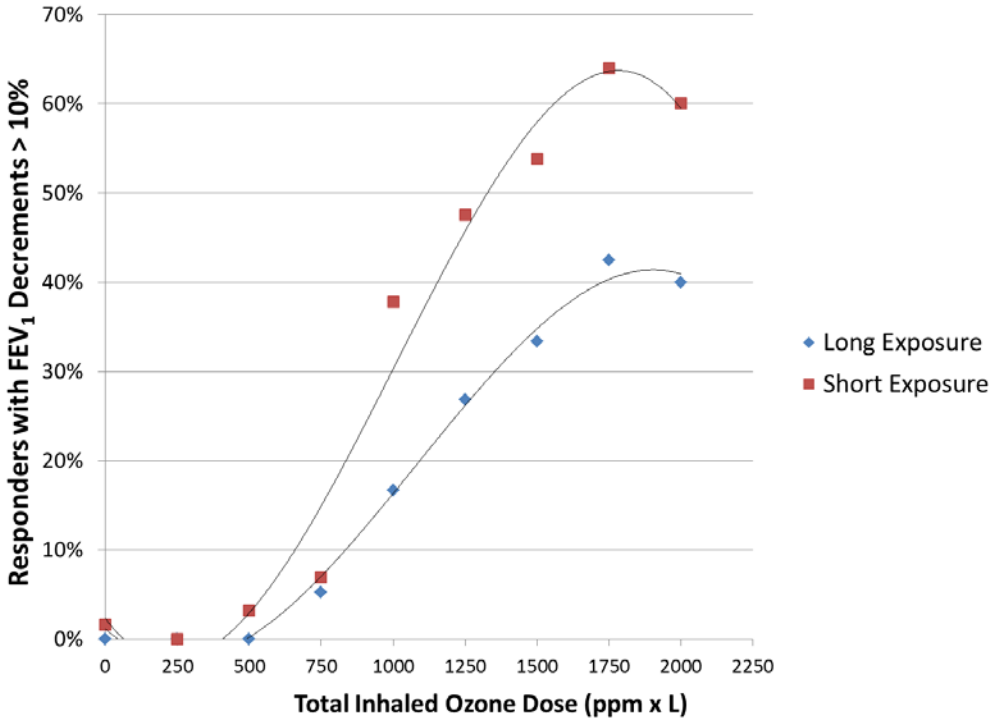

Figure 2. Percent of individuals experiencing >10% FEV_1 decrements in response to ozone exposure. Plot of percent of individuals who experienced FEV_1 decrements greater than 10% at ozone dose increments of 250 ppm x L during short (≤ 3 hour; red squares) and long (6-8 hour; blue diamonds) exposures to ozone.

Fitting other subpopulations to the FEV_1-ozone dose response curves. Our initial ozone-FEV_1 dose-response analyses were conducted using individual data from healthy young adults (18-35 years old). We conducted an additional analysis to compare the responses of healthy young adults to the responses of healthy children (aged 8-11), asthmatic adolescents, and asthmatic adults (these are potential at-risk populations for ozone exposure). To do this analysis, we used group mean data, not individual data, because only group mean data were available for most studies (see reference list for studies used for group mean dose-response).

We plotted the adult asthmatic group mean FEV_1 response with the short- and long-exposure curves for healthy adults and found that for both exposures, the asthmatic responses were similar to those of healthy young adults (**Figure 3 A, B**). Overall, this suggests that adult asthmatics do not demonstrate

increased spirometric responses to ozone, which is consistent with the conclusions reported from many studies (Linn 1994, Balmes 1997, Koenig 1985, Koenig 1987, Stenfors 2002, Nightingale 1999, Basha 1994). There are also data investigating the effects of short-term ozone exposure on healthy and asthmatic adolescents (aged 11 to 18 years old). These studies were conducted with quite low doses, making it difficult to derive a dose-response relationship. Generally, the responses between the healthy and asthmatic adolescents were similar (**Figure 3A**). The group mean response for healthy children (aged 8-11) was also consistent with the dose-response plotted for the healthy adult group mean (**Figure 3A**). These data all show that healthy children and asthmatics have similar FEV_1 responses to ozone as healthy young adults.

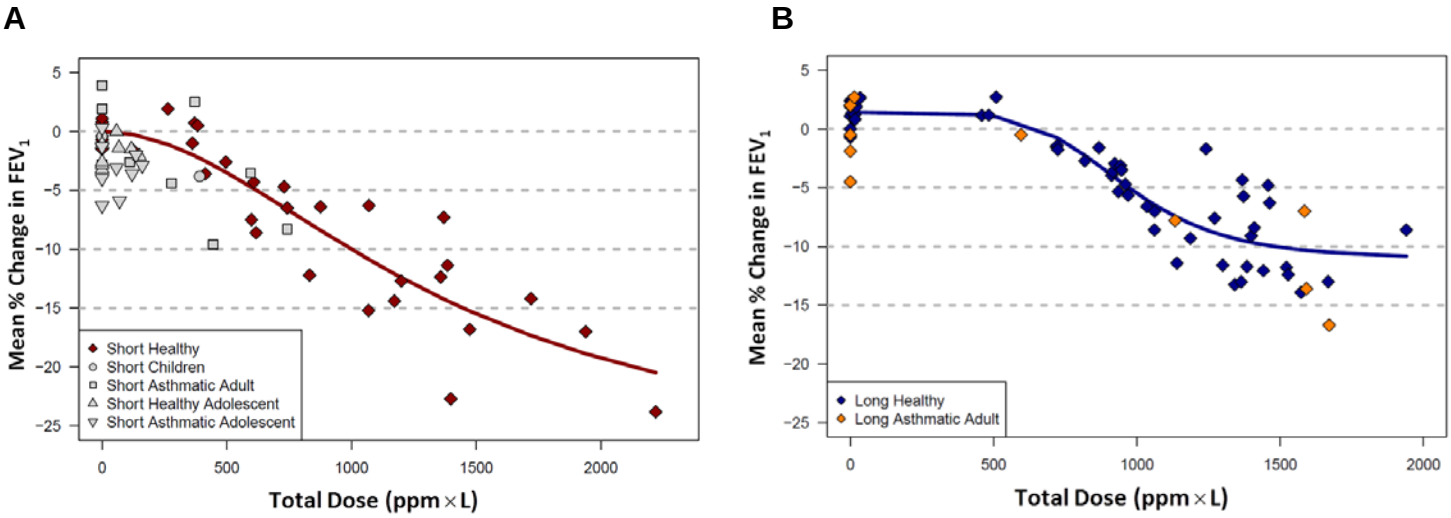

Figure 3. Ozone-FEV_1 dose-response curves that include subpopulations. (A) Total inhaled ozone dose versus group mean percent change in FEV_1 of healthy young adults (dark red diamonds and trend line) exposed for ≤ 3 hours to ozone, and also the group mean responses of healthy children aged 8-11 exposed to ozone (grey circles), adult asthmatics (grey squares), healthy adolescents (grey upward triangles), and asthmatic adolescents (grey downward triangles); **(B)** Total inhaled ozone dose versus mean percent change in FEV_1 of healthy young adults (blue diamonds and trend lines) exposed for six to eight-hours to ozone and adult asthmatics (yellow diamonds).

Application of ozone-FEV_1 dose-response curves to real-world exposures. The threshold doses in **Table 1** are a combination of exposure duration, ventilation rate, and ozone concentration. In contrast, the EPA's ozone National Ambient Air Quality Standard (NAAQS) level is only a concentration. Differences in exposure duration also require consideration of replenishment of detoxifying antioxidants, as evidenced by the different dose-response curves for ≤ 3 hour and 6-8 hour exposures. Incorporating the production of antioxidants into the model at longer exposure durations would raise the values of the FEV_1 decrement thresholds. We considered reasonable, real-world exposure durations and ventilation rates, and combined them with actual ozone concentrations to determine whether the resultant doses would be expected to cause significant FEV_1 decrements.

Guidance documents as well as published information exist about the duration and ventilation rates of people exercising in the general population. Because a person has to be exercising at moderate to vigorous intensity to achieve a significant dose of ozone at current US ambient concentrations (Schelegle 2009, Adams 2006a, etc.), we used information about the exercising population in this analysis. While we did not include exposure location in our analysis, we note that ozone is primarily

an outdoor pollutant (Sarnat et al. 2001, 2005), so these exposure scenarios assume that the person is exercising outdoors. We combined the information about exercise duration and ventilation rate with actual ambient ozone concentrations to calculate the ozone doses that people are expected to receive while exercising outdoors. These doses were compared to the dose thresholds from **Table 1** to determine whether these exposure scenarios are likely to cause the designated FEV_1 decrements.

To determine exposure times and ventilation rates, we used several different EPA guidance documents (US EPA 1994, US EPA 2009), as well as experimental observations made by Samet (1993) and Zuurbier (2003). These values are shown in **Table 2**. For ozone concentrations, we used the Texas Commission on Environmental Quality (TCEQ) Texas Air Monitoring Information System (TAMIS) to determine what would be expected on days that just meet the current NAAQS standard level (75 ppb maximum eight-hour average), or the potential alternative NAAQS standard levels (70 and 65 ppb maximum eight-hour averages). This was done using monitoring data from 10 days where the maximum eight-hour average was 75, 70 or 65 ppb. We used this data to evaluate other maximum averaging times (for 1-14 hours or the 24-hour average; **Table 3**).

Table 2. Real-world exercise duration and ventilation rates

Source	Population	Exercise Intensity	Ventilation Rate (L/min)*	Duration (hours)*
US EPA 2009	Children (6 - < 11 years old)	Sedentary	4.8 (3.7-6)	13.7 (13-15)
		Light	11.3 (9.2-14)	7.4 (5.5-9.6)
		Moderate	21.6 (17-26.8)	2.6 (0.9-4.1)
		High	41.5 (31.4-53.5)	0.3 (0.02-0.9)
	Adult (21 - < 31 years old)	Sedentary	5.3 (3.6-5.9)	12.5 (11.2-13.8)
		Light	11.8 (9.2-14.9)	6.3 (3.8-9.7)
		Moderate	26.1 (18.8-34.4)	5 (1.8-7.6)
		High	49.8 (34.6-67.2)	0.3 (0.05-0.6)
US EPA 1994	Non-occupational	24 hr Ventilation with 8 hrs Manual labor	14	24
	Occupational	Manual labor	22	8
Zuurbier 2003	Adult	Bicycle commute	23.5 (11-47.7)	2
Samet 1993	Child	Outdoor play	16 (12.1-17.4)	1.9
	Child	Bicycling	27.1 (16.7-34.8)	2.1
	Adult	Vigorous bicycling	65 (40.8-87.8)	0.8

* Mean ventilations and times, and where available, the 10th and 90th percentiles in parentheses.

Table 3. Ozone concentrations on days with maximum eight-hr concentrations of 75, 70 or 65 ppb.

Concentration Metric	75 ppb Days (ppb) mean (SD)	70 ppb Days (ppb) mean (SD)	65 ppb Days (ppb) mean (SD)
1-hr max	85.8 (3.5)	77.4 (5.7)	72.4 (4.7)
2-hr max average	84.2 (3.2)	76.2 (5.2)	71.3 (4.1)
3-hr max average	82.8 (2.7)	75.3 (4.8)	70.3 (3.7)
4-hr max average	80.8 (2.2)	74.3 (4.2)	69.6 (3.4)
5-hr max average	79.4 (1.7)	73.3 (3.2)	68.6 (2.6)
6-hr max average	78.2 (1.3)	72.4 (2.1)	67.6 (1.9)
7-hr max average	76.8 (0.9)	71.4 (1.4)	66.6 (1.1)
8-hr max average	75.4 (0.6)	70.2 (0.7)	65.6 (0.8)
9-hr max average	72.6 (4.5)	69 (0.7)	64.5 (1.2)
10-hr max average	71.5 (3.2)	97.6 (1.6)	63.2 (2.0)
11-hr max average	70.4 (2.2)	66.2 (2.4)	61.9 (2.9)
12-hr max average	69.2 (1.8)	64.9 (3.2)	60.6 (3.5)
13-hr max average	68 (1.8)	63.8 (4.0)	59.2 (4.2)
14-hr max average	66.9 (2.1)	62.7 (4.7)	57.9 (4.8)
24-hr average	52.2 (5.5)	51.4 (8.5)	46.2 (6.5)

Note: provided are the mean maximum averages using different time metrics from 10 days with eight-hour maximum averages of 75, 70 or 65 ppb (standard deviation in parentheses). Shaded is the measured eight-hour maximum average.

The exposure ventilation for a certain activity, the time spent at that activity, and the appropriate ozone concentration for that duration and standard level were combined to produce an expected dose (in ppm x L). The following is an example of how that was calculated:

From Table 2: Sedentary child ventilation rate = 4.8 L/min; duration = 13.7 hrs

From Table 3: 14 hr max average (matching the 13.7 hr duration) = 64.7 ppb (at a 75 ppb level)

Total Inhaled Dose at 75 ppb = 4.8 L/min x 13.7 hrs x 60 min/hr x 0.0647 ppm = 255 ppm x L

We plotted the ozone doses associated with each activity as well as the 5%, 10% and 15% group mean FEV_1 decrement thresholds (**Figure 4**). We found that all of these activities are associated with doses below any of the thresholds, regardless of which NAAQS level was used. Changing the standard level made very little difference in expected dose. Only the 24-hour non-occupational exposure at the 75 and 70 ppb standard levels was over even the 5% threshold (but was still well below the 10% FEV_1 threshold that the EPA considers is needed to protect sensitive individuals). This non-occupational scenario assumes a 24-hour outdoor exposure, eight hours of which are spent doing manual labor (US EPA 1994). We also demonstrated that longer exposure times cause smaller decrements at the same total dose (**Figure 1, Figure 2**), and therefore, using the 6-8-hour experimental exposure threshold over-estimates the response to a 24-hour exposure.

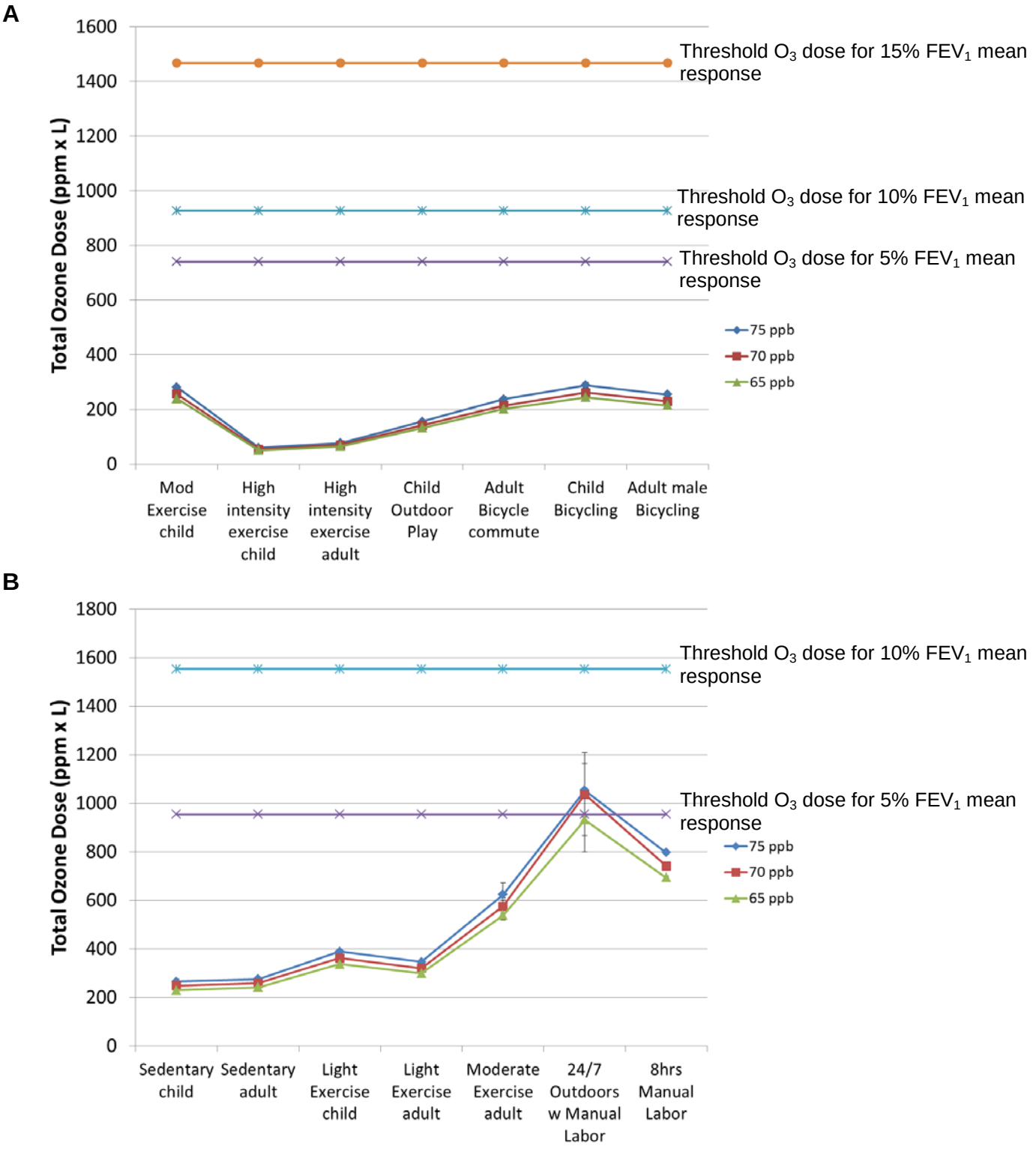

Figure 3. Modeled ozone doses compared to ozone dose-response thresholds. Plotted is the total mean (± SD) ozone dose associated with different exposure scenarios, calculated by multiplying the exposure duration and ventilation rate for each activity (from Table 2), with the ozone concentration for the appropriate duration that would occur if the ambient 8-hour maximum average ozone concentration were 75, 70 or 65 ppb (from Table 3). These are separated into short (≤ 4 hour; **A**) and longer (> 4 hour; **B**) exposure times. The threshold ozone dose at which group mean FEV_1 decrements of 5%, 10% or 15% (15% threshold available for short exposure only) would be expected to occur is also plotted. Standard deviation based on variability in ozone concentrations, not on variability in exposure duration or ventilation rates.

Discussion. A number of papers have been published that describe the relationship between ozone dose and different health endpoints, particularly the FEV_1 response (e.g. McDonnell 2007, Schelegle 2012, McDonnell 2012). The McDonnell (2012) analysis was used to derive the McDonnell-Stewart-Smith (MSS) model on which the EPA relies to model FEV_1 decrements in the Health Risk and Exposure Assessment (US EPA 2014). Our work differs from these papers and from the MSS model in several important ways.

- One way is that we do not subtract the individuals' filtered air response, but rather include it as a zero dose in the dose-response curve. Including a zero-dose is a common practice in modeling dose-response and allows the direct observation of any inter-individual variability that occurs just in response to the study protocol.
- Another difference is that we consider both the mean response, which includes the entire dataset, as well as the number of individuals that have a greater-than-mean response. This allows us to make decisions about protective levels of ozone based on both of these criteria.
- We also consider the data from different subpopulations that have been experimentally exposed to ozone, to determine whether or not the healthy young adult dose-response also adequately represents these populations.
- Finally, unlike the other papers that have published dose-response models, we use real-world ventilation rates and exposure times to allow this information to be applied to the general population, which may aid policy makers in making decisions.

In conclusion, this is a unique analysis that incorporates ozone exposures with group mean and individual FEV_1 responses, and considers other subpopulations, to produce dose-response curves. We compared different threshold doses at which a given mean FEV_1 decrement would be expected to occur to real-world expected exposures incorporating duration, ventilation rate and ozone concentrations. This provides a tool that translates ozone human clinical data into a format that can be used by policy makers to decide on a protective level for the ozone NAAQS. The results shown here demonstrate that the current ozone NAAQS level of 75 ppb is adequate to protect sensitive members of the population when using group mean FEV_1 decrements of 5% or above.

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