How dose-response curves derived from clinical ozone exposures can inform public policy

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Abstract

Ozone is one of the 6 criteria air pollutants whose levels are set by the EPA through the National Ambient Air Quality Standards. Data from animal, human clinical and epidemiology studies are used to decide at which level to set the standard. The purpose of our work is to use data from human clinical studies to inform policy decisions about protective ambient ozone level.s Many studies have been conducted that can be applied to generate ozone dose-response curves, using ozone total inhaled dose (which is calculated from ozone concentration, duration of exposure and ventilation rate) and forced expiratory volume (FEV_1) decrements. Outside of modeling conducted by the EPA, these dose response curves have not been utilized as tools to inform the choice of a protective ambient ozone concentration. In this work we plotted mean FEV_1 response versus total inhaled ozone dose from clinical studies of varying durations (1 – 8 hours). Mode of action (MOA) information was incorporated as appropriate. The initial plot used data from healthy young adults, and additional analyses incorporated data from children and asthmatics to determine whether they differed from the healthy adult dose-response curve. The trend line from this data was employed to make tables demonstrating the ozone concentrations required to produce a given FEV_1 decrement at different exposure times and ventilation rates (i.e. exercise levels). We also plotted ozone doses at which other relevant clinical effects occur (e.g. inflammation) although the variability in technique and lack of consistent quantification makes these difficult to model in a similar way as FEV_1. This type of analysis is crucial for deciding on a protective ambient ozone concentration, because differing levels have significant societal and economic implications. Clinical data provides quantifiable and confident endpoints that can be justifiably used for well-reasoned and scientifically defensible rulemaking.

Introduction

- Ozone (O_3) is one of 6 air pollutants regulated by the National Ambient Air Quality Standards (NAAQS).
- The level of the O_3 NAAQS is currently 75 ppb with an averaging time of a daily 8 hour maximum average, and the EPA is proposing to lower the level into the range of 65 – 70 ppb.
- In clinical studies volunteers were exposed to O_3 at different concentrations and ventilation rates (ie. exercise levels), for different times; these studies measure respiratory endpoints.
- Other groups have used this data to make ozone dose-response curves, using ozone total inhaled dose and decrements in forced expiratory volume in 1 second (FEV_1)[16].
- Outside of the EPA, dose response curves have not been used as a tool to inform the choice of a protective ambient ozone concentration.
- This is important because choosing a protective ambient ozone concentration has societal and economic implications, and clinical data can provide quantifiable endpoints that can be used for rule making.

Ozone Mode of Action

- O_3 is an oxidant which can be scavenged by antioxidants (such as uric acid, glutathione and ascorbic acid) in the extracellular lining fluid of the respiratory tract.
- O_3 in the nasal cavity activates bronchial C-fibers, which initiates a neural reaction, leading to spirometric responses (e.g. FEV_1 decrements).
- O_3 initiates inflammation in all areas of the respiratory tract, measured by influx of neutrophils; this is considered more detrimental than spirometric responses.
- O_3 can impair epithelial barrier function of the respiratory epithelia.
- O_3 increases airway hyper-responsiveness to bronchoconstrictive stimuli, and this may be worse in those with compromised airways.
- None of these effects are correlated with spirometric responses – that is, people with heightened spirometric responses do not necessarily show increased inflammation, loss of epithelial barrier function or airway hyper-responsiveness.
- The ozone mode of action is thoroughly reviewed in the most recent EPA ozone Integrated Science Assessment (2013)[22].

Methods

- Ozone concentration (in ppm), time of exposure (in min) and ventilation rates (in L/min) were extracted from 11 publications[1-5,8,10,13,14,19,20]. These were multiplied to produce **total inhaled dose** (in ppm×L). The associated **mean change in FEV_1** (in % change from baseline) for the group of study subjects was also used.
- The main curve was made using data derived from healthy young adults. We also plotted data from 3 additional studies using mild asthmatics as volunteers[9,11,12], one study using children aged 8-11 as volunteers[15], and one study that exposed elite athletes at very high exercise levels in a hot environment[7].
- Non-linear dose-response curves were fit to the short exposure (≤ 3 hours) and long exposure (> 6 hour) data, using the following sigmoid response model:

$$\%\Delta FEV_1 = \delta + \frac{\alpha - \delta}{1 + \exp\{\beta \ln(\text{Total dose} / \lambda_{50})\}}$$

Where $\%\Delta FEV_1$ is the percent change in FEV_1 after the ozone exposure compared to the pre-ozone exposure, "Total dose" is the total ozone dose defined as ventilation (L/min) × time (min) × ozone (ppm), δ is the top plateau of FEV_1 decrements at minimal dose, α is the bottom plateau of FEV_1 decrements at high dose, β is the slope parameter that defines the steepness of the curve, λ_{50} is the dose at which the response is halved, and δ, α, β and λ_{50} are parameters of the model and can be estimated from observed data.

- Ozone concentration matrix:
  - Exposures ≤ 4 hours: Using the short exposure time curve, the doses at which the mean curve crossed -10% FEV_1 were taken, and then the ozone concentrations were calculated based on the different exposure times and ventilation rates.
  - Exposures > 4 hours: Using the longer exposure time curve, the doses at which the mean curve crossed -10% FEV_1 were taken, and then the ozone concentrations were calculated based on the different exposure times and ventilation rates.
  - The 10% FEV_1 decrement cut-off is based on the EPA's determination that this FEV_1 decrement would cause an adverse effect in sensitive populations (those with respiratory conditions).

Results

Dose Response Curve from O_3 Clinical Data

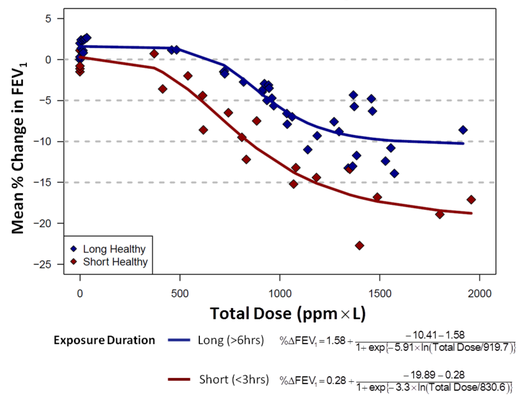

Figure 1: Plot of total inhaled dose (in ppm×L) versus percent change in mean FEV_1; data is derived from mean FEV_1 change of healthy young adults exposed for ≤3 hours (short) or > 6 hours (long) to ozone while exercising. Below the plot are the equations associated with each curve.

Dose Response Curve Characteristics

- Sigmoid-shaped curve:
  - FEV_1 barely changes at low doses (<500 ppm×L)
  - FEV_1 decreases as ozone dose increases and the decreasing rate increases (500-1000 ppm×L) and then decreases (1000-1500 ppm×L) at medium doses
  - the FEV_1 decrements reach a plateau at high total doses (>1500 ppm×L)
- Using regression analysis, there is a significant difference in response rate between long exposure experiments and short exposure experiments.

Dose Response Curve with Sensitive Populations

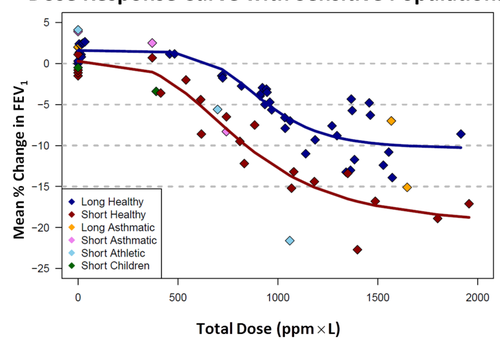

Figure 2: Plot of total inhaled dose (in ppm×L) versus percent change in mean FEV_1 as in Figure 1; also plotted are data from mild asthmatics exposed for < 3 hours (short asthmatic) or > 6 hours (long asthmatic); data from children exposed for < 3 hours (short children); and for elite athletes exposed for 1 hour (short athletic).

Inverse of the dose-response curve for identifying benchmark doses

$$\text{Total dose} = \lambda_{50} \times \exp\left\{\ln\left(\frac{\alpha - \%\Delta FEV_1}{\%\Delta FEV_1 - \delta}\right) / \beta\right\}$$

Table 1: Doses associated with mean changes in FEV_1, derived from long & short dose response curves

Mean % Change in FEV_1	Short exposure dose (ppm×L)	Long exposure dose (ppm×L)
0	228.2	668.5
- 5	606.7	950.7
- 10	**840.4**	**1618.6**
- 15	1173.1	N/A

Exercise Ventilation Rates

Table 2: Ventilation rates in L/min and m^3/day for different exercise levels

Source	Population	Exercise	Ventilation (L/min)	Ventilation (m^3/day)
EPA O_3 ISA 2013[23]	Children (6-11)	Sedentary	4.8	6.9
		Light Intensity	11	15.8
		Moderate Intensity	22	31.7
		High Intensity	42	60.5
	Young adult (21-31)	Sedentary	5.3	7.6
		Light Intensity	12	17.3
		Moderate Intensity	26	37.4
		High Intensity	50	72
Zuurbier 2003[24]	Adult	Commuting by bicycle	23.5	33.8
Samet 1993[18]	Child	Outdoor play	16	23
	Child	Bicycling	27	38.9
	Adult male	Bicycling	65	93.6
TCEQ Guidance 2012[21,22]	Adult worker	Occupational (8 hour day)	22	10
	General Population	Non-Occupational (24 hour day)	14	20

Table 3: Concentrations of O_3 at which a population would be expected to experience an FEV_1 decrement of 10%, given different exposure times and ventilation rates (V_E - ie. exercise levels)

FEV_1 Decrement = 10%

			Ozone Concentration (ppb)									
			Time (hrs)									
Source	Population & Exercise	V_E (L/min)	1	2	3	4	5	6	7	8	12	24
EPA[23]	Sedentary Child	**5**	2917	1458	972	729	1124	937	803	703	468	234
EPA	Sedentary Adult	**5**	2642	1321	881	660	1018	849	727	636	424	212
EPA	Light Int Child	**11**	1273	636	424	318	491	409	350	307	204	102
EPA	Light Int Adult	**12**	1167	583	389	292	450	375	321	281	187	94
TCEQ[21,22]	General Pop (24 hr)	**14**	1000	500	333	250	385	321	275	241	161	80
Samet[18]	Child Outdoor Play	**16**	875	438	292	219	337	281	241	211	141	70
EPA	Med Int Child	**22**	636	318	212	159	245	204	175	153	102	51
TCEQ	Adult Worker (8 hr)	**22**	636	318	212	159	245	204	175	153	102	51
Zuurbier[24]	Adult Bicycle Commute	**24**	596	298	199	149	230	191	164	144	96	48
EPA	Med Int Adult	**26**	538	269	179	135	208	173	148	130	86	43
Samet	Child Bicycling	**27**	519	259	173	130	200	167	143	125	83	42
EPA	High Int Child	**42**	333	167	111	83	128	107	92	80	54	27
EPA	High Int Adult	**50**	280	140	93	70	108	90	77	67	45	22
Samet	Adult Male Bicycling	**65**	215	108	72	54	83	69	59	52	35	17

Note: The highlighted 8 hour time point is the averaging time of the O_3 NAAQS; grey numbers indicate times and ventilation rate combinations that are unlikely to occur. For times ≤ 4 hours, the short dose-response curve was used, and for times > 4 hours, the long dose-response curve was used.

Threshold Doses of Ozone

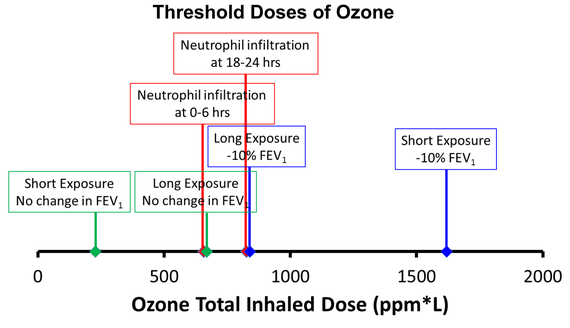

Figure 3: Threshold ozone doses after which one would expect to see various respiratory effects

Uncertainties in Ozone Dose-Response Data

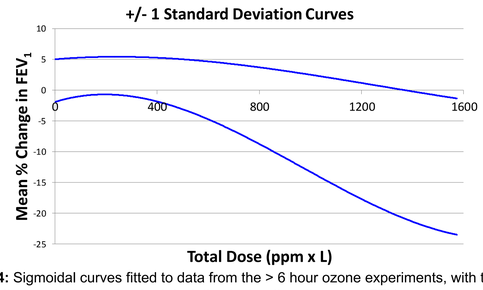

Figure 4: Sigmoidal curves fitted to data from the > 6 hour ozone experiments, with total ozone dose plotted against one standard deviation higher than the mean FEV_1 response and one standard deviation lower than the mean FEV_1 response.

Summary & Conclusions

- O_3 clinical exposure data can be used to derive dose-response curves. All three factors: concentration, time and ventilation, must be taken into account to estimate response.
- O_3 dose-response is dependent on the rapidity of exposure, consistent with a mechanism of antioxidant protection against ozone in the respiratory tract.
- Sensitive populations such as asthmatics and children show similar responses to O_3 as healthy young adults.
- These dose-response relationships can be used to create a tool to provide guidance as to how long populations can be exposed, at what exercise level and O_3 concentration, before experiencing a given FEV_1 decrement.
- This tool can be used by policy makers to help make an informed decision about setting the level of the O_3 standard, based on time activity data that will inform choices about exposure times and ventilation rates.

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