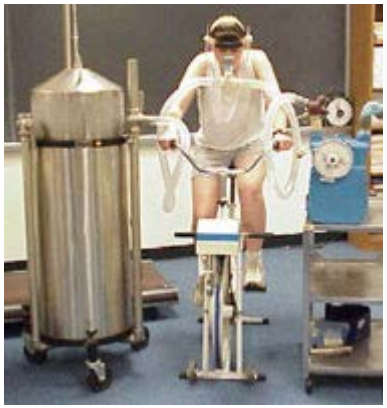
Ozone Clinical Studies and Dose-Response

Sabine Lange, Ph.D.
Toxicology Division
Texas Commission on Environmental Quality
Sabine.Lange@tceq.texas.gov

Human Clinical Studies



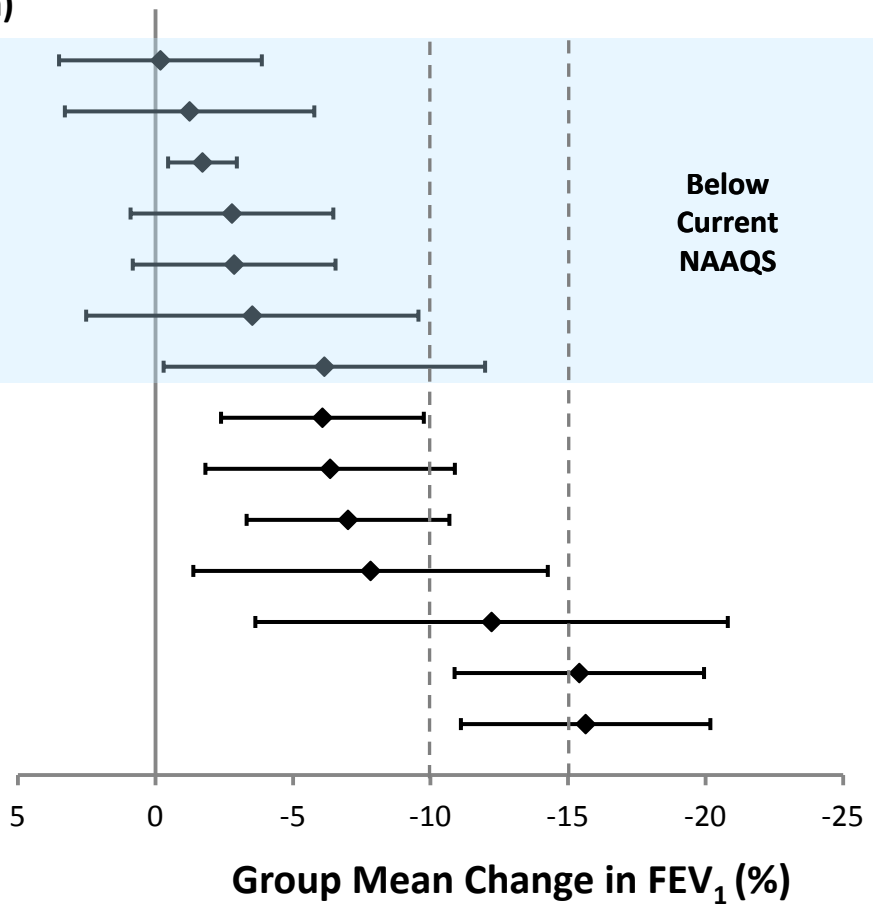
- These studies measure physiological effects, primarily respiratory function (FEV_1)
- They take into account 3 parameters, which make up O_3 ***dose***:
  - O_3 concentration (in ppm)
  - Time of exposure (in min)
  - Ventilation rate (ie. Exercise level; in L/min)

Ozone Dose

- Concentration:
  - 40 ppb to > 500 ppb; 4 studies with concentrations that can inform decisions about the current and alternate NAAQS levels
- Time of exposure:
  - < 1 hour to 8 hour exposures; 8 hour exposures are relevant to the averaging time of the ozone NAAQS
- Ventilation rate
  - From rest (~ 10 L/min) to heavy exercise (> 50 L/min)
- Recent studies have used ambient concentrations (< 100 ppb) for 6.6 hours with exercise for 50 min/hr at a ventilation of ~ 35 L/min – mimics heavy manual labor

Clinical Data at ambient [O_3]

Study	Sample Size	Exposure	Ozone (ppm)
Adams (2006)	30	CH-TRI	0.04
Adams (2002)	30	FM-SQR	0.04
Kim *et al.* (2011)	59	CH-SQR	0.06
Adams (2006)	30	CH-TRI	0.06
Adams (2006)	30	CH-SQR	0.06
Schelegle *et al.* (2009)	31	CH-TRI	0.063
Schelegle *et al.* (2009)	31	CH-TRI	0.072
Adams (2006)	30	CH-SQR	0.08
Adams (2002)	30	FM-SQR	0.08
Adams (2006)	30	CH-TRI	0.08
Schelegle *et al.* (2009)	31	CH-TRI	0.081
Schelegle *et al.* (2009)	31	CH-TRI	0.088
Adams (2002)	30	FM-SQR	0.12
Adams (2002)	30	CH-SQR	0.12



Adapted from Goodman *et al.* (2014)

Adverse Effects

- An adverse effect is one that causes a physiological change resulting in impaired function in a system or an organism that is intense enough to distinguish from normal variability, or that has the ability to increase the susceptibility of that organism or system to other external influences

- Also consider whether the effect is transient or reversible, if it is a precursor to a known overt adverse effect, and how severe the effect is

Adverse Effects - Biomarkers

- ATS, 2000 - “the committee cautions that not all changes in biomarkers related to air pollution should be considered as indicative of injury that represents adverse effect.”

- US EPA, 2014a - “any initiation of inflammation can be considered as evidence that injury has occurred.”

Adverse Effects – FEV_1

- ATS, 2000 - “reversible loss of lung function in combination with the presence of symptoms should be considered adverse.”
- ATS/ERS, 2005 - “two-point, short-term changes of >12% and >0.2L in the FEV_1 are usually statistically significant and may be clinically important” (Pellegrino 2005)
- US EPA 2014b - “…a focus on the mid- to upper-end of the range of moderate levels of functional responses and higher (FEV_1 decrements ≥ 15%) is appropriate for estimating potentially adverse lung function decrements in active healthy adults, while for people with asthma or lung disease, a focus on moderate functional responses (FEV_1 decrements down to 10%) may be appropriate”

O_3 Dose-Response Modeling

- Use ozone doses comprising concentration, time and ventilation rate
- Use FEV_1 responses – typically all FEV_1 decrement data is included; often an individual's response to filtered air is subtracted from their ozone response
  - McDonnell (2012) and EPA's MSS model output only those individuals with FEV_1 decrements > 10, 15 or 20%.
- Most models use individual data of varying amounts – recent modeling has used data from 500 to > 700 individuals who were exposed to ozone

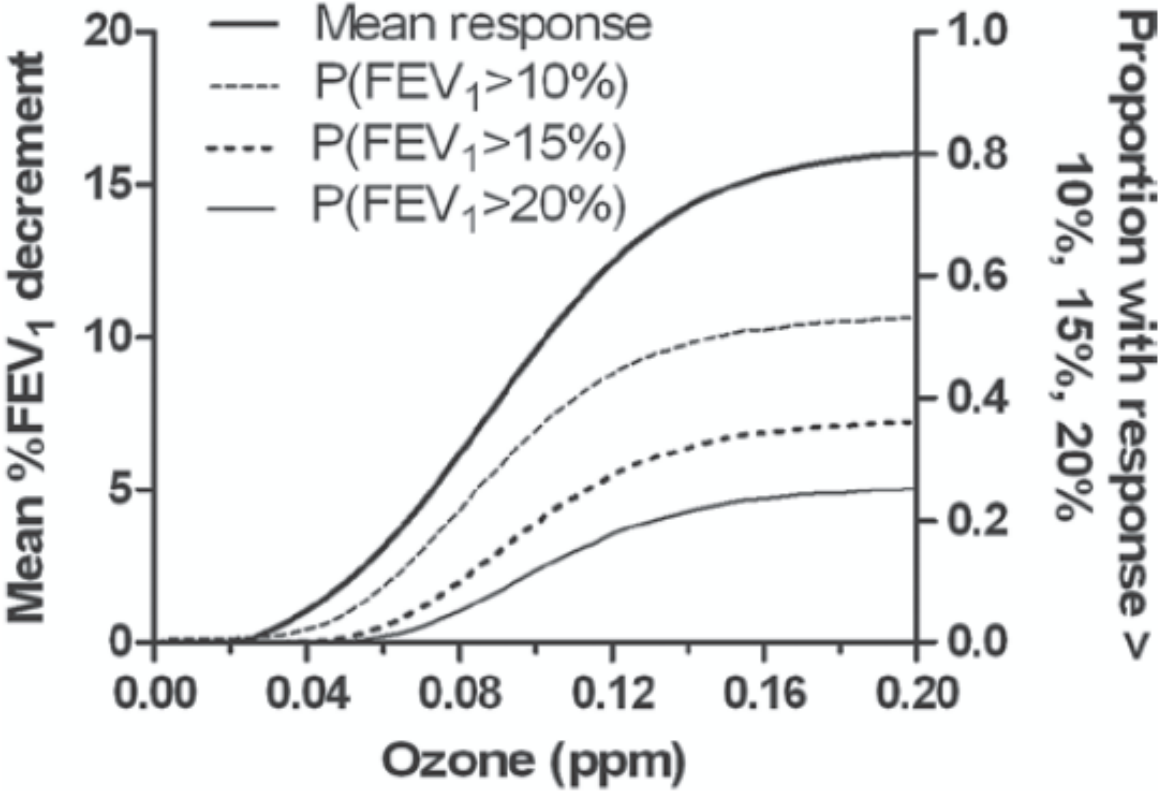
O_3 Dose-Response Modeling

- Most studies model sigmoidal ozone-FEV_1 dose-response curves

- Models have shown that ozone-FEV_1 dose-response is not affected by gender, there are mixed results with body size or body surface area, and there is a decreasing response with increasing age

- Multiple groups have found evidence of thresholds. Eg. Adams (1981) showed a threshold of 400 ppm x L; Schelegle (2012) found a threshold (they called it a dose of onset) of 553 ppm x L

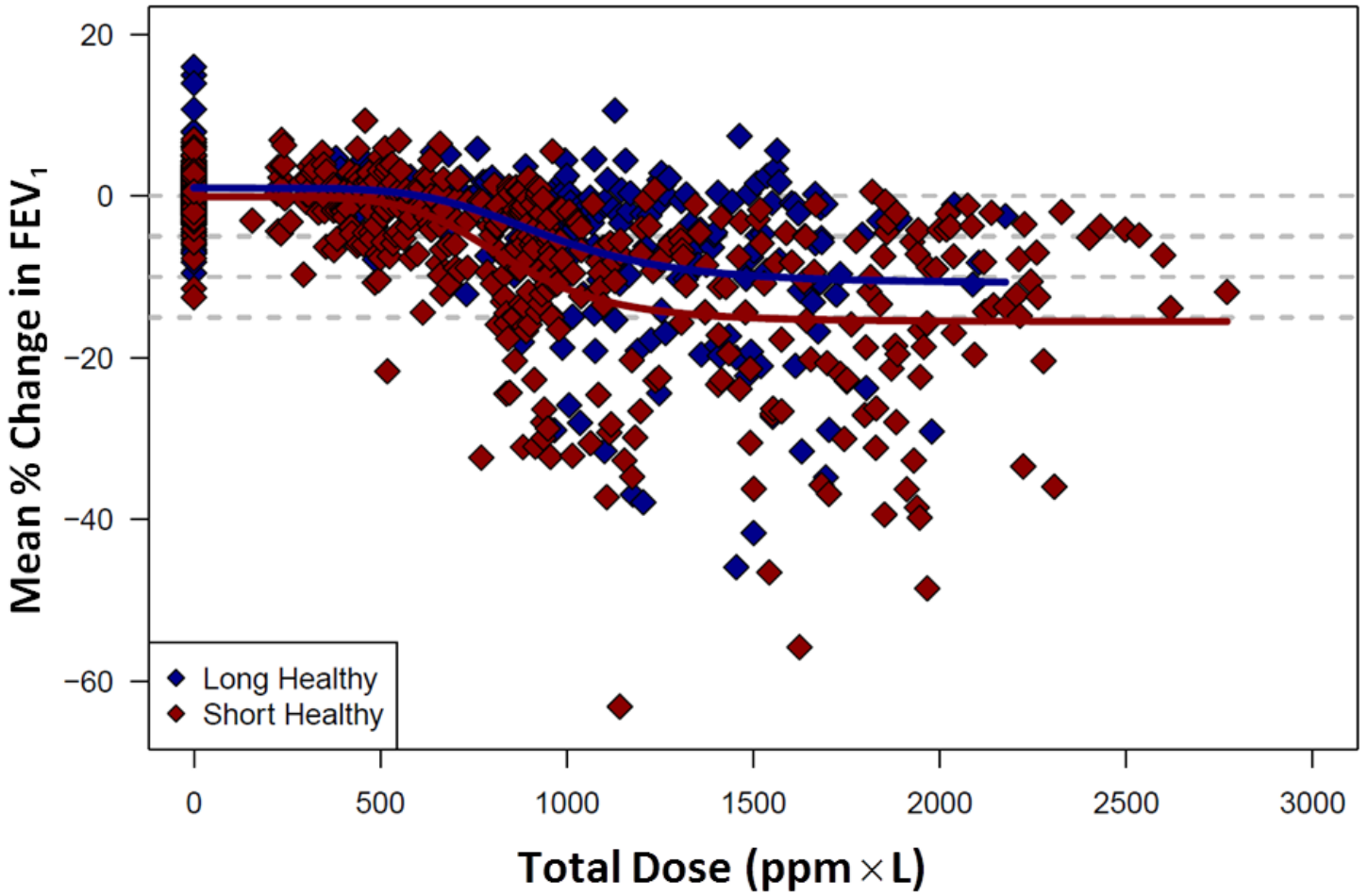
McDonnell 2012 Dose-Response Curve



O_3 Dose-Response for Real World Exposures

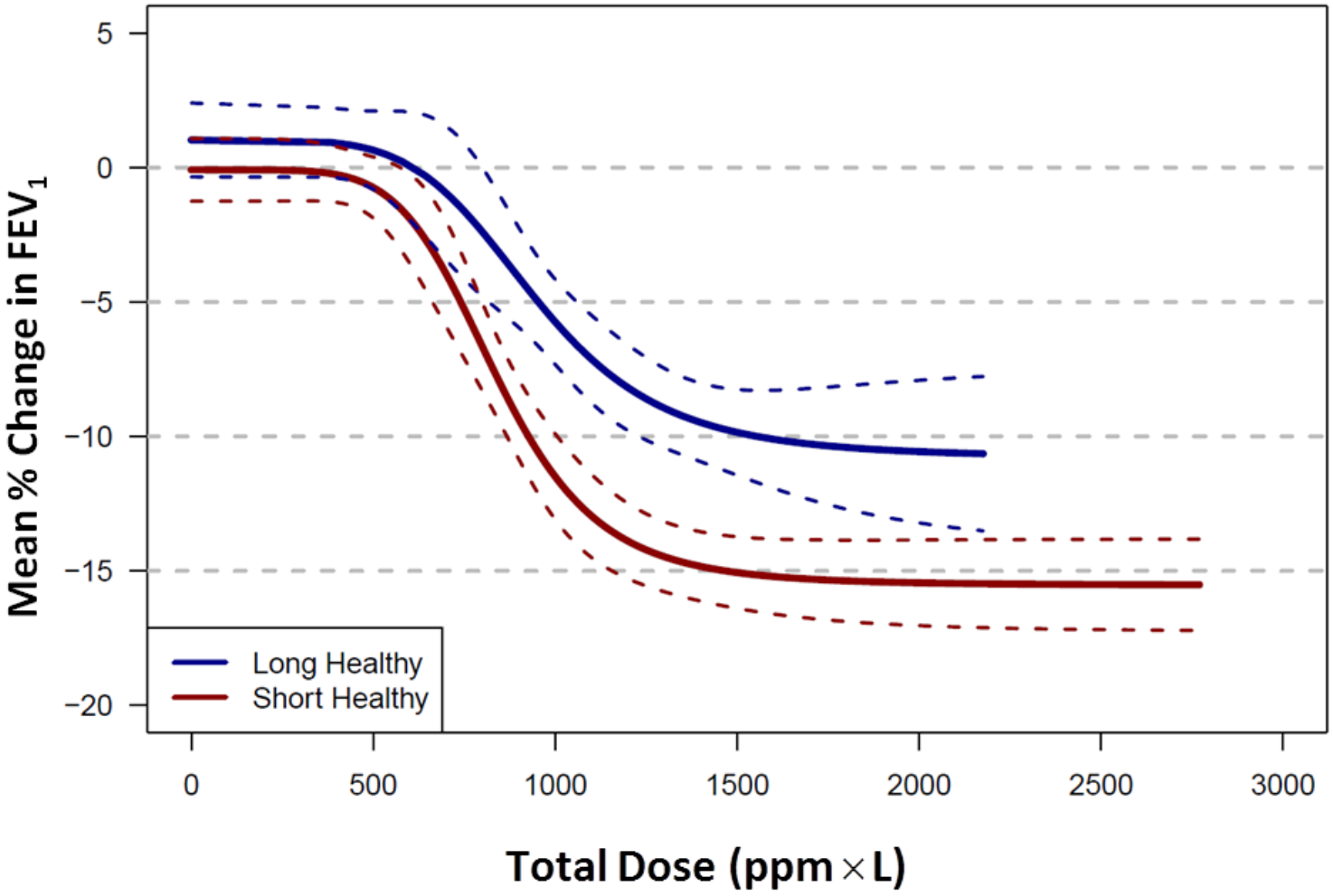
- Besides the McDonnell (2012)-MSS model, these models have not been used to extrapolate to real world exposures and responses
- None of these studies have compared responses of healthy young adults to responses from potentially sensitive subpopulations
- We used individual data and group mean data to model ozone-FEV_1 dose-response, assessed the goodness-of-fit for subpopulations, and then applied threshold doses to real world exposure times and ventilations to determine the range of ozone concentrations expected to cause FEV_1 decrements

O_3 Dose-Response Curves

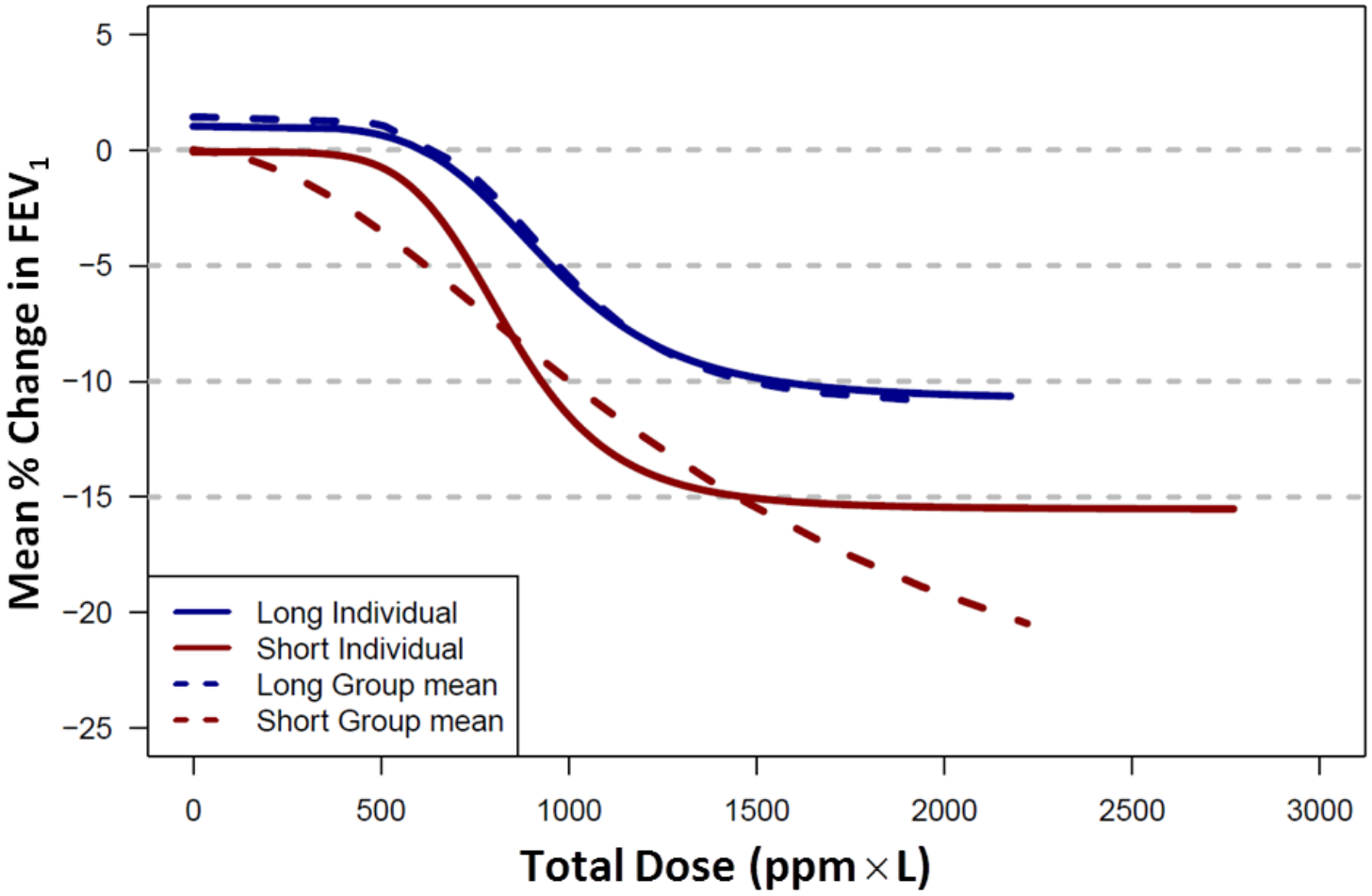


With M. Honeycutt from TCEQ; G. Tao, L. Rhomberg & J. Goodman from Gradient; M. Dourson from TERA

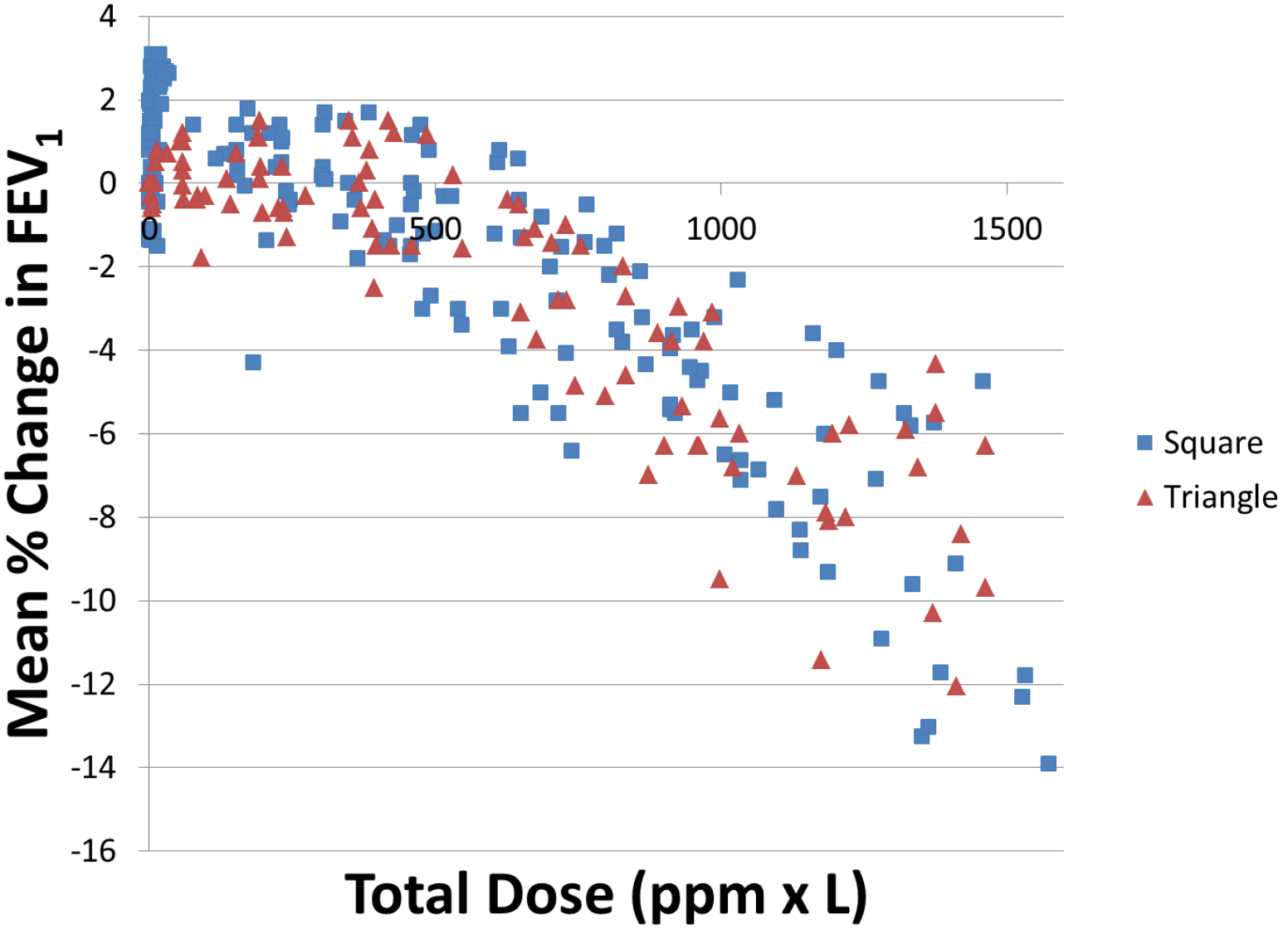
O_3 Dose-Response Curves



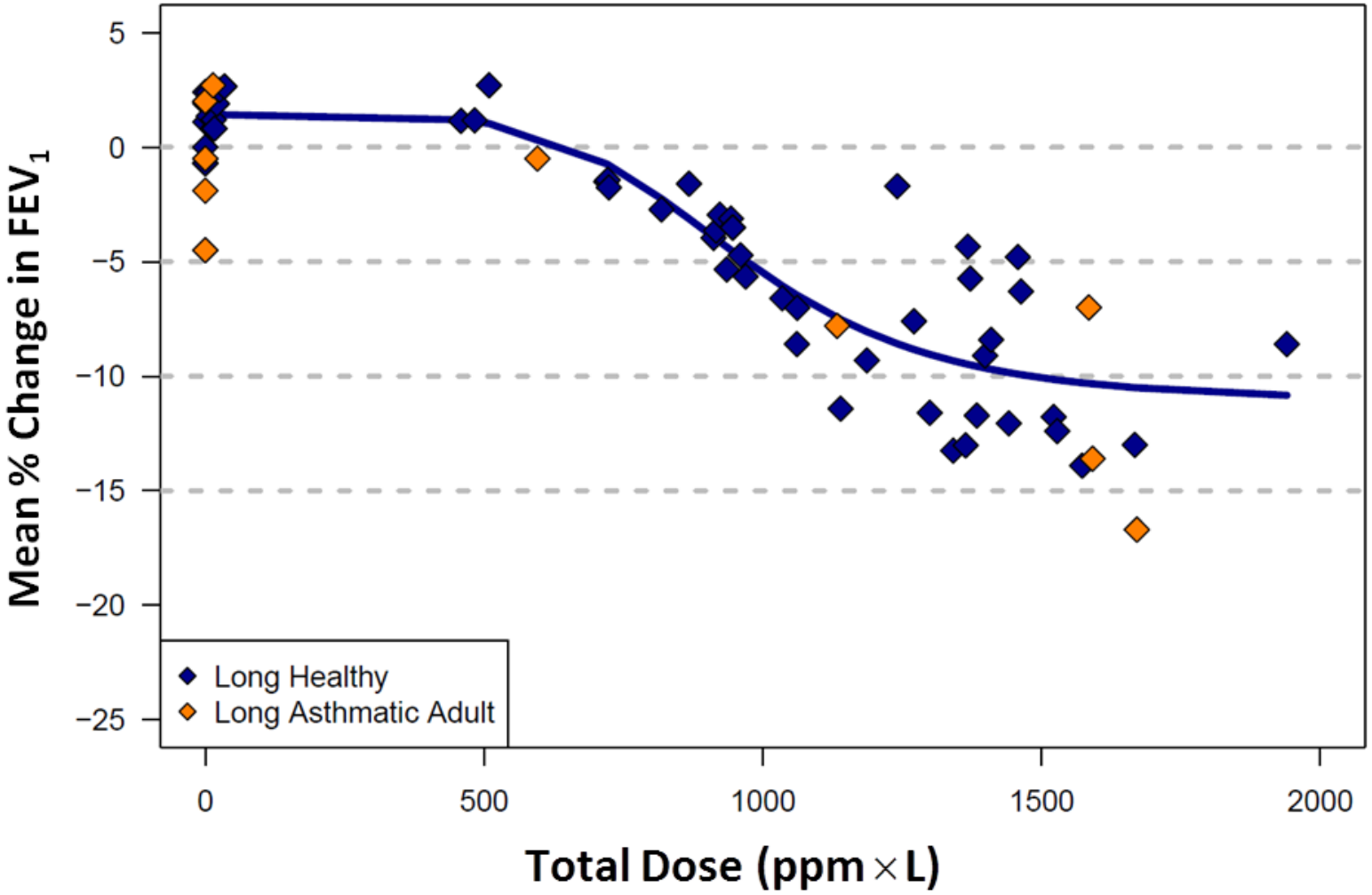
O_3 Dose-Response Curves



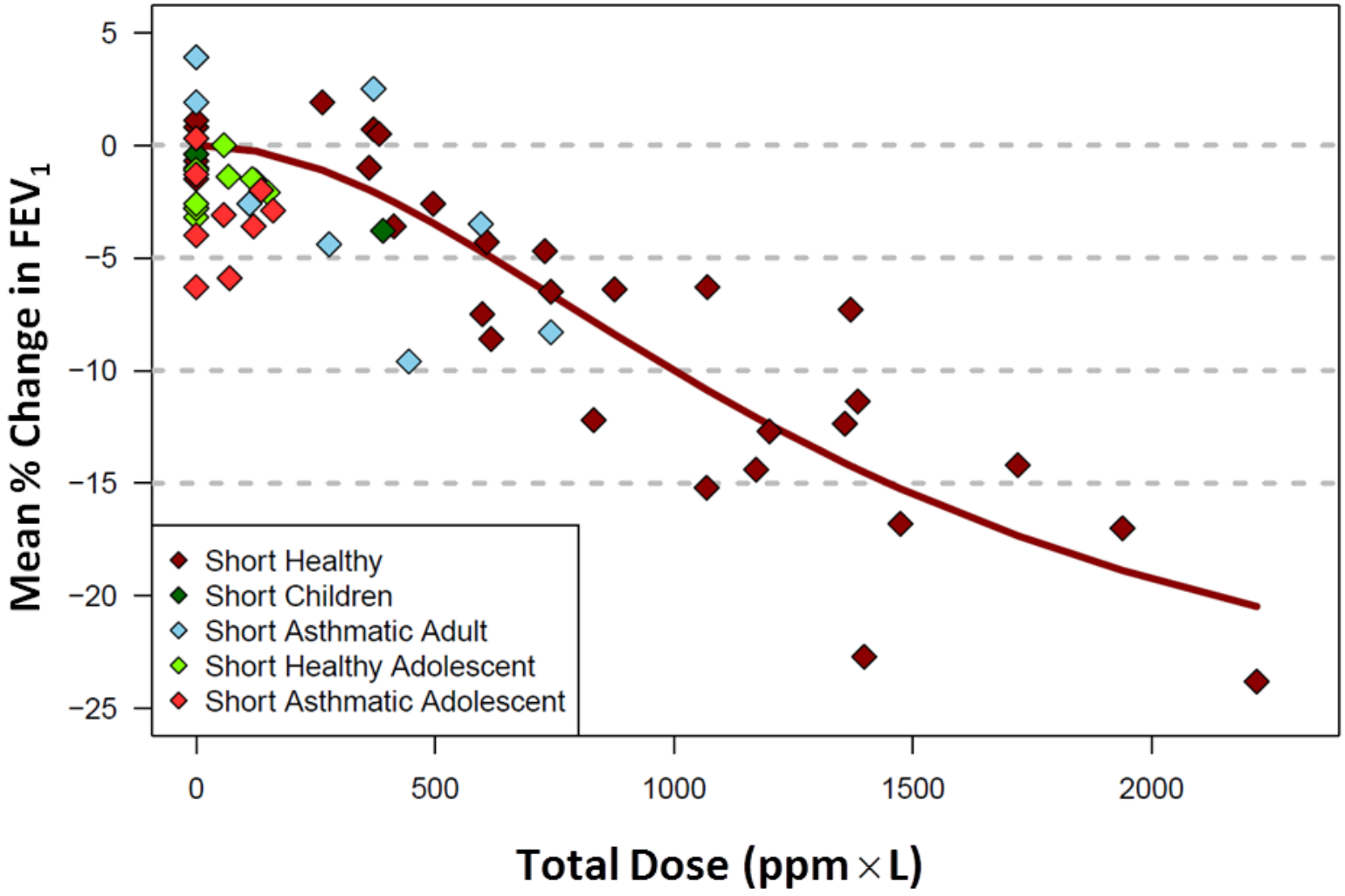
Dose-Response of Exposure Regimens



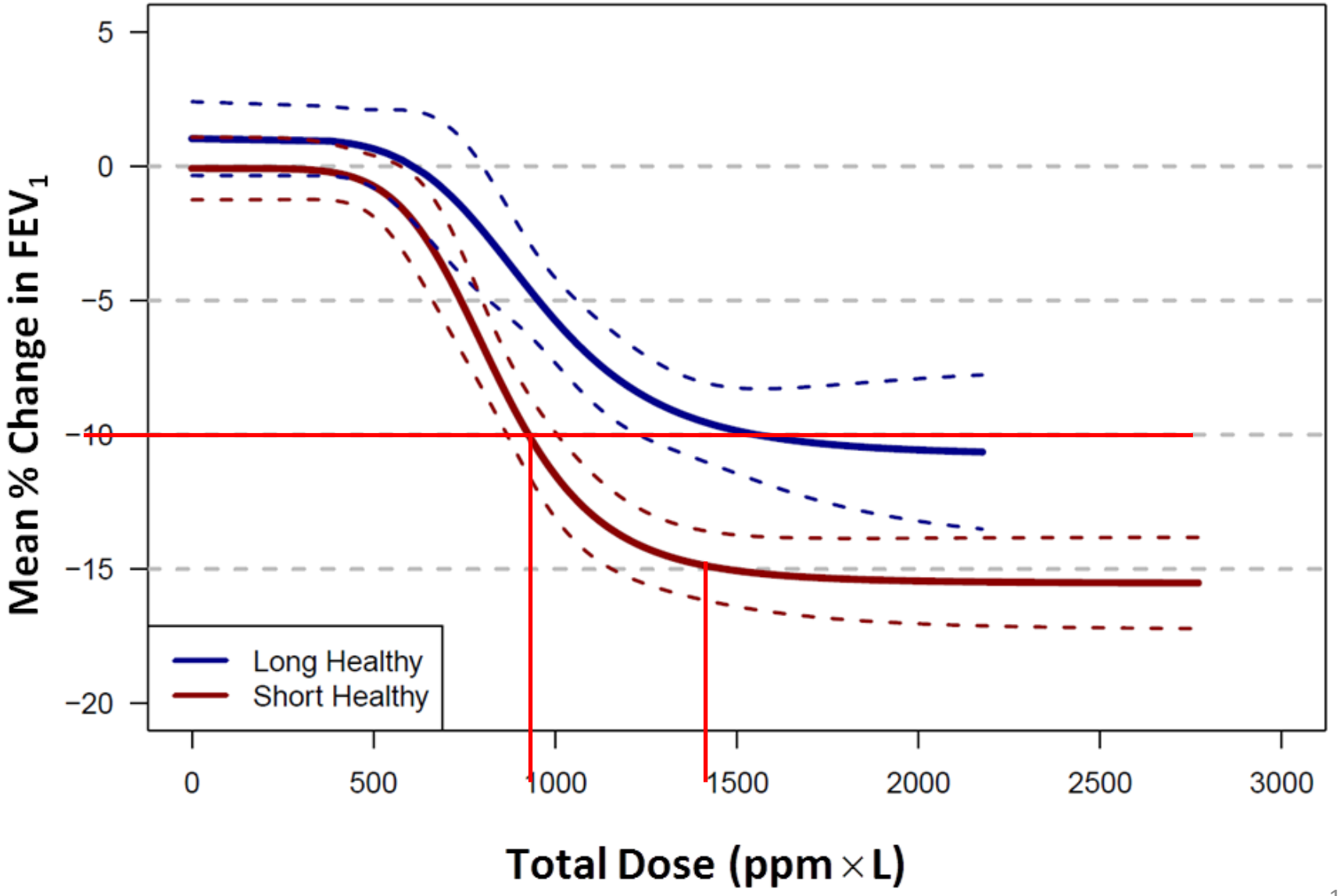
D-R Curves with Sensitive Populations



D-R Curves with Sensitive Populations



Ozone Dose Thresholds



O_3 FEV_1 Dose Thresholds

Individual Data Dose-Response Curves

Mean % Change in FEV_1	Short exposure dose (ppm•L)	Long exposure dose (ppm•L)
0	N/A	608.5
-5	740.2	953.5
-10	926.7	1553.8
-15	1467.4	N/A

Exercise Ventilation Rates

Source	Population	Exercise	Ventilation (L/min)
EPA O_3 ISA 2013	Children (6-11)	Sedentary	4.8
		Light Intensity	11
		Moderate Intensity	22
		High Intensity	42
	Young adult (21-31)	Sedentary	5.3
		Light Intensity	12
		Moderate Intensity	26
		High Intensity	50
Zuurbier 2003	Adult	Commuting by bicycle	23.5
Samet 1993	Child	Outdoor play	16
	Child	Bicycling	27
	Adult male	Vigorously bicycling	65
TCEQ/EPA 1994 Guidance	**Adult worker**	**Occupational (8 hour day)**	**22**
	General Pop	**Non-Occupational (24 hour day)**	**14**

O_3 Concentration Matrix

Concentration of ozone 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	Sedentary Child	5	3219	1609	1073	805	899	899	770	674	449	225
EPA	Sedentary Adult	5	2915	1458	972	729	814	814	698	610	407	203
EPA	Light Int Child	11	1405	702	468	351	392	392	336	294	196	98
EPA	Light Int Adult	12	1288	644	429	322	359	359	308	270	180	90
TCEQ	General Pop (24 hr)	14	1104	552	368	276	308	308	264	231	154	77
Samet	Child Outdoor Play	16	966	483	322	241	270	270	231	202	135	67
EPA	Med Int Child	22	702	351	234	176	196	196	168	147	98	49
TCEQ	Adult Worker (8 hr)	22	702	351	234	176	196	196	168	147	98	49
Zuurbier	Adult Bicycle Commute	24	657	329	219	164	184	184	157	138	92	46
EPA	Med Int Adult	26	594	297	198	149	166	166	142	124	83	41
Samet	Child Bicycling	27	572	286	191	143	160	160	137	120	80	40
EPA	High Int Child	42	368	184	123	92	103	103	88	77	51	26
EPA	High Int Adult	50	309	155	103	77	86	86	74	65	43	22
Samet	Adult Male Bicycling	65	238	119	79	59	66	66	57	50	33	17

Note: for times ≤ 4 hours, the short dose-response curve was used and for times > 4 hours, the long dose-response curve was used

Experimental Ventilations and Times

Reference	Population & Exercise	V_E (L/min)	Time (min)	$[O_3]$ in ppb for -10% FEV_1
Samet 1993	Healthy man, outdoor activities	36.7	114.6	220
	Healthy woman, outdoor activities	18.8	57.9	852
	Healthy boy, outdoor activities	20.1	176	262
	Healthy girl, outdoor activities	17.6	131	402
	Asthmatic female, outdoor activities	35.1	36.1	732
	Man with COPD, outdoor activities	21.5	133.5	323
	Man with IHD, outdoor activities	23.7	174.3	224
Zuurbier 2009	Adult, commuting by bicycle	23.5	120	329
US EPA 1994	General population daily ventilation	14	1440	77
	Healthy worker, manual labor	22	480	147

The highest ozone monitor in Texas in 2014:

- Highest 1 hour max – 135 ppb
- Highest 8 hour max – 95 ppb
- Highest 24 hour average – 44 ppb

(This data can be accessed at: http://www.tceq.state.tx.us/cgi-bin/compliance/monops/ozone_summary.pl)

Tool for Decision Makers

- These matrices are now a tool that can be used by decision makers to set a level of ozone, after making two decisions:
  - Who are we protecting?
  - What are we protecting them from?

Conclusions

- Many people have been exposed to ozone for clinical experiments, some at ozone concentrations relevant to the current ozone NAAQS
- Determining a level of adverse effects is important for deciding what doses are protective, and what doses aren't protective
- Human clinical FEV_1 responses can and have been used to make dose-response models
- We made a dose-response model that fits both individual and group mean data, as well as data from subpopulations
- Thresholds from this model can be used, with experimental ventilation and exposure times, to determine the concentrations of ozone at which certain FEV_1 decrements would occur

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