Modeling of the Kinetics of Carbon Monoxide for Long Term Care Facilities and Hospitals

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Objectives

Assess levels of COHb in vulnerable groups for exposure scenarios equivalent to indoor air CO concentrations and durations recommended by Health Canada and WHO, as well as those proposed by CSA:

- ○ Chronic obstructive pulmonary disease (COPD),
- ○ Cardiovascular disease,
- ○ Anemia
- ○ Elderly patients.

Methodology

The toxicokinetic model of carboxyhemoglobin (COHb) previously developed and validated in healthy subjects in Gosselin et al. (2009) was used in a 4-step approach:

1. Perform a literature review to determine values of the physiological parameters and adapt the model to each vulnerable group,

2. Validate the adapted model and the parametric values by comparing stimulated COHb levels and observed COHb values reported in the literature for specific health statuses and exposure scenarios;

3. Predict, with the adapted model and physiological parameter values, COHb time-profiles for the vulnerable groups under various exposure scenarios of CO in indoor air (i.e. those corresponding to Health Canada and World Health Organization (WHO) guidelines and CSA standards);

4. Determine ranges of CO exposure concentrations for different durations (i.e., 15 min, 1 hour, 8 hour and 24 hours) related to onset of health outcomes reported in vulnerable populations

Background – COHb Model

Physiological parameters that were changed during the simulations based on health status

Exposure Scenario:
CO Levels + Duration

$Q_{ALV} \cdot C_{ext}(t)$

$Q_{ALV} \cdot C_{ALV}(t)$

$A_{CO}(t)$

Burden of CO in alveoli

$D_{LCO} \cdot P_{ALV}(t)$

$D_{LCO} \cdot P_{BL}(t)$

$B_{CO\_free}(t)$

Burden of free CO in blood

$B_{CO\_Hb}(t)$

Burden of CO bound to hemoglobin

$k_{CO} \cdot B_{CO\_Hb}(t)$

$k_{fHb} \cdot B_{CO\_free}(t)$

$k_{Hbf} \cdot B_{CO\_Hb}(t)$

$k_{HbS} \cdot B_{CO\_Hb}(t)$

$k_{CO2} \cdot S_{CO}(t)$

$S_{CO}(t)$

Burden of CO bound to heme proteins in extravascular space

$k_{SHb} \cdot S_{CO\_Hb}(t)$

Endogenous COHb
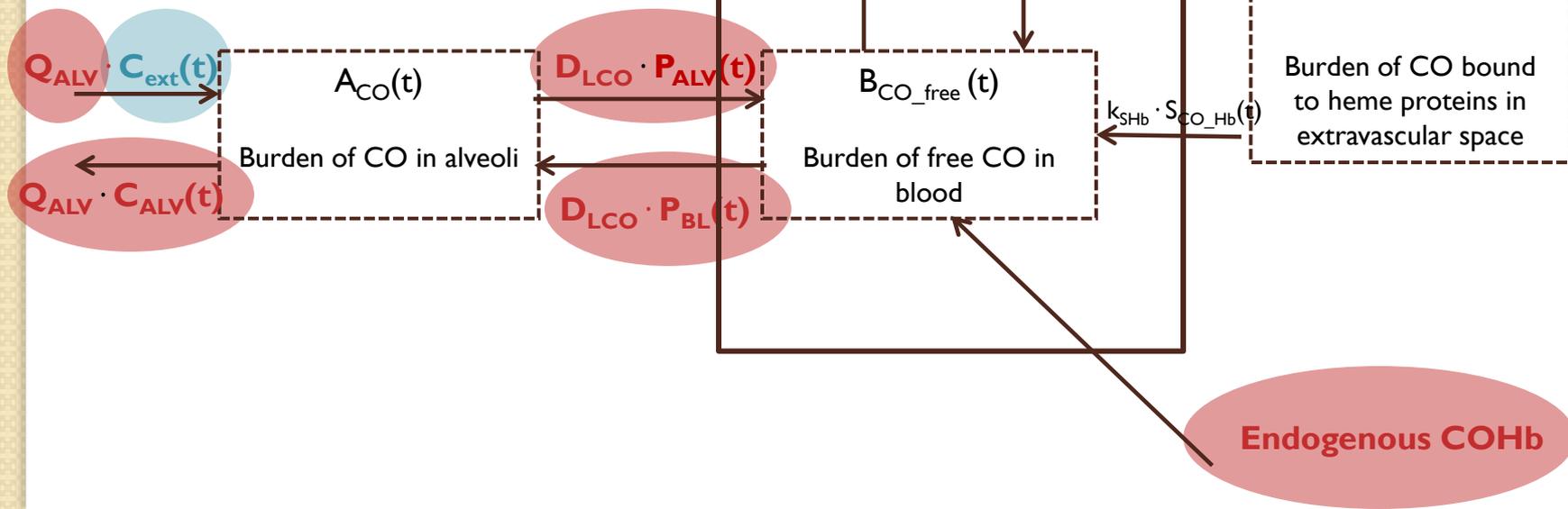
Background –

Background – Variability in Physiological Parameters in Healthy Subjects

Parameters with variability are listed:

- Body weight
- Height
- Age(three age groups with variability were derived: 30, ~60 and ~80 years old)
- Hemoglobin concentration (Hb)
- Alveolar volume (V_{ALV})
- Respiratory frequency (f_R)
- Diffusing capacity of lungs for carbon monoxide (D_{LCO})

Since the distribution of these physiological parameters is expected to be lognormal, the variability was modeled as follows:

$PARA_i$= PARApop·exp(ETAi)

where PARAi is parametric value of subject i, and ETAi is a random number normally distributed with mean 0 and estimated variance ω^2. Measures of statistical dispersion such as variance and standard deviations provided in the literature were used to characterize the variability of these physiological parameters. However, a unique value was used to describe baseline COHb levels.

Central values of the physiological parameters were related to sitting workload to represent the typical workload in LTC facilities and hospitals, with the exception of the 24-hr exposure simulations for which 10, 7.5 and 6.5 hours corresponded to sleeping, sitting and light exercise workloads

STEP 1 – Physiological Parameters in Vulnerable Populations

Based on the literature review, there is no significant difference between healthy subjects and patients with cardiovascular disease.
AGE included in the different physiological parameters allowed the simulations for elderly subjects

Target Population	Physiological Parameters		Reference
COPD patients	Dead Space (V_D)	$1.6 \times V_{D\_health}$	Diaz et al. (2001) Barrocas et al. (1971)
	Respiratory frequency (f_{R_health})	$1.15 \times f_{R\_health}$	Gorman et al. (2002) Loveridge et al. (1984)
	Diffusing capacity of lungs for CO (D_{Lco})	$0.5 \times D_{Lco\_health}$	Ries et al. (1991) Barrocas et al. (1971
	Partial pressure of oxygen in lung capillaries (P_{O2})	$P_{O2\_health}/1.4$	Ries et al. (1991) Diaz et al. (2001) Mahut et al. (2012) Naeije (1992)
Anemic patients	Endogenous COHb	$1.71 - 7.57 \times 10-3$ mL/min/kg	Coburn (2012) Coburn et al., 1963
	Hemoglobin concentration (Hb)	Moderate anemia- Hb= 9 g/dL	WHO (2011)

STEP 2 – Validation with Experimental Studies with COHb Levels in Vulnerable Populations

Published experimental studies if the following information was available:
1) measurements of COHb levels (individual or study population-level values),
2) measurements of corresponding CO air concentrations
3) duration of CO exposure.

COHb simulated with the model (100 replicates) were compared with the published levels

Health Status	Studies	Exposure Scenarios
Anemic patients	Aronow et al. (1984)	50 ppm during 60 min
COPD patients	Aronow et al. (1977)	100 ppm during 60 min
	Bathoorn et al. (2007)	100 ppm during 120 min 125 ppm during 120 min
Cardiovascular patients	Allred et al. (1989)	117 ± 4.4ppm during 50-70 min 253 ± 6.1ppm during 50-70 min
	Aronow et al. (1981)	50 ppm during 60 min
	Aronow and Isabell (1973)	50 ppm during 120 min
	Aronow et al. (1972)	53 ±6 ppm during 90 min
	Chaitman et al. (1992) Dahms et al. (1983)	159 ± 25 ppm during 60 min followed by 19.3 ± 0.8 ppm during 90 min 292 ± 31 ppm during 60 min followed by 31.0 ± 1.2 ppm during 90 min
	Sheps et al. (1991)	100 ppm during 60 min 200 ppm during 60 min
	Hinderliter et al. (1989)	100 ppm during >60 min 200 ppm during >60 min

STEP 3 – Simulations of Time-COHb Profiles in Vulnerable Populations

The toxicokinetic model and validated physiological parameters were used to simulate the time-COHb levels for different age groups (i.e., ~30, ~60 and ~80 years old) and sex based on WHO and Health Canada indoor air guidelines and Canadian Standards Association 6.19.01 (CSA) (100 replicates) – Maximum and average concentrations were computed

CO concentrations (ppm)	Exposure Duration
WHO Guidelines based on 2% COHb	
87	15 minutes
31	1 hour
9	8 hours
6	24 hours
Health Canada Guidelines based on 2% COHb	
25	60 minutes
10	24 hours
CSA Standards based on 10% COHb	
70 ± 5	1 – 4 hours
150 ± 5	10 – 50 minutes
400 ± 10	4 – 15 minutes

STEP 4– Maximum COHb Levels for Vulnerabl Population

The model was used to derive CO air concentrations needed to obtain COHb associated with observed onset of health outcomes.
CO air concentrations were determined considering exposure durations of 15 minutes, 1 hour, 8 hours and 24 hours.

Health Status	Lowest COHb for measured response (%)	Health Outcome	Response
Respiratory disease	4.08	Exercise performance	Decrease in mean exercise time until dyspnea in patients with COPD [from 218.5 to 146.6 seconds (p<0.001)
Anemic subjects	3.38 ± 0.83	Exercise performance	Reduction in exercise duration [18% reduction]
Elderly	5.0	Neurophysical function	No observable response [No effects on reaction time and late positive component of visual evoked potential]

Results / Conclusion

# STEP 2- Validation (Example in Subjects with Cardiovascular Disease)

Predicted time profiles of COHb in subjects with stable angina exposed to 50 ppm of CO for 60 minutes and comparison with observed COHb level reported by Aronow et al. (1981)
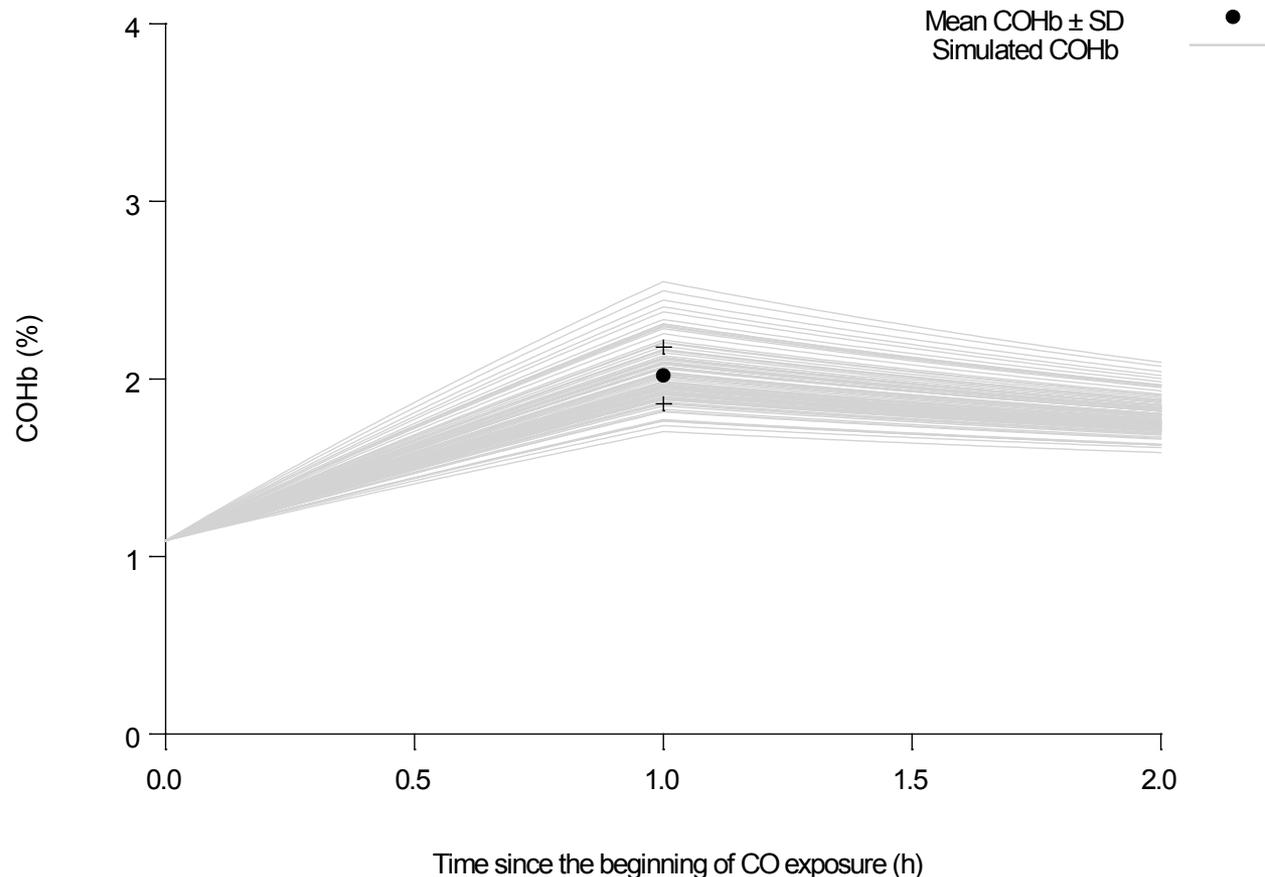
STEP 2- Validation (Example in COPD Subjects)

Predicted time profiles of COHb in subjects with coronary artery disease exposed to 100 ppm and 200 ppm of CO for 60 minutes and comparison with observed COHb level reported by Hinderliter et al. (1989)
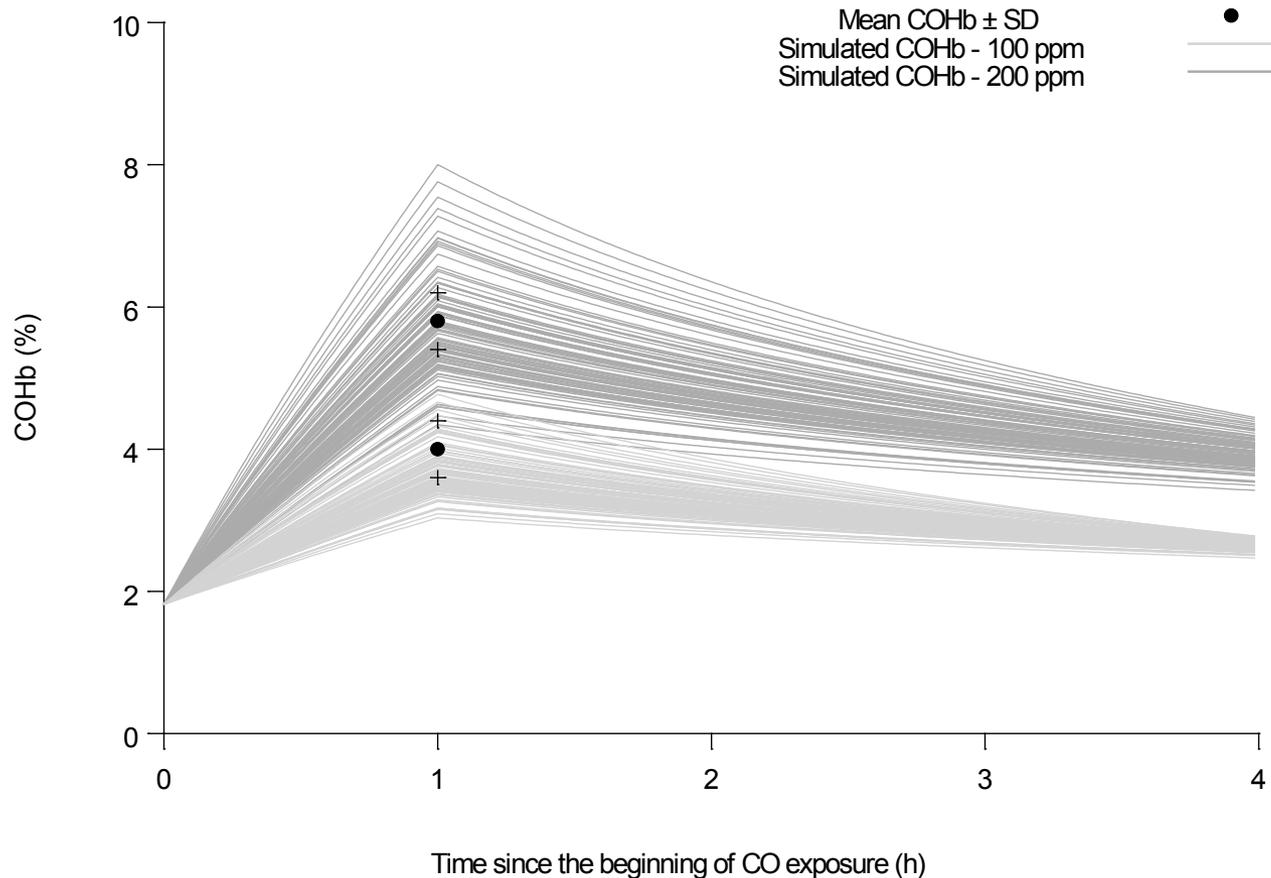
STEP 2- Validation - All

Mean COHb levels predicted by the model are in good agreement with those reported in the literature
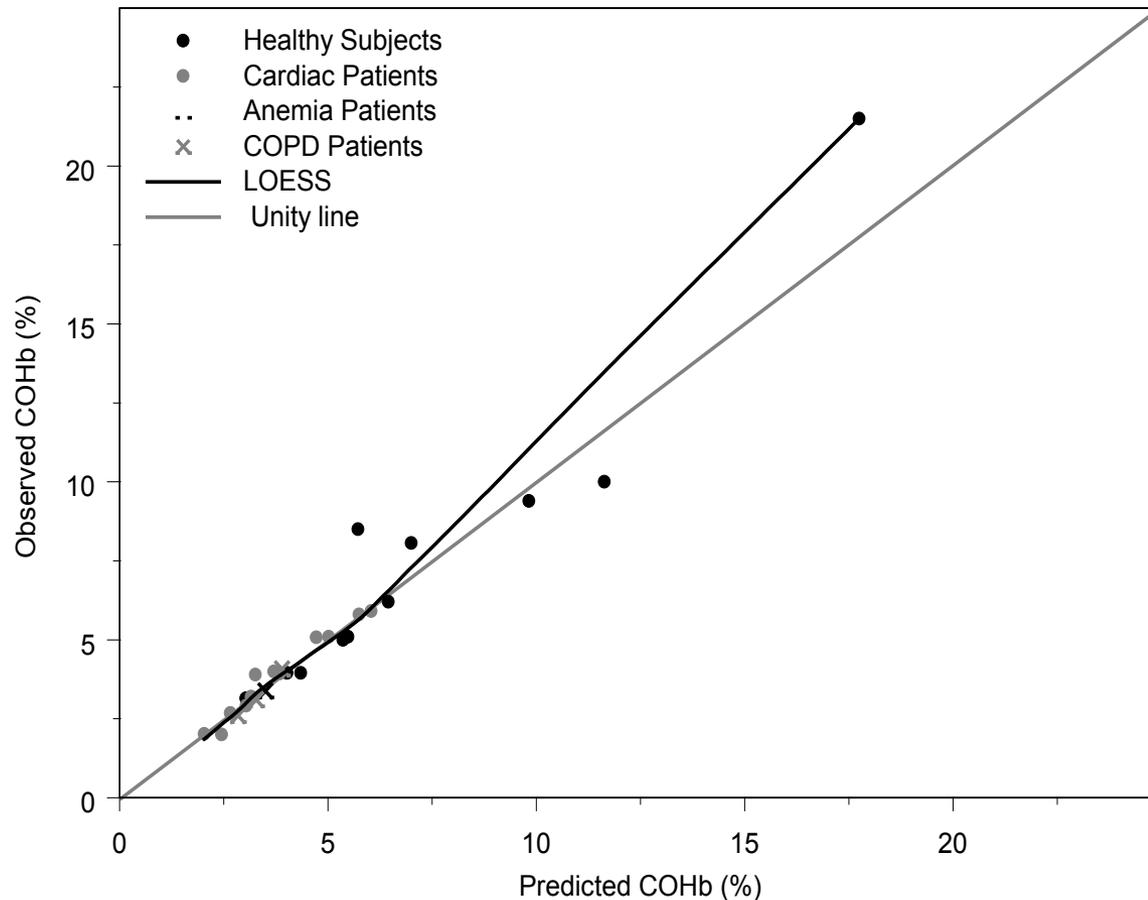
LOESS: locally weighted scatterplot smoothing

STEP 3- Simulations for Vulnerable Population - Example of Time-Profiles

Predicted time profiles of COHb in COPD women (30 years old)
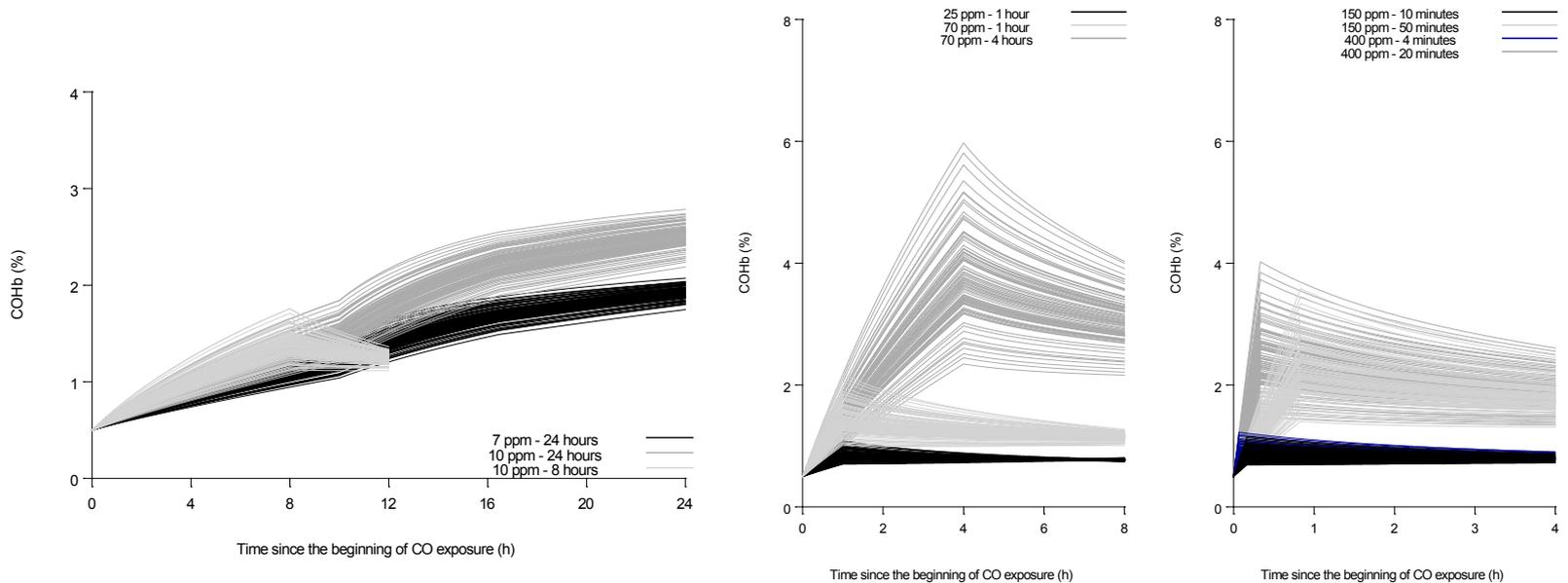
STEP 3- Maximum COHb Levels – Patients with Cardiovascular Disease /Healthy Subjects

10 ppm during 24 hours (Health Canada recommendations)

Slightly higher levels in elderly subjects (0.25% of difference)
No difference between men and women
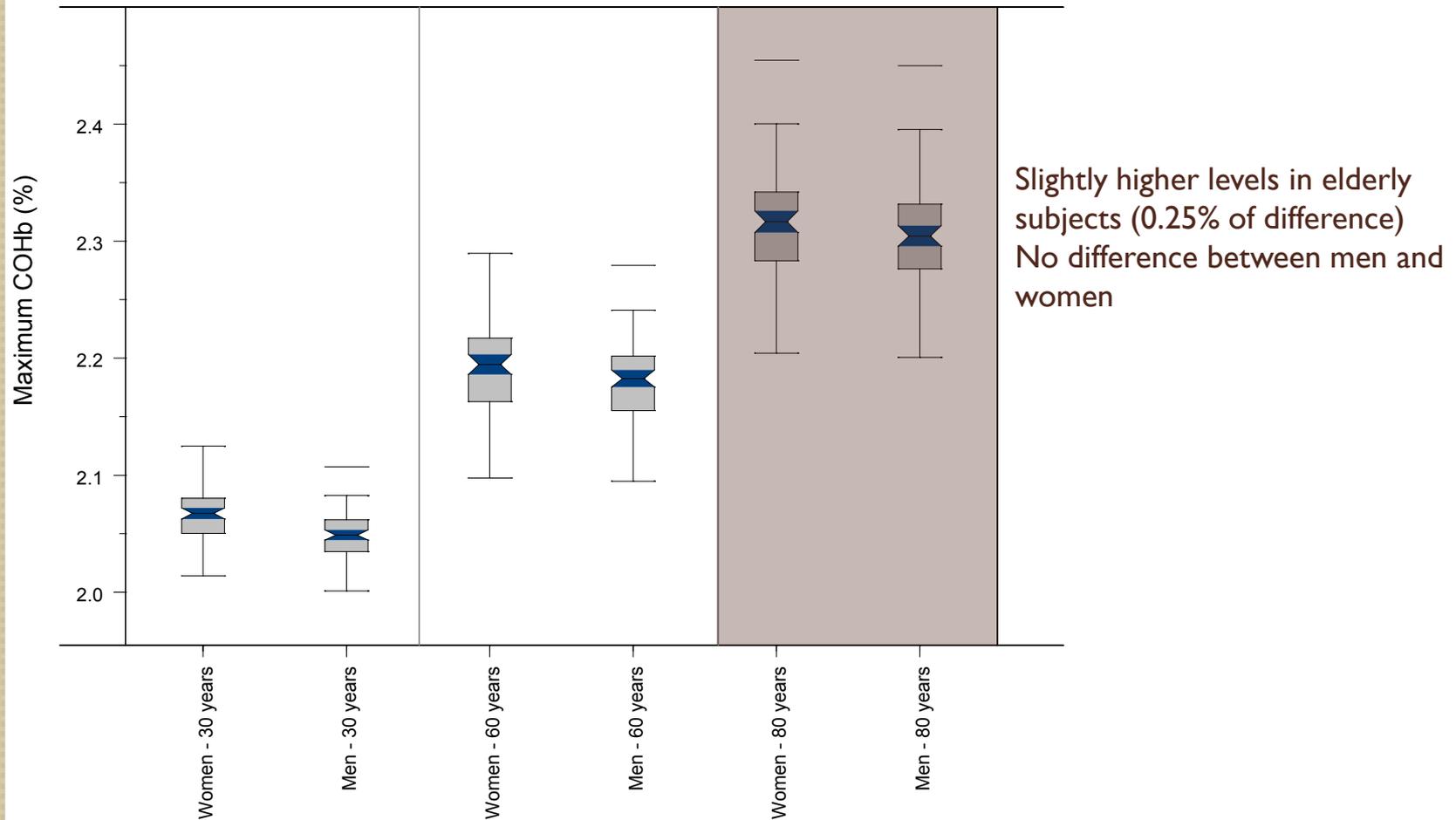
STEP 3- Maximum COHb Levels - COPD

10 ppm - 24 hours (Health Canada recommendations)
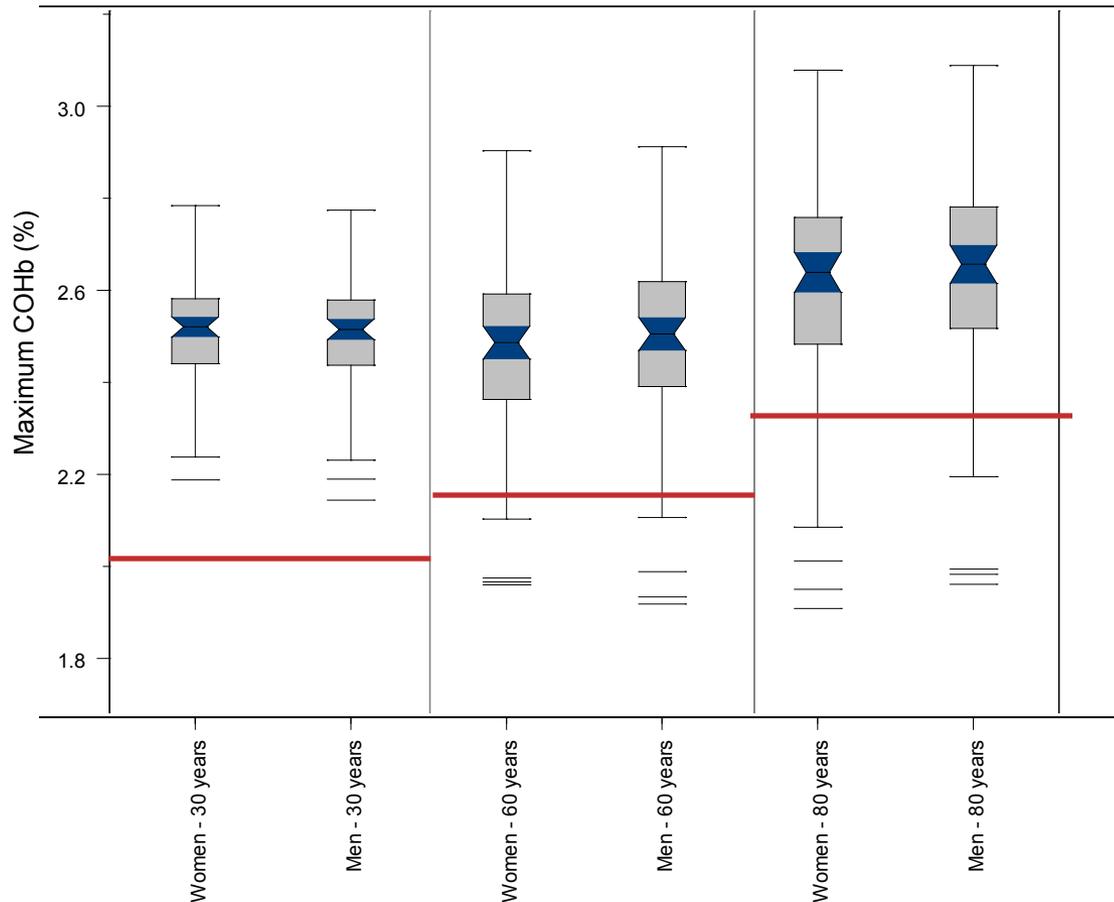
Maximum COHb (%)

Women - 30 years | Men - 30 years | Women - 60 years | Men - 60 years | Women - 80 years | Men - 80 years

Red lines represent values derived in healthy subjects

STEP 3- Maximum COHb Levels – Anemic Patients (Low Endo)
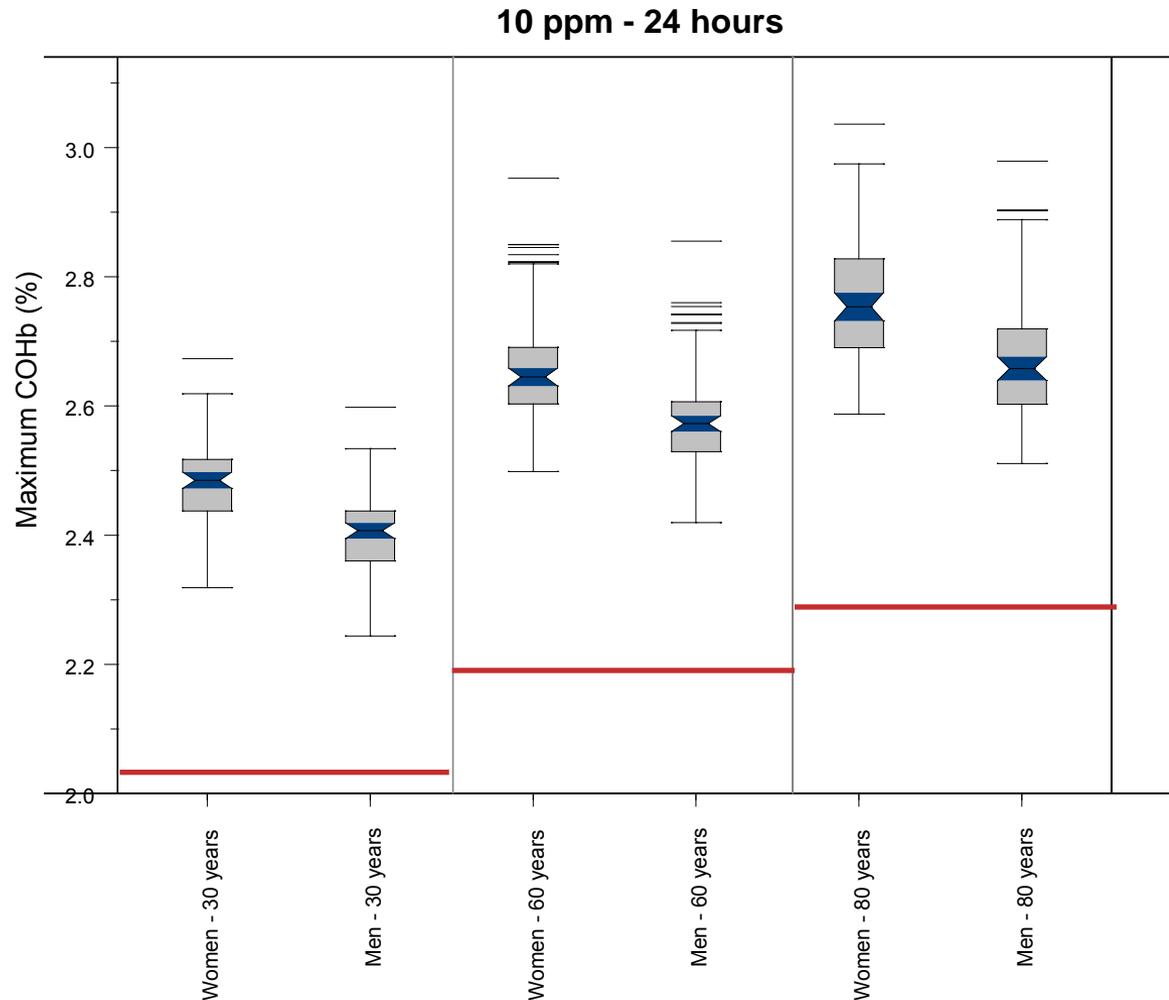
10 ppm - 24 hours

Red lines represent values derived in healthy subjects

STEP 3- Maximum COHb Levels – Anemic Patients (High Endo)

10 ppm - 24 hours (Health Canada recommendations)
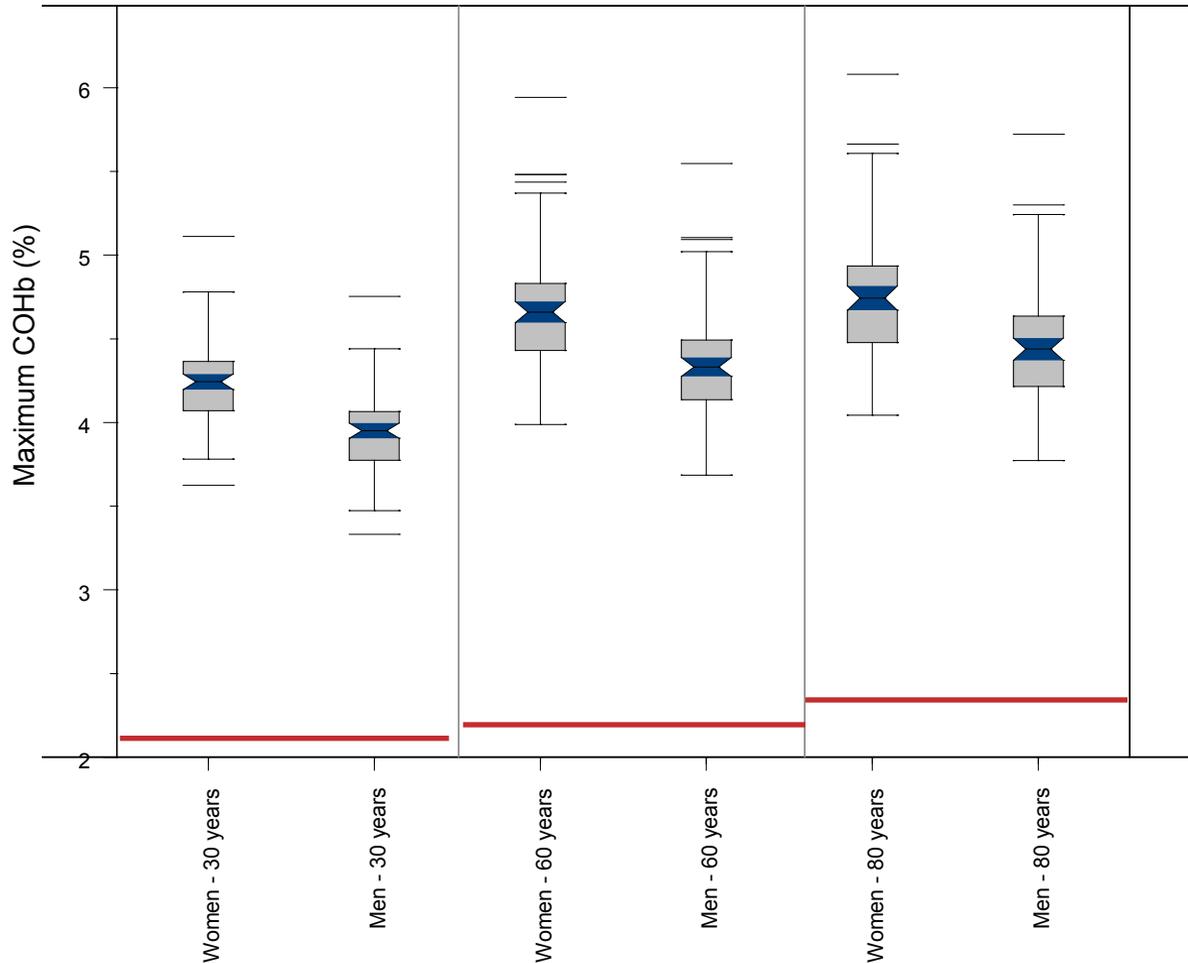
Red lines represent values derived in healthy subjects

STEP 3- Maximum COHb Levels – Comparison between Groups (all ages)

10 ppm - 24 hours
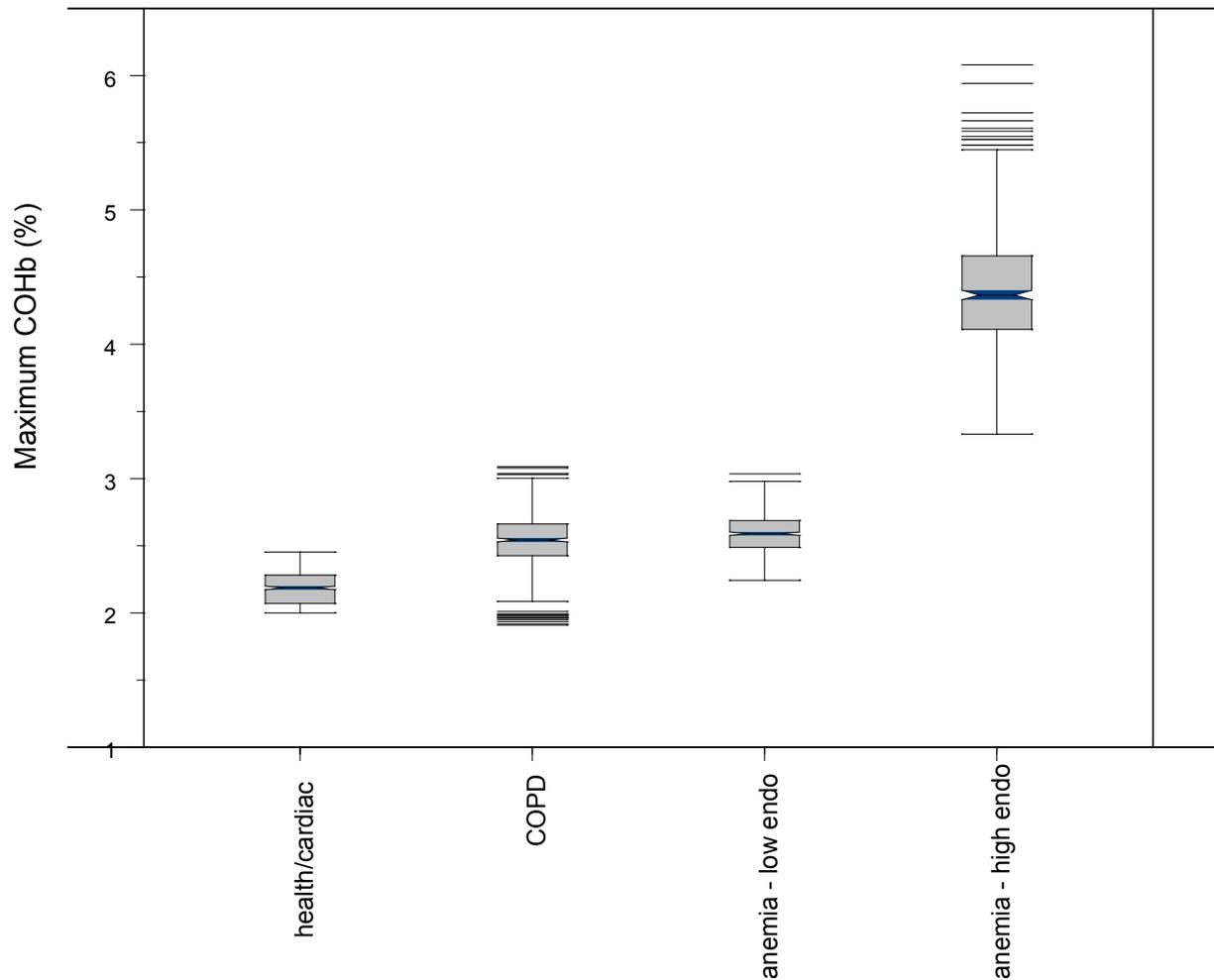
STEP 3- Simulations based on WHO and Healt Canada Recommendations-
Peak COHb

Population	Peak COHb Levels Mean (CV%)					
	6 ppm CO – 24 hr	10 ppm CO – 24 hr	9 ppm CO – 8 hr	25 ppm CO – 1 hr	31 ppm CO – 1 hr	87 ppm CO – 15 min
Healthy/cardiac subjects	1.63 (5.3%)	2.18 (5.0%)	1.46 (7.8%)	0.97 (10.1%)	1.16 (12.2%)	1.02 (11.8%)
COPD subjects	1.97 (5.8%)	2.54 (7.6%)	1.40 (11.8%)	0.86 (8.2%)	1.01 (17.1%)	0.89 (15.3%)
Anemic subjects low CO endogenous	2.22 (4.5%)	2.59 (5.6%)	2.49 (4.4%)	2.64 (3.5%)	2.92 (5.4%)	2.88 (5.9%)
Anemic subjects high CO endogenous	3.96 (10.1%)	4.41 (9.7%)	3.94 (7.2%)	3.11 (6.5%)	3.31 (4.5%)	3.13 (5.3%)

Recommendations based on 2% COHb

STEP 3- Simulations based on WHO and Health Canada Recommendations –Average COHb

Population	Average COHb Levels Mean (CV%)					
	6 ppm CO – 24 hr	10 ppm CO – 24 hr	9 ppm CO – 8 hr	25 ppm CO – 1 hr	31 ppm CO – 1 hr	87 ppm CO – 15 min
Healthy/cardiac subjects	1.14 (4.4%)	1.61 (5.3%)	0.98 (6.7%)	0.74 (7%)	0.76 (12.2%)	0.73 (7.3%)
COPD subjects	1.25 (6%)	1.67 (9.3%)	0.94 (9.6%)	0.67 (7.3%)	0.73 (11%)	0.67 (9.7%)
Anemic subjects low CO endogenous	1.88 (6.8%)	2.43 (4.9%)	2.20 (9.7%)	2.40 (2.1%)	2.48 (2.8%)	2.46 (3.1%)
Anemic subjects high CO endogenous	3.14 (10%)	3.67 (7.9%)	3.13 (4.5%)	2.56 (2%)	2.65 (2.6%)	2.5 (3%)

Recommendations based on 2% COHb

STEP 3- Simulations based on CSA Standards Peak COHb

Population	Maximum COHb Levels Mean (CV%)					
	70 ppm CO		150 ppm CO		400 ppm CO	
	1 hour	4 hours	10 minutes	1 hour	4 hours	15 minutes
Healthy/cardiac subjects	1.84 (16.0%)	4.80 (16.5%)	1.02 (12%)	2.95 (18.8%)	1.07 (12.8%)	3.26 (20.4%)
COPD subjects	1.40 (19.7%)	3.59 (26.4%)	0.85 (11.8%)	2.12 (25.0%)	0.88 (13%)	2.30 (26.6%)
Anemic subjects low CO endogenous	3.92 (9.8%)	7.40 (12%)	2.90 (6.4%)	5.60 (14.2%)	3.03 (8%)	6.24 (16.1%)
Anemic subjects high CO endogenous	4.09 (14.5%)	8.31 (11%)	3.06 (4.6%)	5.87 (13.4%)	3.14 (5.8%)	6.10 (21.4%)

Recommendations based on 10% COHb

STEP 3- Simulations based on CSA Standards - Average COHb

Population	Average COHb Levels Mean (CV%)					
	70 ppm CO		150 ppm CO		400 ppm CO	
	1 hour	4 hours	10 minutes	1 hour	4 hours	15 minutes
Healthy/cardiac subjects	1.19 (13%)	2.86 (16.5%)	0.76 (8.1%)	1.76 (16.4%)	0.78 (8.7%)	1.9 (17.8%)
COPD subjects	0.96 (15.4%)	2.14 (24.1%)	0.67 (8.4%)	1.32 (20.5%)	0.68 (9.2%)	1.41 (22%)
Anemic subjects low CO endogenous	3.07 (6.8%)	5.13 (11.5%)	2.52 (3.7%)	3.93 (10.8%)	2.56 (4.2%)	4.22 (12.2%)
Anemic subjects high CO endogenous	2.98 (22.5%)	5.65 (11.1%)	2.59 (4.6%)	4.07 (10.3%)	2.58 (4.2%)	4.01 (22.6%)

Recommendations based on 10% COHb

STEP 4- CO Levels in Ambient Air Potentially Related to Health Outcomes

CO exposure concentrations for different durations related to onset of health outcomes reported in vulnerable populations

Health Status	Outcome	COHb for measured response (%)	CO Concentration Range in air (ppm), depending on Age Group			
			15 min	1 hour	8 hours	24 hours
COPD subjects	Exercise performance	4.08	870 - 1275	228 – 340	30 – 53	17 – 18
Anemic subjects	Exercise performance	3.38 ± 0.83	143 – 186	46 – 59	16.5 – 18	13 - 16
Elderly	Neurophysical function	5.0	752 – 900	204 -243	41-46	24

Conclusion

- For anaemic subjects, due to their high endogenous levels, simulated COHb were about 2-fold higher than those predicted for other groups
  - with the exception of anemic subjects with lower endogenous CO production where COHb levels were about 1.25 fold higher, considering a 24-hour exposure scenario.
- COHb of healthy elderly subjects present
- Predicted COHb levels were higher than 2% COHb for CO exposure scenarios based on Health Canada and WHO recommendations:
  - Anemic subjects: all scenarios
  - COPD and with cardiovascular disease: 24 hours at 10 ppm
- Predicted COHb levels derived with the CSA exposure scenarios (i.e., 2.30 – 8.31%) were all lower than the target COHb of 10% used by CSA.
- CO levels in ambient air that would result in COHb levels with potential health outcomes are:
  - 13 – 24 ppm for 24 hours of CO exposure
  - 30 – 53 ppm for 8 hours of CO exposure
  - 46-340 for 1 hour of CO exposure
  - 143-1275 for 15 minutes of CO exposure