BLOOD CARBOXYHÆMOGLOBIN LEVELS AS A BIOMARKER FOR URBAN AIR POLLUTION EXPSOURE

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1. INTRODUCTION

Epidemiological studies have shown that exposure to vehicle air pollution causes a significant threat to human health, especially for vulnerable groups in the population such as young children (Bearer *et al.*, 1995, Gauderman, 2006, Brugge *et al.*, 2007), those undergoing heavy work because of their elevated breathing rate and those suffering from anemia because of their low hemoglobin levels (Hauck and Neuberger, 1984). However, the relationship between air pollution levels (as determined by fixed air pollution monitoring stations) and individual exposure remains poorly understood (di Marco *et al.*, 2005). In addition to the significant limitations associated with determining the actual exposure resulting from people's movement throughout the day (from home to work or school, etc), there is also limited understanding of the variability in the uptake of pollutants between individuals due to differences in physiology and metabolism. For example, how and to what extent would the uptake of pollutants be different between a group of university students compared to a group of elderly people exposed to the same air pollution levels? And how much inter-person variability can one expect in uptake *within* specific groups of the population?

In this study, we exploit the fact that the uptake of carbon monoxide (a pollutant for which traffic is the dominant source), in the form of blood carboxyhæmoglobin, is reliably described by the established and verified Coburn-Forster-Kane model (Coburn *et al.*, 1965). Much work has been done to validate the model in terms of the impact of the various model physiological parameters (such as blood volume, endogenous production of CO, etc) on uptake in the form of sensitivity analyses of the model (Petersen and Stewart, 1970). Despite its age, the CFK model is still regarded as the best all-round model for predicting COHb levels for low-level exposures (WHO, 1999).

One of the limitations of the model is that the model physiological variables needed as input to the model (such as the blood volume, endogenous production of CO (produced within the body in the absence of environmental exposure), and the pulmonary diffusing capacity (capacity of the lungs for gas transfer)) are difficult and expensive to measure for large groups and on a routine basis.

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However, studies have been carried out to relating these model physiological variables and easily-measured physiological variables (such as weight, height, age and gender) thus avoiding the need for extensive lab-based physiological measurements. For example, it has been established that there is a clear relationship between a person's weight (and to a lesser extent their age) and their blood volume (Gibson and Evans, 1937). This suggests that if we know the age, gender, weight and height of an individual (or the distribution of these variables within a population) we can estimate their model physiological variables and subsequently make estimates of their expected uptake of CO using the CFK or other suitable model.

The first aim of this study is to look at existing results from the literature on the relationship between the CFK model physiological parameters and the so-called 'easily-measurable physiological parameters' to determine the reliability in applying the CFK model to epidemiological studies of air pollution within specific populations. The second aim is to evaluate the modelling using a field trial involving human subjects. The results of this study may ultimately help in understanding the health impacts of air pollution exposure of target groups within the population.

2. BACKGROUND

2.1 The CFK Model of Uptake of CO

The Coburn, Forster and Kane (1965) model is a non-linear differential equation used to describe the physiological variables that determine blood COHb levels. The model is given by

$$\frac{d[COHb]}{dt} = V_{CO} - \frac{[COHb]}{[O_2Hb]}\frac{P_C O_2}{M\,B} + \frac{P_I CO}{B} \qquad (1)$$

where

$$B = \frac{1}{D_L CO} + \frac{P_L}{V_A}\,. \qquad (2)$$

The first term on the right hand side of Equation 1 represents the endogenous production (the COHb produced in the body in the absence of any CO exposure), the second is the removal through exhalation and the third is the uptake due to environmental exposure to CO. Table 1 defines all of the terms in this equation, and gives the values for the quantities that are constant, as suggested by Peterson and Stewart (1970). Under the assumption that the oxyhæmoglobin concentration, [O_2Hb], is constant (rather than being a

function of COHb), Equation 1 is linear. This has been found to be a good approximation for relatively low COHb levels (Coburn *et al*., 1965), as is generally the case in outdoor exposure situations.

The solution to the differential equation is given by

$$\frac{\frac{[COHb]P_CO_2}{[O_2Hb]M} - V_{CO}B - P_ICO}{\frac{[COHb]_O P_CO_2}{[O_2Hb]M} - V_{CO}B - P_ICO} = \exp\left(-\frac{P_CO_2\, t}{M\, V_B [O_2Hb] B}\right) \quad (3)$$

as given in Hauck and Neuberger (1984). In order to determine COHb levels for complex CO variations, a discrete model solution is needed. This may be found by replacing the derivative in Equation 3 by its forward difference equivalent, i.e.

$$[COHb]_{n+1} = [COHb]_n\left(V_B - \frac{P_cO_2T}{[O_2Hb]M\,B}\right) + T\left(V_{CO} + \frac{P_ICO}{B}\right) \quad (4)$$

where T is the sampling interval and the subscripts *n* and *n+1* represent the n^{th} and $(n+1)^{th}$ data samples, respectively, as given in Dirks et al., 2006).

Table 1. Definitions and units for all of the terms in the Coburn, Forster and Kane model. Included are the values set for the quantities that are constant.

Symbol	Unit	Value	Name/Description
V_B	mL		Blood volume
V_{CO}	mL CO $(min)^{-1}$		Endogenous production of CO
P_cO_2	mmHg	100	Average partial pressure of O_2
M	(no units)	218	Haldane coefficient
$[O_2Hb]$	mL O_2 (mL Blood)$^{-1}$	0.2	Volume of O_2 per mL of blood
D_LCO	mL CO (min mmHg)$^{-1}$		Pulmonary CO diffusing capacity
P_L	mmHg	713	Barometric pressure –water vapour pressure
V_A	mL $(min)^{-1}$		Alveolar ventilation rate
[COHb]	mL CO (mL Blood)$^{-1}$		Volume of CO per volume of blood
P_ICO	mmHg		Partial pressure of CO in inhaled air

A test of the CKF model reveals that the response rate in the body of CO exposure at ambient levels is sufficiently slow that for CO data averaged on a 1-minute, 10-minute or hourly basis, the model predicts effectively the same COHb traces (as shown in Figure 1). In addition, a previous study (Dirks *et al.*, 2006) showed that the actual solution and the solution using the discrete model with a 10 minute sampling interval produced almost identical predictions. The uptake of COHb in the body therefore depends only on the exposure pattern of an individual and their model physiological variables, and is not affected by the averaging time used (whether 1 minute, 10 minutes or hourly.

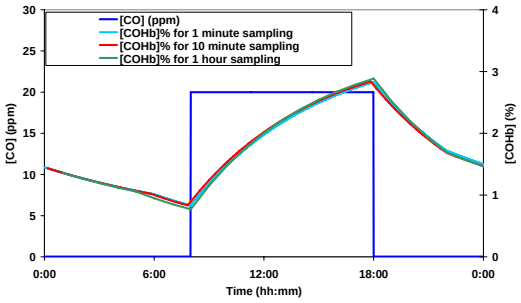

Figure 1. Effect of averaging time of CO trace on modeled COHb uptake in the body.

2.2 Relationship Between Model Physiological Variables and Easily-Measured Physiological Variables

The CFK model requires individual information on a person's blood volume, their endogenous production of CO (the production within the body in the absence of any exposure), their alveolar ventilation rate (the volume of gas per unit of time reaching alveoli), and the pulmonary diffusion capacity (the gas exchange ability of the lungs). We would like to be able to estimate these quantities for individuals based on their gender, age, weight and height. This section presents the results of a literature search into existing studies that provide the necessary information to be able to do this.

2.2.1 Relationship between Blood Volume and Easily-Measured Physiological Variables

Firstly, can the blood volume of an individual be estimated based on their age, gender, weight and height (all easily measured quantities)? Gibson and Evans (1937) conducted a study looking at the relationship between body mass, gender, height and age on blood volume for 90 healthy adults aged 16 to 89 years and found the strongest association with body mass, as shown in Figure 2. Note that the blood volume per kg of mass is higher for men than for women.

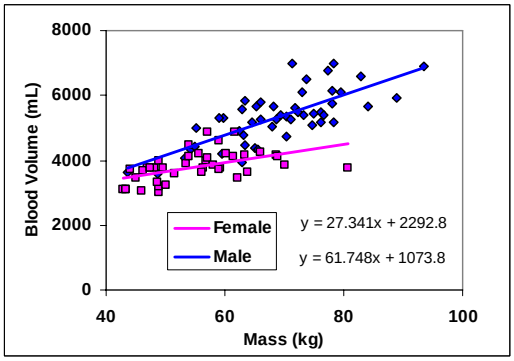

Figure 2. Blood volume as a function of body mass for males and females separately (from Gibson and Evans, 1937).

Based on these findings, blood volume (V_B) can be estimated using:

$$V_B = 61.8m + 1074 \text{ (males)} \quad (5a)$$

$$V_B = 27.3m + 2293 \text{ (females)} \quad (5b)$$

where *m* is the body mass (in kg). Significantly weaker associations were found with age with a tendency for blood volume (per kg body mass) to decrease (Gibson and Evans, 1937).

2.2.2 Physiological Variables Affecting the Pulmonary Diffusing Capacity for CO

The pulmonary diffusing capacity for CO is a measure of the integrity of the alveolar-capillary surface area of the lungs for gas transfer). Can the pulmonary diffusing capacity of an individual (required for the CFK model) be estimated for an individual based on their age, gender, weight and height? A study by Ogilvie *et al.* (1956) found that there is no significant trend with age and a trend similar for height as for body mass. Figure 3 shows the relationship between pulmonary diffusing capacity and body mass (as shown in Figure 3) based on data from Ogilvie *et al.* (1956).

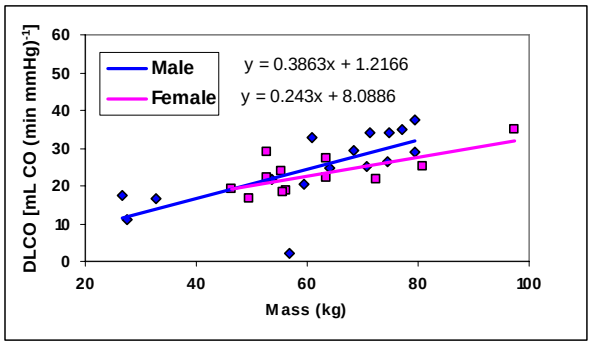

Figure 3. Pulmonary CO diffusing capacity as a function of body mass for males and females separately (from Ogilvie *et al.*, 1956).

Our best estimate of the relationship between pulmonary diffusing capacity and body is:

$$DLCO = 0.39m + 1.22 \quad \text{(males)} \quad (6a)$$

$$DLCO = 0.24m + 8.08 \quad \text{(females)} \quad (6b)$$

where *DLCO* is the pulmonary diffusing capacity in mLCO (min mmHg)$^{-1}$ and *m* is the body mass (in kg).

2.2.3 Physiological Variables Affecting the Endogenous Production of COHb

Endogenous production is the production of COHb within the body in the absence of environmental exposure. The endogenous COHb levels in humans are estimated to be about 0.1 to 1.0% and are believed to be produced primarily by the liver (WHO, 1979). Elevated endogenous levels are observed in neonates as well as in females during the progesterone phase of the menstrual cycle and to an even greater extent in pregnancy (Delivoria-Papadopoulos *et al.*, 1970). Can the endogenous production of COHb of an individual be estimated based on the age, gender, weight and height of an individual? Some early work by Coburn *et al.* (1963) showed an increase in endogenous production with age in healthy males as shown in Figure 4. In the same study, the relationship to weight was found to be non-significant. Therefore our best estimate of the endogenous production (V_{CO} in mL/h) is given by:

$$V_{CO} = 0.0028a + 0.3351 \quad \text{(males)} \quad (7)$$

where *a* is the age in years. Note that this is for males only and there are no data within the 0-20 years age range.

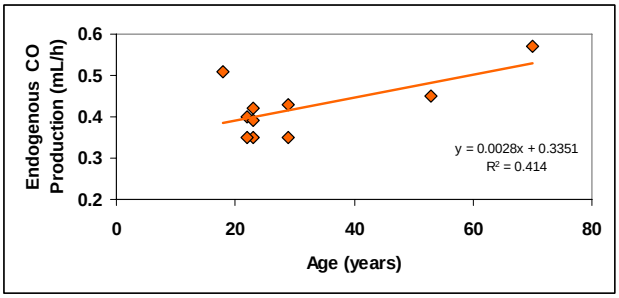

Figure 4. Endogenous production as a function of age for healthy males (from Coburn *et al.*, 1963).

2.2.4 Physiological Variables Affecting the Alveolar Ventilation Rate

The alveolar ventilation rate depends significantly on the level of physical activity of the person in question. For this study, the alveolar ventilation rate is assumed to be $V_A = 3000 mL \min^{-1}$ while asleep, $V_A = 4000 mL \min^{-1}$ while awake and sedentary and $V_A = 5000 mL \min^{-1}$ while awake and undergoing light exercise.

2.2.5 Conclusions

Based in the literature, it is possible to use easily-measured physiological variables to predict the values of the CFK model parameters required to predict the COHb levels of individuals. The uncertainty in these estimates is likely to be dominated by our ability to estimate the alveolar ventilation rate of an individual which is heavily dependent on their activity pattern throughout the course of the day.

3. METHODS

For the validation part of the study, eight subjects were recruited for each of the two weeks of the study period. This includes two subjects who participated for the full two-week period. The subjects were asked to carry out pre-determined activities including riding the bus, driving in a car, walking on the footpath along inner city roads, and sitting in a car in an indoor carpark. The activities

were designed to present the subjects with a range of exposures to carbon monoxide that can be characterised in detail and which may be considered representative of typical occupational and domestic exposure profiles. The subjects were grouped into pairs or groups of three or four depending on the activity and while they were not necessarily in exactly the same location all the time, they were carrying out the same activity in close proximity and subject to the same influences in terms of air pollution. Each group's exposure to carbon monoxide was measured using a portable monitor. The subjects were asked to log their activities throughout the day and to log any potentially high exposures at night. At the start and end of each working day, all of the subjects reported to the hospital to provide a small (<1 mL) blood sample for the purpose of measurement of their carboxyhæmoglobin level by gas analysis. Every night, one subject was asked to bring home a portable monitor to provide continuous traces for three of the subjects at any time.

4. RESULTS

The 14 subjects recruited for the study were all male and ranged in age from 18-41 years. Their body masses ranged from 57.1kg to 138kg providing us with a very wide range. Two of the subjects participated in the study for two weeks while the remaining participated for one week.

Figure 5 shows an example of CO exposure for the three portable monitors carried by three individuals carrying out essentially the same activity. On the first day, the subjects spent the day riding about an inner suburban loop on a bus. On the second day, they spend the morning driving around in a car and in the afternoon sat in a car (with open windows) in an indoor carpark.

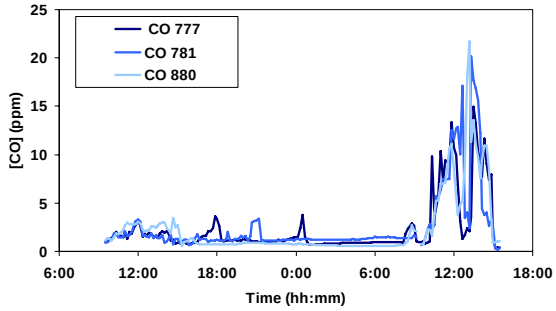

Figure 5. A day-night-day trace of carbon monoxide concentrations for the portable monitors carried by three subjects participating in the same activities (Bus on first day and in a car and in an indoor carpark on the second day).

In the case of the bus, the subjects were sitting in different seats but in the same bus, and on the second day the subjects were in cars following each other in convoy. While sitting in the carpark, the cars were parked in spaces within about 20 m of each other. Of interests is the large amount of variability between the three monitors considering they were carrying out the same activity at essentially the same location. These results highlight once again the extent of the spatial variability in air pollution concentrations over very short distances and the challenges this presents in terms of determining individual exposure.

Also worth noting is the fact that the levels experienced while commuting on the bus were very low, as were the levels while driving around in a car even though both were along an inner suburban loop. Moderately elevated levels were only observed when the subjects were exposed to levels found in the indoor carpark.

Figures 6 and 7 show the average COHb levels in the blood of the subjects, both in the morning (yellow) and in the afternoon (purple) for the two weeks of the study based on gas analysis of the blood samples that were collected. Note that the levels are always more elevated in the afternoon compared with the morning following a day of light to moderate exposure. The days showing the most significant increases in COHb levels were the days when the subjects were asked to spend time in the indoor carpark (Days 4, 8 and 9). This is consistent to what was observed in the corresponding CO traces. In fact, during most of the days when the subjects were doing activities other than being in the indoor carpark, there was found to be no significant increase in COHb levels in the afternoon compared with the morning.

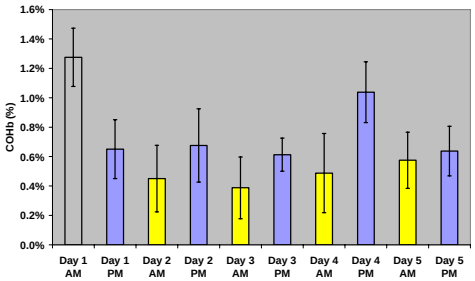

Figure 6. Average COHb(%) levels of subjects as determine by blood gas analysis for the first week of field study. The error bars represent the standard errors of the mean (SEM). (Note the suspicious value for the first collection because a different technique was used).

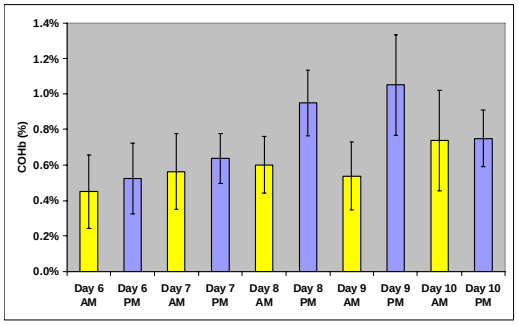

Figure 7. Average COHb (%) levels of subjects as determine by blood gas analysis for the second week of the field study. The error bars represent the standard errors of the mean.

Figure 8 shows the predicted COHb levels (based on the CFK model) for the 12 subjects taking into account their individual physiology and assuming that they had all been exposed to exactly the same CO trace as measured using one of the monitors ((CO 777) from Figure 5). This gives an indication of the extent of inter-subject variability in uptake for adult males. Not that the dotted trace (in red) represents the predictions for the subject of body mass 138 kg. This subject would be expected to experience a significantly reduced rate of uptake because of his high blood volume and would be less affected by short-duration events than people with lower blood volumes.

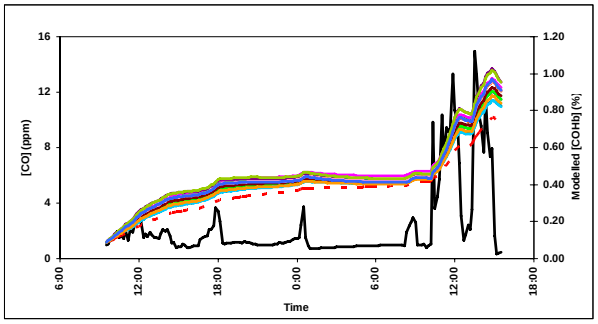

Figure 8. Intersubject variability in predicted COHb levels for subjects exposed to the same carbon monoxide trace. The differences are due to differences in physiology between the subjects (age and body mass). The dotted trace is for a subject with an unusually-large body mass 138 kg.

Figure 9 shows the CFK model predicted COHb traces for the two subjects that were exposed to the CO trace measured by CO 777 and the associated blood COHb values determined by blood gas analysis. Note that while there are significant differences between the measured and modeled values, there is reasonable consistency for the second day when the levels are predicted to be relatively high. Similar plots were produced for the other days of observation.

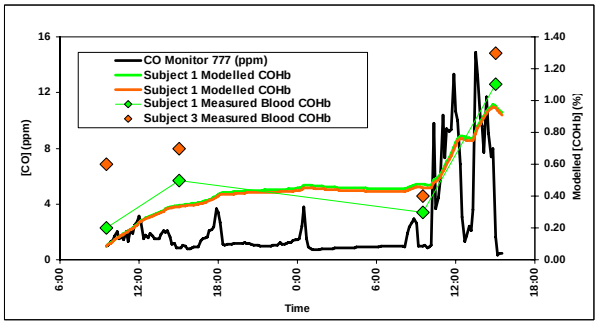

Figure 9. Note neither subject was with the monitor overnight (both were very similar in body mass, hence there similar predicted COHb levels).

Ultimately, it is hopes that this study will help in understanding the health impacts of air pollution on specific groups of the population, such as children. Unfortunately, the studies outlined above relating the model physiological variables to the easily-measured variables are based entirely on the adult population. However, given that blood volume and body mass have been found to be linearly related, in the absence of any further information one can reasonably assume that this relationship can be extrapolated down to children. Also, a large observation study by Adams (1983) indicated that the alveolar rate of children at rest is not significantly different from that of adults. If we also extrapolate the adult trends for the endogenous production and the pulmonary diffusing capacity (which both have a relatively small impact on COHb levels), then it is possible to estimate COHb traces for children. Figure 10 shows the CFK model-predicted COHb trace for a 6 year-old boy assumed to be 25 kg. This is compared with a trace based on the average of the 14 subjects (modeled), as well as the trace predicted for the 138 kg subject. This shows that children respond significantly more quickly to air pollution events than do adults, primarily because of their small body mass.

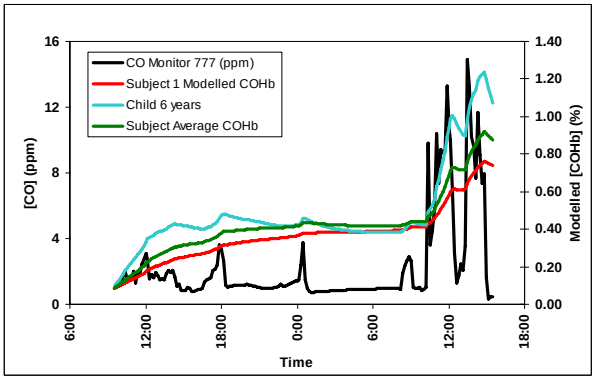

Figure 10. Model predicted and observed (by blood gas analysis) COHb levels for a day-night-day trace for three subjects: the 138 kg subject, the average of all subjects, and a hypothetical 6-year old child.

5. DISCUSSION AND CONCLUSIONS

The results of this study suggests that:

1. There is a large amount of spatial variability in CO traces experienced by people undergoing essentially the same activity at the same time and at the same place, affected by the same meteorology and sources of pollution. This highlights one of the challenges associated with determining individual air pollution exposure.

2. There is a significant amount of inter-subject variability in COHb patterns amongst people with the same exposure patterns because of differences in their physiology. Some of this can be explained by the variability in the 'easily-measured physiological variables' within the subject group. Providing the CO exposure is known, it is possible to predict the expected COHb levels for individuals and population subgroups.

However, physiological information for children is limited.

3. Body mass has a significant impact on the rate of uptake of pollutants. Children experience significantly higher rates of uptake than adults.

4. A significant limitation in our ability to predict the uptake of CO is in our ability to estimate the alveolar ventilation rate which is heavily dependent on the activity level of an individual. The activity levels of children tend to be high, exacerbating their high rate of uptake relative to the adult population.

By combining information on the inter-subject variability in physiology and COHb modelling, we move towards an understanding of the possible health impacts of air pollution exposure for the population as a whole and well as for specific subsets of the population.

Acknowledgements

The authors would like to acknowledge the support of the Health Research Council of New Zealand for providing funding for this project and to the Faculty of Medical and Health Sciences, The University of Auckland for providing support financial support for one of the researchers in the team (KF).

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