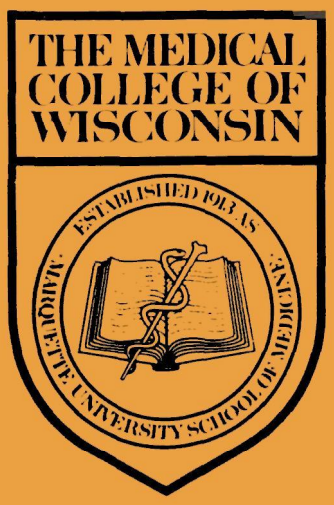

Predicting The Carboxyhemoglobin Levels Resulting From Carbon Monoxide Exposures

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PREDICTING THE CARBOXYHEMOGLOBIN LEVELS RESULTING FROM CARBON MONOXIDE EXPOSURES

By

Jack E. Peterson, Ph. D.

Richard D. Stewart, M. D.

Following is an alphabitical list of those persons who contributed information contained in this report:

Eleanor Bachand, R. N.
Edward D. Baretta, M. S.
Hugh C. Dodd, B. S.
Karen K. Donohoo, B. S.
Sally A. Graff, B. S.
Carl L. Hake, Ph. D.
Paul E. Newton, M. S.

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From the Department of Environmental Medicine, The Medical College of Wisconsin, Allen-Bradley Medical Science Laboratory, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226

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SUMMARY

Data from a series of human exposures to carbon monoxide were analyzed to determine the fit to the theoretical Coburn, Forster, Kane (CFK) equation as a function of experiment duration and CO concentration, exercise level, and sex. The equation was found to predict carboxyhemoglobin (COHb) levels for both men and women at exercise rates ranging from sedentary to 300 kp-m/min when they were exposed to steady CO concentrations of 50, 100, and 200 ppm for 0.33 to 5.25 hours. In addition, the equation accurately summed the results of a discontinuous exposure to CO.

Methods for determining values of each of the variables in the CFK equation were collected and a rational, efficient procedure for solving the equation by trial and error was outlined. The CFK equation was then used to prepare a graph relating COHb saturation to exposure duration and concentration, and also to describe the effect of several variables on the rate of CO uptake and equilibrium COHb levels.

INTRODUCTION

From the time of Orfila (who first established a relationship between dose and effect), acute effects of toxins have been related to the dose administered by ingestion, by injection, and more recently, by skin absorption. With the advent of inhalation experiments, however, the concept of "dose" (or the amount of material in the body - the body burden) became nebulus as there was no simple relationship between dose and exposure parameters. Consequently, effects of experimental inhalation exposures have been related to concentration and to exposure duration instead of to body burden or dose.

If quantitative information is available on excretion of the material administered (or on one of its metabolites), that data can often be described by an empirical equation which can then be used to calculate a value proportional to the total body burden.[1, 2, 3] The main difficulty with this or any other empirical approach is that while the results may be useful for interpolation, they will not be useful for extrapolation to conditions other than those of the experiment. Nevertheless, the empirical treatment of excretion data to estimate body burden is an extremely important first step toward true exposure integration.

The technique called the "time-weighted average" has been used in lieu of true exposure integration and even has a more-or-less official sanction.[4] If an inhalation exposure is broken into time intervals, t, each of a generally steady concentration, c, then the time-weighted average (TWA) is found as:

$$TWA = \Sigma ct / \Sigma t \qquad (1)$$

Use of equation 1 for estimating dose tacitly assumes that molecules inhaled at the beginning of the exposure contribute to the total dose or body burden equally with those molecules inhaled at the end of the exposure. This assumption can be true only if none of the material is excreted during the exposure or if each exhalation excretes 100% of the total body burden at that time. Either of these conditions may be approached, but neither is likely to be fulfilled for any real gas or vapor exposure, and therefore the TWA cannot be an accurate representation of the dose received.

Even though the TWA based on "interval" sampling does not accurately represent the dose, it does correspond quite well to concentrations found by cumulative air sampling methods. (A good cumulative air sampler operated throughout an exposure does not "excrete" any of the trapped material.) Furthermore, methods to supplant the TWA have not been available, nor has there been any tremendously pressing demand for their development. That the TWA is used almost universally today to represent dose, testifies that its errors are not large for most materials in comparison with other errors inherent in the evaluation of inhalation hazards. But with the advent of automated general area air samplers, personal "dosimeter samplers" and computer data analysis and reduction, the "other errors inherent in the evaluation of inhalation hazards" are becoming smaller. [5, 6] Consequently, there is a demand for summation or integration techniques capable of producing numbers more truly representative of the dose received than the TWA technique allows. Because they are based on experimental data, empirical

methods of estimating man's body burden from excretion data will usually give better results than the TWA. However, still better results can be expected from models of uptake and excretion based on a good theoretical approach. Of course, all models must be verified by experiment.

Carbon monoxide is almost the ideal gas for which to formulate a theoretical uptake-excretion equation. Inhaled CO passes through the lungs to the blood stream where it attaches firmly but reversibily to proteinaceous material, chiefly hemoglobin. Its concentration in blood (as carboxyhemoglobin, COHb) readily becomes high enough for accurate determination by inexpensive methods while still being low enough to have no delaterious effects. Furthermore, CO stays in the blood, does not react appreciably with other materials, tissues or fluids, [7] and is excreted unchanged and quantitatively through the lungs. The one minor complication is that CO is produced in small quantities in the body and thus the blood always contains a background endogenous level of COHb.

The rate of endogenous CO production is increased by some disease states, specifically those which result in red cell destruction. Investigators of this and other related phenomena have felt a need for a mathematical model of the way the human body handles CO so that they could better understand the effects of disease. None of the proposed models was particularly successful until 1965 when Coburn, Forster and Kane published the derivation of a new model. [8] They used this model successfully in a study of endogenous CO production, but they did not study inhaled (exogenous) CO.

Their model (the CFK equation) was tested by Peterson and Stewart in 1970 with data from the exposure of sedentary, male Caucasians [9]. Those experiments included oxygen inhalation therapy, long and short-term exposure to constant concentrations, a discontinuous exposure, and an exposure to a steadily rising concentration. In all cases, the CFK equation "fit" the data very well when average values were used for most of the subject-specific variables. The purposes of the present study were to extend the testing of the equation to include women as well as men at several exercise levels and to extend the computer program used for solving the equation to treat as variables several of the previously constant parameters.

THE CFK EQUATION

The basic form of the CFK equation is as follows:

$$\frac{A[COHb]_t - \dot{V}_{CO}B - P_{I_{CO}}}{A[COHb]_o - \dot{V}_{CO}B - P_{I_{CO}}} = \exp(-tA/V_bB) \qquad (2)$$

where:

$$A = \bar{P}_{C_{O_2}}/M[O_2Hb]$$

$$B = \frac{1}{D_{L_{C_O}}} + \frac{P_L}{\dot{V}_A}$$

M = Ratio of the affinity of blood for CO to that for O_2

$[O_2H_b]$ = milliliters of O_2 per milliliter of blood

$[COHb]_t$ = milliliters of CO per milliliter of blood at time t

$[COHb]_o$ = milliliters of CO per milliliter of blood at the beginning of the exposure interval

$\bar{P}_{CO_2}$ = average partial pressure of oxygen in lung capillaries, mm Hg

$\dot{V}_{CO}$ = rate of endogenous CO production ml/min

$D_{L_{CO}}$ = diffusivity of the lung for CO, ml/(min) (mm Hg)

P_L = barometric pressure minus the vapor pressure of water at body temperature, mm Hg

V_b = blood volume, ml

$P_{I_{CO}}$ = partial pressure of CO in the inhaled air, mm Hg

$\dot{V}_A$ = alveolar ventilation rate, ml/min

t = exposure duration, min

exp = 2.7182 . . . the base of natural logarithms raised to the power of the bracketed expression

In the original solution of this equation for exogenous exposure to CO, [9] all variables were considered constant except t, P_L, $[COHb]_t$ and $P_{I_{CO}}$. The remaining variables are not constant, however, and methods are needed for their evaluation.

The Affinity Constant (M):

Several investigators have reported values for the ratio of the affinity of hemoglobin for CO to that for O_2. This ratio varies widely between species, and also varies from individual to individual. For man, values ranging from about 150 to 300 have been used as "average" or "normal".

Rodkey, et al[10] determined the ratio of the affinity for 13 male and 2 female subjects in whole blood and hemoglobin solutions. The values found ranged from 197 to 229, averaging 217.7, with a standard deviation of 7.32. An average of 218 appears to be appropriate for man.

Average Partial Pressure of Oxygen in Lung Capillaries ($\overline{P}_{C_{O_2}}$):

Data for values of $\overline{P}_{C_{O_2}}$ are extremely difficult to obtain. Coburn, Forster, and Kane suggest a value of 100 mm Hg, and this is probably adequate if the partial pressure of O_2 (P_{O_2}) in the air that is breathed does not differ greatly from 150 mm Hg in air saturated with water at body temperature. However, if pure O_2 is being breathed, or, if the exposure takes place under a reduced or elevated total pressure (on a mountain or in a caisson, for instance), a value of 100 mm Hg for $\overline{P}_{C_{O_2}}$ will be incorrect.

When the inhaled P_{O_2} is greater than "normal", the value of $\overline{P}_{C_{O_2}}$ will be greater than 100 mm Hg. To determine an approximate value the following technique appears reasonable:

> For a barometric pressure, P_B in (in mm of Hg), and a vapor pressure of water at body temperature of 47 mm of Hg, the partial pressure of oxygen in saturated inspired air ($P_{I_{O_2}}$) can be calculated from the fraction of oxygen in inspired air ($F_{I_{O_2}}$):
>
> $$P_{I_{O_2}} = F_{I_{O_2}} (P_B - 47)$$

If "normal" values are applied in this equation, the P_{IO_2} is found to be 149 mm Hg. To reach the 100 mm Hg recommended for $\bar{P}_{CO_2}$ in these circumstances, 49 must be subtracted. This number (49) represents the level of CO_2 in alveolar air and also the effect of averaging over all lung capillaries. If this value is reasonable under normal conditions, it should be in most others and consequently,

$$\bar{P}_{CO_2} = P_{IO_2} - 49 \quad (P_{IO_2} \geq 149 \text{ mm Hg})$$

When P_{IO_2} is less than 149 mm Hg, $\bar{P}_{CO_2}$ will be less than 100 mm Hg. At these lower values of P_{IO_2} the relationship between the partial pressure of oxygen in air and blood is no longer linear because hemoglobin cannot be assumed to be saturated (or nearly so). The average partial pressure in lung capillaries cannot be greatly different from that in mixed arterial blood, and data for estimating oxygen partial pressure in arterial blood as a function of inspired oxygen partial pressure are available.[11] These data were submitted to a computerized regression program, resulting in:

$$\bar{P}_{CO_2} = P_{aO_2} = 1/(0.072 - 0.00079\, P_{IO_2} + 0.000002515\, P_{IO_2}^2)$$

where P_{IO_2} is the partial pressure of oxygen in the inhaled air in mm of Hg.

Rate of Endogenous CO Production ($\dot{V}_{CO}$):

The normal rate of production of CO by the body is approximately 0.007 ml/min STPD., but some diseases can cause an increase.[8]

Diffusivity of the Lung for CO ($D_{L_{CO}}$):

Lung diffusivity varies with many conditions including the molecular species, body size, rate of work, temperature, pressure, etc. In this case, only the diffusivity of the lung for CO is of concern at an assumed normal body temperature (37°C). Body size effects on diffusivity at rest were assembled and graphed by Coburn.[12] A regression equation for his data was derived:

$$D_{L_{CO}} = 1/[-0.0287 + 0.1188/A]$$
$$(r = 0.994)$$

where $D_{L_{CO}}$ is diffusivity in ml CO/min-mm Hg and A is the body surface area in m^2.

Similarly, data on the effect of work rate as indicated by the oxygen consumption rate [13] were submitted to a computer regression program. The resulting equation is:

$$D_{L_{CO}} = 1/[0.105 - 0.0246 \log (\dot{V}_{O_2})]$$
$$(r = 0.775)$$

where $\dot{V}_{O_2}$ is the oxygen consumption rate in ml/min.

Blood Volume (V_b):

The blood volume of average men is 74 ml per kilogram of body weight, while that for women is 73 ml per kilogram.[14] Prolonged strenuous exercise

may increase these values. Coburn, Forster and Kane use a value of 5500 ml, which they assume to be average for all body weights.

Partial Pressure of Inhaled CO ($P_{I_{CO}}$):

Gas or vapor concentrations of interest are usually expressed in parts per million by volume (ppm). Conversion to partial pressure is easily done.

$$P_{I_{CO}} = \text{(ppm) (barometric pressure in mm Hg)}/10^6$$

Alveolar Ventilation Rate ($\dot{V}_A$):

If the total rate of ventilation, in ml/min, is $\dot{V}_E$, the dead space (ml) is V_D, and the respiration rate (min^{-1}) is f, the alveolar ventilation rate $\dot{V}_A$ (ml/min, BTPS) is:

$$\dot{V}_A = \dot{V}_E - f V_D \qquad (3)$$

Unfortunately, the dead space, V_D, is not constant but increases with exercise. At rest for normal men, V_D is about 170 ml, but in heavy exercise may reach 350 ml. The relationship between dead space and total ventilatory rate appears to be linear[15] so that equation 9 can be revised:

$$\dot{V}_A = \dot{V}_E - f\,(132 + 0.067\,\dot{V}_E)$$

At low exercise rates, total lung ventilation increases linearly with exercise, and also with the oxygen consumption rate, $\dot{V}_{O_2}$, but begins to increase more rapidly at higher exercise rates. This rate increase varies with each subject but on the average, a $\dot{V}_{O_2}$ of 1000 ml/min (STPD) requires a $\dot{V}_E$ of approximately 22,000 ml/min (BTPS).

Oxyhemoglobin Concentration ($[O_2Hb]$):

If the concentration of COHb in the blood is low, $[O_2Hb]$ can be considered constant at a value determined by the individual's hemoglobin concentration. At standard conditions (STPD, or 760 mm Hg, 0°C, dry), one gram of hemoglobin will hold 1.38 ml of oxygen.[16] The maximum number of ml of O_2 per ml of blood is found as:

$$[O_2Hb]_{max} = 1.38\ Hb/100$$

where Hb is the hemoglobin concentration, g/100 ml. This value is, of course, also the number of ml of CO per ml of blood at 100% saturation and since both CO and O_2 compete for sites on hemoglobin, oxyhemoglobin concentration is never $[O_2Hb]_{max}$ but something less. During and after an exposure to CO, the value of $[O_2Hb]$ that must be used in equation 2 is actually $[O_2Hb]_{max} - [COHb]_t$. But, $[COHb]_t$ is the variable being determined; it appears on both sides of the equation and in an exponent of e on one side.

Under these circumstances, no direct solution of equation 2 is possible, and a "trial-and-error" method must be used but the "new" value of $[COHb]_t$

must not be the previously calculated one or the solution may diverge. A successful procedure is indicated in the following steps:

a. Assume a value for $[COHb]_t$ (such as zero) and find $[O_2Hb] = [O_2Hb]_{max} - [COHb]_t$

b. Calculate a new value for $[COHb]_t$ using equation 2

c. Check to see if the difference between the old and new values of $[COHb]_t$ is acceptable. (A maximum difference of 0.00001 may be used). If so, the problem is solved; if not, proceed to step (d).

d. Set the "old" value of $[COHb]_t$ equal to the one found in step (b).

e. Calculate a new value of $[O_2Hb]$ using equation 4 and proceed to step (b).

$$P = Q [1 - R/(R + S)] \quad (4)$$

where:

P = the new value of $[O_2Hb]$

Q = $[O_2Hb]_{max}$

R = the old value of $[COHb]_t$

S = the old value of $[O_2Hb]$

This procedure converges on a solution for all values of $[COHb]_t$, but is most rapid if a good guess of the proper value of $[COHb]_t$ can be made in step (a).

Carboxyhemoglobin Concentration ([COHb]):

The concentration of COHb found in the previous step at time t is expressed in ml of CO/ml blood. To convert this value to the more conventional "percentage saturation", multiply by 100 and divide by $[O_2Hb]_{max}$.

The value of $[COHb]_o$ used in equation 2 may range from the nominal for a non-smoker of about 0.5 to 1.5%, averaging 1.2% saturation (about 0.0024 ml CO per ml blood) to the heavy smoker's 5 to 7% (about 0.012 ml/CO/ml blood) to the concentration of $[COHb]_t$ calculated by using equation 2. By using the just-calculated value of $[COHb]_t$ successively as the new value of $[COHb]_o$, any exposure or any series of exposures to any concentration of CO (including zero) for any time interval can be summed.

TESTING THE EQUATION*

In the previously reported use of the CFK equation for exogenous CO exposure[9] no attempt was made to individualize the subject - specific variables. For the present study, all available data on each subject were used and "average" values were used only in those cases where individual data were not available. Specifically, data were available or were obtained for 22 subjects on non-exposed COHb level, hemoglobin concentration, and alveolar ventilation rate at several exercise levels. Data on height and weight were used to calculate blood volume and resting lung diffusivity for CO.

Data specific to each subject will be found in Table I. Particularly noteworthy is the variability of alveolar ventilation rates when the subjects were sedentary. Values of $\dot{V}_A$ ranged from 6.2 L/min to over 17 L/min,

*Data were collected from several experiments, some previously published, carried out by the staff and faculty of the Department of Environmental Medicine, Medical College of Wisconsin.

and the differences were apparently real. Values for hemoglobin, non-exposed COHb level, blood volume and lung diffusivity did not vary as greatly, and averaged to expected levels.

Volunteer subjects were exposed to CO in the chamber previously described. Concentrations of CO varied from 50 to 200 ppm, and during any single exposure the coefficient of variation (the standard deviation of concentrations expressed as a percentage of the mean) was less than 5%. Exposure durations ranged from 0.33 to 5.25 hours.

Blood samples were obtained prior to exposure, periodically during exposure, and in the post-exposure period, occasionally for several hours. These samples were analyzed on an IL CO-Oximeter which was kept in calibration and continually compared with samples analyzed by a gas chromatographic method.[17] Expired air samples were also used to confirm blood levels when such confirmation was felt to be appropriate. All analytical methods were in complete agreement throughout the study.

In all but experiment 51, when none of the subjects exercised, the following protocol was used: Blood samples were obtained and the subjects then entered the exposure chamber (the 20 x 20 x 8 ft. room previously described)[18] in which the concentration of CO in air was being maintained. After initial procedures which took from 10 to 18 minutes (carefully timed), the first group of four people began a 45-minute ride on the bicycle ergometers (Krogh Monark). Just prior to the end of that ride, blood samples were obtained from the second group of four subjects through an arm-port in the chamber door. When the first group finished, the second group began to ride

while blood samples were obtained from the first group. When the second group finished, blood samples were obtained from all subjects and then all persons remained sedentary for the remainder of the exposure.

The ergometers were used at a constant pedal speed of 50 rpm (a metronome was used to pace the subjects) and at loads of 1, 0.5, and 1.0 which resulted in work rates of 0 (WBL or working baseline), 150, and 300 kp-m/min. At a time near the end of each ride, the expired air was collected for an accurately-timed two minutes, and during that period a count was made of the number of respirations. The expired air volume and respiratory frequency were later used to determine the alveolar ventilation rate with equation 3. The 2 to 6 determinations of $\dot{V}_A$ were later averaged for each subject (Table I).

At least two expired air samples were collected from each subject while he or she was sedentary. Ventilation rate and frequency were used to determine the alveolar ventilation rate as during exercise.

All 22 subjects participated in sedentary experiments, but only 15 exercised. Most of the exercise work was done at the highest of the three levels. In all, 11 experiments were performed at other than sedentary levels, and of those, 8 were at the highest rate. All of the female subjects participated in the exercise studies.

A pre-exposure blood sample was obtained from each subject. In the few cases where that data were lost, the average non-exposed level for that subject was substituted. (These levels were determined during control

experiments.) This level was taken as the initial COHb level for use in equation 2. The duration of an exposure segment for the subject under consideration was then taken as the length of time he or she was exposed until the next blood sample was taken.

Available then, were an initial level of COHb, and an actual final level for that exposure segment. Using subject-specific and exposure-specific parameters, equation 2 was used to calculate a predicted COHb level. The actual and predicted levels were then used to form the statistics necessary for their comparison. Then, the actual COHb level was used as the initial COHb level for the next exposure segment. This procedure was also followed for post-exposure data which were obtained. The statistics were accumulated so that an examination could be made of the effects of the experiment, of the subject, and of the exercise level on the ability of the CFK equation to predict COHb concentrations. For this determination, both the standard error and the correlation coefficient were used.

Table II contains a list of the experiments conducted, including the nominal CO concentration and the number of subjects. (Details of each experiment are in the appendix.) These data show that there was no effect of CO concentration on the fit of the CFK equation. This was so even in experiment 51 where the concentration varied from 0 to 164 ppm.

Table IV is similar to Table II, except in this case the variable analyzed was subject number. There was no evident sex bias and, in general, correlation coefficients were high.

Table V shows that the ability of the CFK equation to predict COHb concentrations was not a function of exercise level as the equation performed equally well at the high level of exercise and with sedentary subjects. The high exercise level (300 kp-m/min) was equivalent to an oxygen consumption rate of about 1.0 L/min, or to the energy expenditure of a man driving a truck in traffic. This level is not high in comparison to that in many athletic endeavors, but may be representative of the work being done during many industrial exposures to CO.

In experiment 51, the subjects were exposed for 60 minutes to approximately 150 ppm CO. They then left the chamber for 30 minutes. While they were gone the concentration was reduced to about 50 ppm so that when they reentered they were exposed to the lower concentration. After an hour at 50 ppm they again left for 30 minutes while the concentration was increased to about 100 ppm in preparation for the final exposure hour.

Venous blood samples were obtained every 20 minutes in the chamber, at the end of each 30-minute period outside the chamber, and then twice at the conclusion of the experiment. Details of this exposure will be found in Table III. Values of COHb percentage saturation in experiment 51 for the seven subjects (sedentary white males) were averaged and plotted against time in Fig. 1. (Individual values will be found in the Appendix.) The CFK equation was then used to predict COHb levels for each subject at the end of each experimental segment. An average value of 30 ml/min-mm Hg was used for D_L, and 6000 ml/hr was assumed for V_A; these data were not available for this group

of people. In each case, the pre-exposure COHb level was used in equation 2 for $[COHb]_o$, and then $[COHb]_t$ was calculated for a 20-minute exposure to 150 ppm. Then that value (not the actual level found) was used as the $[COHb]_o$ for the next (164 ppm) segment, etc. For each exposure segment, the values of $[COHb]_t$ were averaged for the seven subjects and plotted in Figure I as predicted values.

The remarkable ability of the CFK equation to sum exposures to CO is well illustrated in Figure 1. Only at the beginning and end of the first 30-minute period of non-exposure was the prediction in error by more than 0.5% saturation. That error may well have been in the "actual" values as indicated by the low slope of this curve over the first zero-exposure segment. (All of the non-exposure segments should have about the same slope.) Furthermore, after 90 minutes both actual and predicted values are very close; the nature of this kind of prediction is that an early error tends to be propagated and no propagation was seen. At any rate, the error was small, and the theoretical CFK equation was shown well able to sum the results of this type of exposure.

CONCLUSIONS

The CFK equation appears to predict COHb levels as well for women as it does for men even though the female subjects did absorb CO more rapidly than did most of the male subjects. Furthermore, exercise sufficient to increase the alveolar ventilation rate by a factor of about 2.5 from sedentary

levels did not materially alter the fit of the equation to the data. Finally, a discontinuous exposure to varying CO concentrations was summed with exceptionally good results. All of this information indicates that the CFK equation is a good theoretical model of the uptake and excretion of carbon monoxide.

Because the model is based on a theory which extensive experimentation has yet to contradict, moderate extrapolation from the experimental data should be practical. On this basis Figure 2 was constructed, relating percentage carboxyhemoglobin to exposure duration for a series of CO concentrations in ambient air and nominal values of other parameters. The lowest concentration, 8.7 ppm, is equivalent to that allowed by the Environmental Protection Agency to exist for eight hours in the ambient air no more often than once per year. [19] No human experimentation has been conducted at this concentration.

A concentration of 50 ppm was chosen because this is the current Threshold Limit Value (TLV) of the American Conference of Governmental Industrial Hygienists. [4] A level of 35 ppm was used because this concentration has been proposed as a new TLV: 100 ppm was the TLV for many years. The remaining concentrations, 25, 200, 500 and 1000 ppm were chosen because human exposures have been conducted recently at these levels. [9] The CFK equation was shown to fit the resulting data very well. (A graph similar to Figure II was published previously. [9] That graph is in error at high levels of COHb and long exposure durations because $[O_2Hb]$ was regarded as a constant, not a variable, in solving the CFK equation.)

Information in Figure 2 pertains to many CO exposures, but many exposures also take place under other conditions. To show the relative effect of some of the exposure and person-specific parameters on CO uptake, Table VI was constructed. Values of % COHb saturation were found by solving equation 2 using the parameter levels listed in Table VI. In each case, the parameter indicated was the only one changed from the value indicated in Figure 2. Also, levels of each parameter were chosen to represent real but extreme conditions which might be encountered. Results of this exercise give at least a partial indication of the effect of each parameter on the uptake of CO.

Figure 2 shows that equilibrium is approached very slowly at low concentrations, taking about 24 hours at 25 ppm and below. On the other hand, equilibrium is complete in about 8 hours at 1000 ppm. Therefore, in Table VI, the 1000 ppm column at 480 minutes is representative of the effect at equilibrium of any (except CO concentration) of the parameter changes. Only barometric pressure and oxygen concentration appear to have any great effect on COHb levels at equilibrium. All of these parameters, on the other hand, exert at least some effect on the rate at which equilibrium is approached.

As parameters were varied one at a time in constructing Table VI, the effects of varying two or more at once are not apparent. Experimentation with equation 2 shows that such effects can be much more than additive, especially where the rate of CO uptake is concerned. For instance, a fire

in an enclosed space will result in a low oxygen concentration and a high CO_2 level. The high CO_2 level can, in turn, cause more rapid respiration and therefore, a high $\dot{V}_A$. A combination of 10% oxygen, a $\dot{V}_A$ of 25 L/min, and a CO concentration of only 1000 ppm can be found to result in a COHb level of 57.1% in 60 minutes (the equilibrium value in this case is 82.5%).

Even though the CFK equation has not been completely tested at all levels of all parameters (and such testing is, in fact, impossible), present indications are that it describes uptake and excretion of CO very well. This equation appears suitable for general use in predicting the consequences of specific circumstances as well as for summing more ore less long-term exposures to varying concentrations.

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TABLE I

SUBJECT INFORMATION

Subject	COHb %	H_b g/100 ml	V_b ml	Sed.	$\dot{V}_A$ in ml/min. WBL	150	300	$D_{L_{CO}}$
1	0.89	17.06	5213	6233	--	--	20480	--
6	1.36	17.45	6223	17057	--	--	29021	--
7	0.71	14.41	5213	13721	--	--	25619	--
8	1.19	14.17	5718	10714	--	--	19665	--
9	0.69	16.10	5718	12939	--	--	24516	33.0
10	1.50	16.93	7400	10334	--	--	27441	--
11 ♀	0.79	13.92	3716	8424	--	--	15946	--
12 ♀	0.58	14.43	4645	9770	--	--	20188	--
21 ♀	0.86	13.63	4380	9025	10388	12918	21886	23.7
22	0.89	15.27	4709	6518	10876	17439	21189	25.7
25	1.02	16.07	5214	7461	13893	20798	24440	30.5
29	0.93	14.70	4877	10513	19630	20332	25924	28.1
31	1.05	15.82	5550	10888	11423	16514	20513	30.2
32	1.39	16.66	6593	7426	18845	16710	25525	38.6
33	1.39	16.42	4204	7710	9614	17176	23816	22.0
40	1.20	14.54	5348	--	--	--	--	--
58	1.4	15.96	5381	--	--	--	--	--
59	1.3	16.54	5247	--	--	--	--	--

continued. . .

TABLE 1, SUBJECT INFORMATION - continued

Subject	COHb %	H_b g/100 ml	V_b ml	$\dot{V}_A$ in ml/min. Sed.	WBL	150	300	$D_{L_{CO}}$
60	1.4	15.86	5886	--	--	--	--	--
63	2.3	15.07	4541	--	--	--	--	--
64	1.5	15.45	4877	--	--	--	--	--
65	1.3	15.30	5886	--	--	--	--	--
Average ♂	1.18	15.78	5437	10126	14047	14828	24012	29.7
Average ♀	0.78	13.99	4313	9073	--	--	19673	--

TABLE II

Fit of the CFK Equation
As a Function of Experiment

Experiment Number	Number of Subjects	Nominal ppm CO	Minutes of Exposure	Total Segments	Standard Error	Correlation Coefficient
1	8	100	315	32	1.23	0.94
2	8	50	300	24	0.60	0.94
3	8	200	310	24	3.13	0.95
6	8	50	290	55	0.68	0.84
7	7	200	265	47	1.72	0.92
10	8	100	265	55	1.06	0.88
41	7	200	274	21	3.10	0.96
43	7	200	270	21	1.92	0.99
44	7	200	268	21	1.47	0.98
47	7	200	255	21	1.56	0.96
50	6	200	270	18	2.31	0.97
51	7	**	240	90	0.58	0.90

**Fluctuating concentration. See Table III

TABLE III

Fluctuating Concentrations in Experiment 51

Segment	Duration, min.	CO Concentration, ppm
1	20	150
2	20	164
3	20	142
4	30	0
5	20	45
6	20	52
7	20	49
8	30	0
9	20	105
10	20	88
11	20	122
12	15	0
13	15	0

TABLE IV

Fit of the CFK Equation
To Exercise Data for Individual Subjects

Subject No.	Segments	Standard Error	Correlation Coefficient
1	21	0.74	0.9892
6	29	1.97	0.9075
7	30	2.20	0.9352
8	30	1.21	0.9782
9	30	1.36	0.9701
10	27	0.81	0.9832
11 ♀	35	1.54	0.9573
12 ♀	35	1.22	0.9758
21 ♀	15	2.52	0.9287
22	15	1.95	0.9436
25	15	1.93	0.9550
29	15	2.69	0.9587
31	15	2.45	0.9623
32	12	1.28	0.9723
33	15	2.09	0.9459
40	12	0.60	0.9123
58	13	0.79	0.7909
59	13	0.58	0.9158
60	13	0.55	0.9183

TABLE 4, continued

Subject No.	Segments	Standard Error	Correlation Coefficient
63	13	0.68	0.8338
64	13	0.54	0.9101
65	13	0.56	0.9084

TABLE V

Fit of CFK Equation
at Four Exercise Levels

Exercise Level	Segments	Standard Error	Correlation Coefficient
Sed.	344	1.53	0.9712
WBL	7	1.34	0.9553
150	13	2.55	0.7929
300	61	1.02	0.9654

TABLE VI

Effect of Various Parameters on COHb Saturation
(Values are % COHb Levels Calculated from the CFK Equation
by Changing Only the Indicated Parameter.)

Parameter	60-Minute Exposure PPM CO					480-Minute Exposure PPM CO				
	8.7	35	50	100	1000	8.7	35	50	100	1000
Nominal (Fig. II)	0.93	1.58	1.96	3.20	25.0	1.42	4.48	6.18	11.6	61.4
P_B = 400 mmHg	0.96	1.54	1.88	3.00	22.8	1.69	5.03	6.89	12.9	68.7
P_B = 600 mmHg	0.94	1.58	1.94	3.14	24.4	1.51	4.69	6.46	12.1	63.9
P_B = 1500 mmHg	0.39	0.83	1.08	1.90	15.5	0.23	0.84	1.18	2.30	18.9
$\dot{V}_A$ = 15 L/min.	1.00	2.14	2.79	4.95	40.2	1.47	5.22	7.25	13.5	62.2
$\dot{V}_A$ = 50 L/min.	1.08	2.82	3.81	7.06	52.4	1.47	5.45	7.59	14.1	62.2
$\dot{V}_A$ = 100 L/min.	1.11	3.07	4.17	7.80	55.2	1.47	5.47	7.62	14.1	62.2
V_b = 1000 ml	1.30	3.82	5.23	9.82	59.6	1.63	5.65	7.79	14.3	62.2
V_b = 2000 ml	1.11	2.67	3.55	6.47	49.5	1.61	5.55	7.66	14.1	62.2
V_b = 7000 ml	0.90	1.43	1.73	2.72	20.3	1.34	4.06	5.58	10.5	60.4
$[COHb]_o$ = 2%	1.94	2.60	2.97	4.21	25.9	1.73	4.77	6.46	11.8	61.4
$[COHb]_o$ = 7%	6.13	6.77	7.14	8.36	29.7	3.00	5.97	7.61	12.9	61.5
D_L = 10 ml/min-mmHg	0.90	1.37	1.63	2.52	18.2	1.37	3.90	5.31	9.91	59.6
D_L = 50 ml/min-mmHg	0.94	1.65	2.06	3.41	27.0	1.43	4.61	6.38	12.0	61.7
% O_2 = 10	1.02	1.71	2.10	3.42	26.8	2.25	6.71	9.21	17.3	81.2
% O_2 = 100	0.44	0.87	1.11	1.93	15.5	0.25	0.90	1.27	2.47	20.0
Hb = 10 g/100 ml	0.99	1.93	2.46	4.25	34.4	1.52	5.07	7.01	13.1	62.1
Hb = 20 g/100 ml	0.90	1.40	1.69	2.64	19.5	1.33	3.98	5.46	10.2	60.2

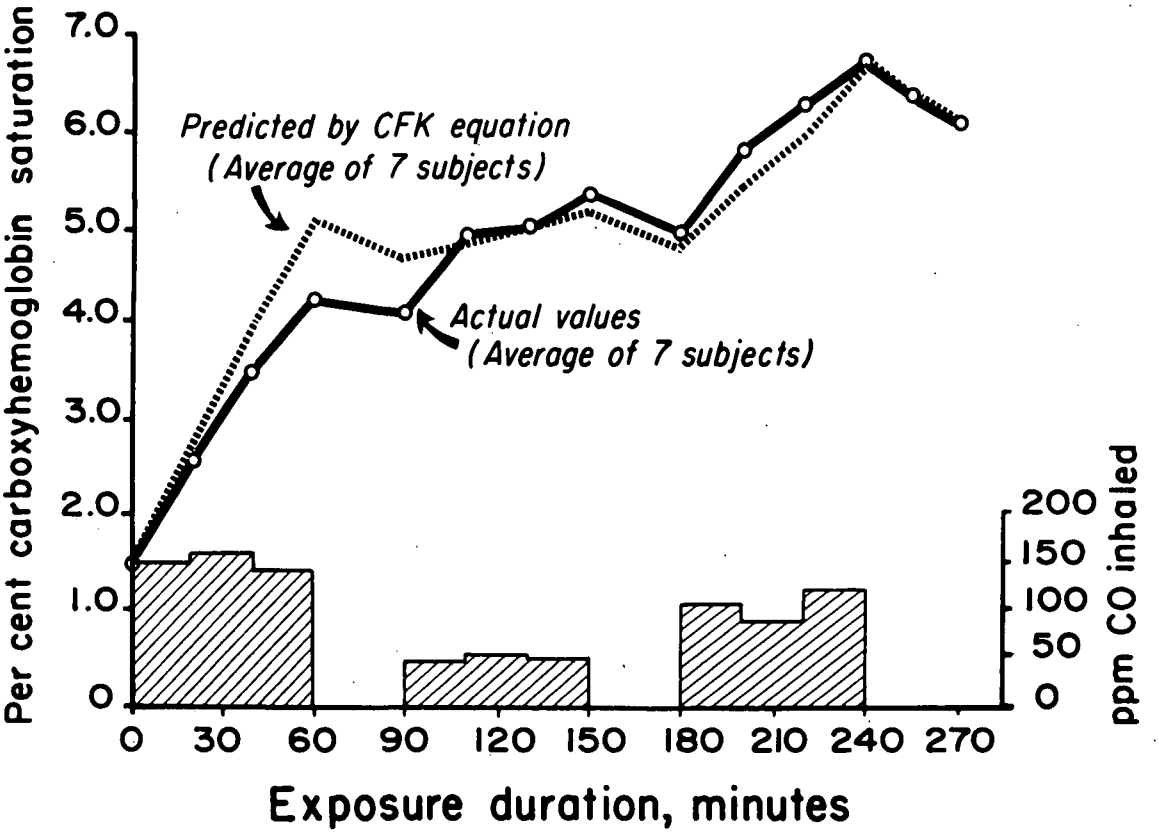

Figure I Average carboxyhemoglobin levels of subjects in experiment 51 compared with values calculated by using the CFK equation.

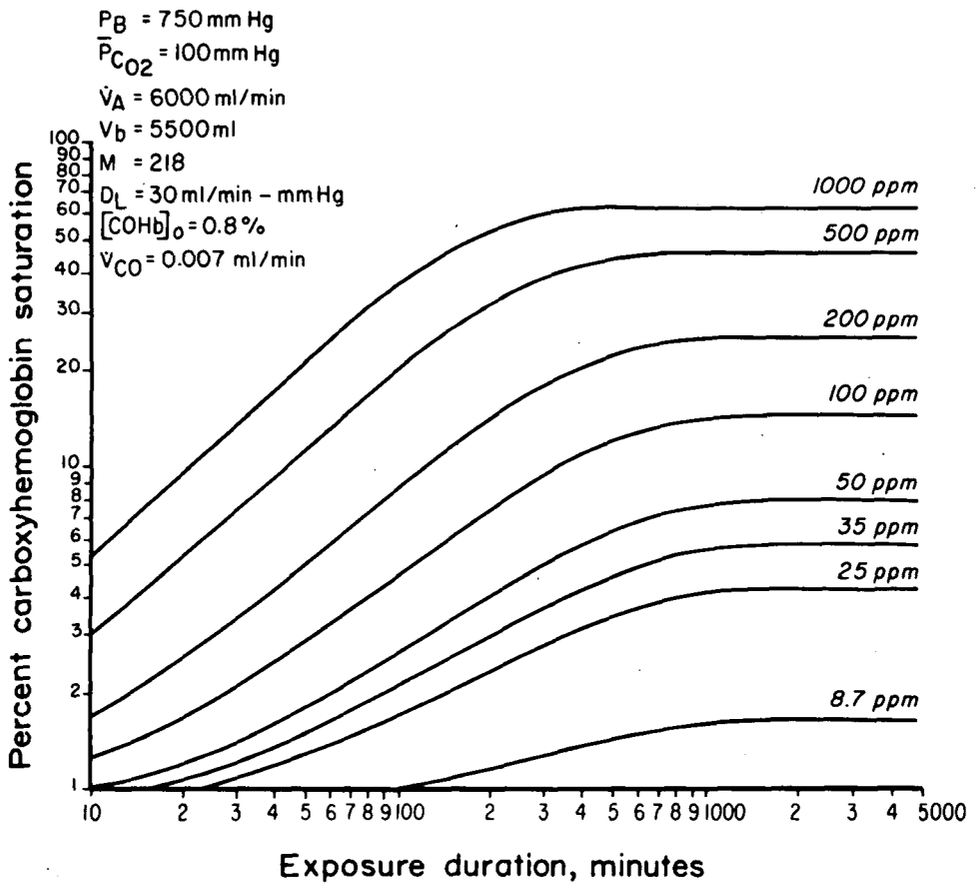

Figure II Carboxyhemoglobin levels for man as a function of exposure duration and of the CO concentration as determined by solving the CFK equation.

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APPENDIX

EXPERIMENT 1

Actual Carboxyhemoglobin Saturation at the Conclusion of Each Exposure Segment

Conc., ppm		0	98.4	101.8	100.5	101.23	1.4	1.4			
Dur., min.		0	12	45	45	213	30	30			
Subject No.	1	0.9	--	2.6	6.2*	9.9	8.5	8.0			
	6	1.6	--	2.9	5.7*	8.7	8.0	7.7			
	7	0.1	--	2.9	6.1*	8.9	--	--			
	8	0.5	--	5.0*	6.1	10.1	--	--			
	9	0.4	--	4.2*	6.1	9.9	--	--			
	10	1.1	--	4.2*	5.2	8.7	--	--			
	11	0.7	--	3.7	8.2*	11.0	9.1	7.5			
	12	0.2	--	5.6*	7.4	11.1	8.7	7.7			

*Exercise at 300 kp-m/min.

EXPERIMENT 2

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment.

Conc., ppm		0	49.5	50.6	51.1	50.6					
Dur., min.		0	12	45	45	198					
SUBJECT NUMBER	1	1.2	--	3.1*	4.2	5.5					
	6	2.0	--	2.7	3.7*	5.0					
	7	0.5	--	2.6*	3.2	5.1					
	8	0.9	--	3.2*	3.9	6.2					
	9	0.2	--	1.9	3.4*	5.1					
	10	0.7	--	2.1*	3.5	5.8					
	11	0.3	--	1.9	4.7*	6.7					
	12	0.4	--	1.6	4.1*	6.2					

*Exercise at 300 kp-m/min.

EXPERIMENT 3

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	198.6	199.4	198.4	196.5					
Dur., min.		0	10	45	45	210					
SUBJECT NUMBER	1	1.1	--	8.8*	11.1	15.8					
	6	2.1	--	5.4	9.5*	14.2					
	7	1.0	--	8.0*	10.1	15.5					
	8	1.2	--	7.9*	10.5	16.6					
	9	0.7	--	4.8	10.7*	18.0					
	10	1.2	--	6.2*	9.1	15.1					
	11	0.7	--	5.4	13.0*	17.8					
	12	0.3	--	5.9	12.3*	17.8					

*Exercise at 300 kp-m/min.

EXPERIMENT 6

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm	0	47.4	47.8	48.0	49.7	0.7	1.0	0.3	0.7	0.7
Dur., min.	0	12	45	45	188	30	30	60	60	60
1	0.8	--	2.6*	4.0	5.3	5.0	5.0	--	--	--
6	1.9	--	3.1	3.8*	5.4	5.6	5.0	--	--	--
7	0.3	--	2.5*	3.2	4.4	4.4	4.4	4.3	4.0	2.2
8	1.2	--	2.9*	3.5	5.8	5.7	5.1	4.8	4.4	3.9
9	0.2	--	2.1	4.0*	4.8	5.7	4.2	3.8	3.6	3.5
10	1.8	--	3.3*	3.7	6.2	6.2	5.2	--	--	--
11	1.2	--	2.8	4.7*	6.0	5.4	4.8	3.7	3.1	2.7
12	0.1	--	1.9	3.7*	4.3	4.6	4.2	3.5	2.6	2.8

SUBJECT NUMBER

*Exercise at 300 kp-m/min.

EXPERIMENT 7

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	199.8	202.7	201.6	202.1	0	0.3	0	0.3	0
Dur., min.		0	10	45	45	165	30	30	60	60	60
SUBJECT NUMBER	6	1.5	--	5.6	9.9*	15.4	14.1	13.5	12.1	10.1	9.1
	7	0.7	--	7.5*	10.3	16.5	14.6	13.4	--	--	--
	8	1.3	--	9.5*	12.6	18.3	16.3	14.7	--	--	--
	9	0.3	--	5.4	12.5*	17.3	15.2	13.5	--	--	--
	10	1.9	--	8.8*	11.2	17.0	15.2	14.2	13.0	11.3	10.1
	11	0.9	--	6.2	14.9*	20.0	16.6	14.8	11.8	9.3	7.7
	12	0.9	--	6.5	14.3*	19.2	16.8	15.0	9.7	7.6	7.3

*Exercise at 300 kp-m/min.

EXPERIMENT 10

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	94.9	92.7	95.5	96.0	2.6	0.8	0.8	0	0
Dur., min.		0	8	45	45	167	30	30	60	60	60
SUBJECT NUMBER	1	1.1	--	4.4*	6.0	9.5	8.6	8.1	--	--	--
	6	2.1	--	3.4	6.5*	8.5	8.6	7.6	--	--	--
	7	0.8	--	4.5*	7.0	9.3	8.6	8.2	5.2	7.1	4.6
	8	1.3	--	4.9*	6.3	9.1	8.5	8.0	6.3	7.0	5.0
	9	0.7	--	4.2	7.0*	9.6	9.4	8.0	5.6	6.6	4.5
	10	2.6	--	4.9*	6.4	9.4	9.3	8.6	--	--	--
	11	1.7	--	3.8	8.8*	10.9	9.5	8.4	5.0	5.6	4.7
	12	0.6	--	2.9	7.1*	10.5	9.2	7.8	5.2	5.6	4.4

*Exercise at 300 kp-m/min.

EXPERIMENT 41

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	190.4	193.5	200.8	201.1					
Dur., min.		0	30	45	45	154					
SUBJECT NUMBER	21	0.8	--	4.9	10.0*	16.8					
	22	0.9	--	4.2	8.6*	15.5					
	25	0.8	--	4.4	8.6*	14.6					
	29	0.8	--	4.2	8.9*	16.0					
	31	0.8	--	5.6*	8.0	15.6					
	32	0.9	--	5.7*	8.2	14.9					
	33	0.8	--	5.7*	8.0	15.2					

*Exercise at 150 kp-m/min.

EXPERIMENT 43

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Ea ch Exposure Segment

Conc., ppm		0	199.2	205.5	201.9	214.3					
Dur., min.		0	14	45	45	166					
SUBJECT NUMBER	21	0.9	--	8.1	13.2*	19.0					
	22	1.1	--	6.8	10.9*	17.6					
	25	1.2	--	6.2	10.6*	17.0					
	29	1.3	--	7.0	11.7*	19.1					
	31	1.1	--	6.7*	9.8	16.2					
	32	1.4	--	6.7*	9.4	15.8					
	33	1.7	--	8.2*	10.3	16.7					

*Exercise at 0.0 kp-m/min. (working baseline)

EXPERIMENT 44

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	182.8	185.9	207.5	199.0				
Dur., min.		0	10	45	45	168				
SUBJECT NUMBER	21	1.1	--	6.4	15.6*	19.6				
	22	1.1	--	5.6	13.4*	17.7				
	25	0.7	--	6.2	12.8*	18.2				
	21	0.9	--	5.6	13.2*	18.6				
	31	1.0	--	8.0*	11.2	17.2				
	32	3.0	--	9.4*	12.6	17.1				
	33	1.8	--	9.6*	13.2	18.3				

*Exercise at 300 kp-m/min.

EXPERIMENT 47

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	186.8	191.4	198.5	200.5					
Dur., min.		0	10	45	45	155					
SUBJECT NUMBER	21	1.5	--	13.0*	16.0	19.9					
	22	1.4	--	12.2*	16.2	18.7					
	25	1.5	--	10.9*	14.8	18.0					
	29	1.1	--	10.4*	13.0	18.2					
	31	1.2	--	6.1	12.4*	17.7					
	32	1.4	--	5.8	11.6*	17.6					
	33	1.8	--	6.9	14.8*	19.2					

*Exercise at 300 kp-m/min.

EXPERIMENT 50

Actual Carboxyhemoglobin Percentage Saturation
at the Conclusion of Each Exposure Segment

Conc., ppm		0	206.3	201.8	193.8	196.7					
Dur., min.		0	15	45	45	170					
SUBJECT NUMBER	21	0.8	--	8.8*	12.1	16.8					
	22	1.4	--	8.4*	11.4	16.1					
	25	1.2	--	8.0*	10.6	15.2					
	29	0.6	--	9.0*	12.5	17.1					
	31	1.0	--	5.1	10.0*	15.5					
	33	1.8	--	6.8	12.4*	16.7					

*Exercise at 150 kp-m/min.

EXPERIMENT 51

Actual Carboxyhemoglobin Saturation at the Conclusion of Each Exposure Segment

Conc., ppm	0	149.0	163.5	142.8	0	45.0	51.8	49.0	0	105.1	87.8	122.4	0	0
Dur., min.	0	20	20	20	30	20	20	20	30	20	20	20	15	15
Sub. No.														
40	1.2	2.2	3.5	4.5	4.2	5.3	4.8	5.6	5.0	6.0	6.4	7.0	--	5.6
58	1.4	1.9	2.8	3.6	3.4	3.8	4.1	4.7	4.5	5.1	5.3	5.1	5.7	5.6
59	1.3	2.3	3.2	3.9	4.1	4.6	4.7	5.1	4.8	5.6	6.2	6.7	6.3	6.1
60	1.4	2.6	3.3	4.1	4.0	5.0	4.8	5.2	5.0	5.8	6.2	6.9	6.4	6.3
63	2.3	3.5	4.3	5.0	5.1	6.0	6.0	6.0	5.5	6.4	6.6	7.5	7.0	6.6
64	1.5	3.0	4.0	4.5	4.3	5.1	5.4	5.5	5.2	6.0	6.6	7.0	6.5	6.3
65	1.3	2.5	3.4	4.0	3.8	4.7	5.1	5.2	4.4	5.4	6.4	6.5	6.0	5.9