8. EFFECTS ON HUMANS

8.1 Healthy subjects

8.1.1 Introduction

Many direct experiments investigating the effects of carbon monoxide on humans have been conducted during the last century. Although many reports describe inadvertent exposures to various levels of carbon monoxide, there are a considerable number of precise and delineated studies utilizing human subjects. Most of these have been conducted by exposing young adult males to concentrations of carbon monoxide equivalent to those frequently or occasionally detected during ambient monitoring. Research on human subjects, however, can be limited by methodological problems that make the data difficult to interpret. These problems include (1) failure to measure blood carboxyhaemoglobin levels; (2) failure to distinguish between the physiological effects from a carbon monoxide dose of high concentration (i.e., bolus effect) and the slow, insidious increment in carboxyhaemoglobin levels over time from lower inhaled carbon monoxide concentrations; (3) failure to distinguish between normal blood flow and blood flow increased in response to hypoxia (compensatory responses); and (4) the use of small numbers of experimental subjects. Other factors involve failure to provide (1) control measures (e.g., double-blind conditions) for experimenter bias and experimenter effects; (2) control periods so that task-learning effects do not mask negative results; (3) homogeneity in the subject pool, particularly in groups labelled "smokers"; (4) control of possible boredom and fatigue effects; and (5) adequate statistical treatment of the data.

8.1.2 Acute pulmonary effects of carbon monoxide

8.1.2.1 Effects on lung morphology

Results from human autopsies have indicated that severe pulmonary congestion and oedema were produced in the lungs of individuals who died from acute smoke inhalation resulting from fires (Fein et al., 1980; Burns et al., 1986). These individuals, however, were exposed to relatively high concentrations of carbon monoxide as well as other combustion components of smoke, such as carbon...
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dioxide, hydrogen cyanide, various aldehydes (e.g., acrolein), hydrochloric acid, phosgene and ammonia. If carbon monoxide, contained in relatively high concentrations in the inhaled smoke, was responsible for the pathological sequelae described in fire victims, then to what extent can oedema be attributed to the primary injury of capillary endothelial or alveolar epithelial cells?

In a study by Parving (1972) on 16 human subjects, transcapillary permeability to $^{131}$I-labelled human serum albumin increased from an average 5.6% per hour in controls to 7.5% per hour following exposure to carbon monoxide. The subjects were exposed for 3–5 h to 0.43% (4900 mg/m$^3$ [4300 ppm]) carbon monoxide, resulting in approximately 23% carboxyhaemoglobin. There were no associated changes in plasma volume, haematocrit or total protein concentration.

The only other relevant permeability studies were conducted with cigarette smoke. Mason et al. (1983) showed rapidly reversible alterations in pulmonary epithelial permeability induced by smoking using radiolabelled diethylenetriaminepentaacetic acid ($^{99m}$Tc-DTPA) as a marker. This increased permeability reverted to normal fairly rapidly when subjects stopped smoking (Minty et al., 1981). Using a rat model, the permeability changes associated with cigarette smoke were demonstrated later by Minty & Royston (1985) to be due to the particulate matter contained in the smoke. The increase in $^{99m}$Tc-DTPA clearance observed after exposure to dilute whole smoke did not occur when the particles were removed, suggesting that the carbon monoxide contained in the gaseous phase does not alter permeability of the alveolar–capillary membrane.

8.1.2.2 Effects on lung function

Human studies of pulmonary function are mostly devoted to the identification of effects occurring in the lungs of individuals exposed to relatively high concentrations of carbon monoxide. Older studies in the literature describe the effects of brief, controlled experiments with high carbon monoxide–air mixtures. Chevalier et al. (1966) exposed 10 subjects to 5700 mg carbon monoxide/m$^3$ (5000 ppm) for 2–3 min until carboxyhaemoglobin levels reached 4%. Measurements of pulmonary function and exercise studies were performed before and after exposure. Inspiratory capacity and total lung capacity decreased 7.5% ($P < 0.05$) and 2.1% ($P < 0.02$), respectively, whereas maximum breathing capacity increased 5.7% ($P < 0.05$) following exposure.
Mean resting diffusing capacity of the lungs decreased 7.6% ($P < 0.05$) compared with air-exposed controls. Fisher et al. (1969) exposed a small number ($n = 4$) of male subjects, aged 23–36 years, to 6% (69 000 mg/m$^3$ [60 000 ppm]) carbon monoxide for 18 s, resulting in estimated carboxyhaemoglobin concentrations of 17–19%. There were no significant changes in lung volume, mechanics or diffusing capacity. Neither of these studies was definitive, however, and no follow-up studies were reported.

More recent studies in the literature describing the effects of carbon monoxide on pulmonary function have been concerned with exposure to the products of combustion and pyrolysis from such sources as tobacco, fires or gas- and kerosene-fuelled appliances and engines. One group of individuals, representing the largest proportion of the population exposed to carbon monoxide, is tobacco smokers. A second group evaluated for potential changes in acute ventilatory function includes occupations in which individuals are exposed to variable, and often unknown, concentrations of carbon monoxide in both indoor and outdoor environments. Firefighters, tunnel workers and loggers are typical examples of individuals at possible risk. Unfortunately, these individuals are also exposed to high concentrations of other combustion components of smoke and exhaust. It is very difficult to separate the potential effects of carbon monoxide from those due to other respiratory irritants.

Firefighters have previously been shown to have a greater loss of lung function associated with acute and chronic smoke inhalation (as reviewed by Sparrow et al., 1982). None of these earlier studies, however, characterized the exposure variables, particularly the concentrations of carbon monoxide found in smoke, nor did they report the carboxyhaemoglobin levels found in firefighters after exposure. Most reports of lung function loss associated with other occupational exposures also fail to characterize exposure to carbon monoxide. The following studies have attempted to monitor, or at least estimate, the carbon monoxide and carboxyhaemoglobin levels found in occupational settings where lung function was also measured.

Sheppard et al. (1986) reported that acute decrements in lung function were associated with routine firefighting. Baseline airway responsiveness to methacholine was measured in 29 firefighters from...
one fire station in San Francisco, California, USA, who were monitored over an 8-week period. Spirometry measurements were taken before and after each 24-h work shift and after each fire. Exhaled gas was sampled 55 times from 21 firefighters immediately after each fire and was analysed for carbon monoxide. Despite the use of personal respiratory protection, exhaled carbon monoxide levels exceeded 110 mg/m$^3$ (100 ppm) on four occasions, with a maximum of 150 mg/m$^3$ (132 ppm), corresponding to predicted carboxyhaemoglobin levels of 17–22%. Of the 76 spirometry measurements obtained within 2 h after a fire, 18 showed a greater fall in FEV$_1$ and/or FVC compared with routine work shifts without fires. Decrement in lung function persisted for as long as 18 h in some of the individuals, but they did not appear to occur selectively in those individuals with pre-existing airway hyperresponsiveness.

Evans et al. (1988) reported on changes in lung function and respiratory symptoms associated with exposure to automobile exhaust among bridge and tunnel officers. Spirometry measurements were obtained in and symptom questionnaires were administered on a voluntary basis to 944 officers of the Triborough Bridge and Tunnel Authority in New York City, New York, USA, over an 11-year period between 1970 and 1981. Regression analyses were performed on 466 individuals (49%) who had been tested at least three times during that period. Carboxyhaemoglobin levels were calculated from expired-air breath samples. Small but significant differences were found between the bridge and tunnel officers. Estimated levels of carboxyhaemoglobin were consistently higher in tunnel workers than in bridge workers for both non-smoking individuals (1.96% and 1.73%, respectively) and smoking individuals (4.47% and 4.25%, respectively). Lung function measures of FEV$_1$ and FVC were lower, on average, in tunnel workers than in bridge workers. There were no reported differences in respiratory symptoms except for a slightly higher symptom prevalence in tunnel workers who smoked. Because differences in lung function between the two groups were small, it is questionable if the results are clinically significant or if they were even related to carbon monoxide exposure.

Hagberg et al. (1985) evaluated the complaints of 211 loggers reporting dyspnœa and irritative symptoms in their eyes, noses and throats after chain-saw use. Measurements of lung spirometry, carboxyhaemoglobin and exposure to carbon monoxide, hydrocarbons
and aldehydes were conducted on 23 loggers over 36 work periods lasting 2 h each. Ventilation levels during tree felling averaged 41 litres/min. Carboxyhaemoglobin levels increased after chain-saw use \((P < 0.05)\) but were weakly although significantly \((P < 0.001)\) correlated \((r = 0.63)\) with mean carbon monoxide concentrations of 19 mg/m\(^3\) (17 ppm) (5–84 mg/m\(^3\) [4–73 ppm] range) in non-smokers. Corresponding carboxyhaemoglobin levels were apparently <2%; unfortunately, the absolute values before and after exposure were not reported. Bronchoconstriction, measured by a decreased FEV\(_1\)/FVC \((P < 0.03)\) and forced expiratory flow measured at 25–75% of FVC \((P < 0.005)\), was found after the work periods, but no correlations were obtained between lung function, carboxyhaemoglobin levels and exposure variables. There were no reported significant changes in FEV\(_1\) or FVC.

The potential effects of indoor combustion products of kerosene space heaters on lung function were evaluated by Cooper & Alberti (1984). Carbon monoxide and sulfur dioxide concentrations were monitored in 14 suburban homes in Richmond, Virginia, USA, during January and February of 1983 while modern kerosene heaters were in operation. Spirometry measurements were obtained in 29 subjects over a 2-day period, randomizing exposures between days with and without the heater on. During heater operation, the carbon monoxide concentration was 7.8 ± 6.8 mg/m\(^3\) (6.8 ± 5.9 ppm) (0–16 mg/m\(^3\) [0–14 ppm] range), and the sulfur dioxide concentration was 1.1 ± 1.1 mg/m\(^3\) (0.4 ± 0.4 ppm) (0–2.9 mg/m\(^3\) [0–1 ppm] range). On control days, the indoor carbon monoxide concentration was 0.16 ± 0.61 mg/m\(^3\) (0.14 ± 0.53 ppm), whereas sulfur dioxide was undetectable. Six of the homes had carbon monoxide concentrations exceeding 10 mg/m\(^3\) (9 ppm). Corresponding outdoor carbon monoxide concentrations were 0–3.4 mg/m\(^3\) (0–3 ppm). Carboxyhaemoglobin levels significantly increased from 0.82 ± 0.43% on control days to 1.11 ± 0.52% on days when kerosene heaters were used. Exposure to heater emissions, however, had no effect on FVC, FEV\(_1\) or maximum mid-expiratory flow rate.

Most of the published community population studies on carbon monoxide have investigated the relationship between ambient carbon monoxide levels and hospital admissions, deaths or symptoms attributed to cardiovascular diseases. Little epidemiological information is
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available on the relationship between carbon monoxide and pulmonary function, symptomatology and disease.

One study by Lutz (1983) attempted to relate levels of ambient pollution to pulmonary diseases seen in a family practice clinic in Salt Lake City, Utah, USA, during the winters of 1980 and 1981, when heavy smog conditions prevailed. Data on patient diagnoses, local climatological conditions and levels of carbon monoxide, ozone and particulate matter were obtained over a 13-week period. Pollutant levels were measured daily and then averaged for each week of the study; absolute values were not reported. For each week, weighted simple linear regression (values not reported) and correlation analyses were performed. Significant correlations ($P = 0.01$) between pollution-related diseases and the environmental variables were found for particulate matter ($r = 0.79$), ozone ($r = ! 0.67$) and percentage of smoke and fog ($r = 0.79$), but not for carbon monoxide ($r = 0.43$) or percentage of cloud cover ($r = 0.33$). The lack of a significant correlation with carbon monoxide was explained by a small fraction (2%) of diagnoses for ischaemic heart disease compared with a predominance of respiratory tract diseases such as asthma, bronchitis, bronchiolitis and emphysema.

Daily lung function in a large community population exposed to indoor and outdoor air pollution was measured in Tucson, Arizona, USA, by Lebowitz and co-workers (Lebowitz et al., 1983a,b, 1984, 1985, 1987; Lebowitz, 1984; Robertson & Lebowitz, 1984). Subsets of both healthy subjects and subjects with asthma, allergies and airway obstructive disease were drawn from a symptom-stratified, geographic sample of 117 middle-class households. Symptoms, medication use and peak flow measurements were recorded daily over a 2-year period. Indoor/outdoor monitoring was conducted in a random sample of 41 representative houses. Maximum 1-h concentrations of ozone, carbon monoxide and nitrogen dioxide and daily levels of total suspended particulates, allergens and meteorological variables were monitored at central stations within 0.8 km of each population subset. Because gas stoves and tobacco smoking were the predominant indoor sources, indoor pollutant measurements were made for particles and carbon monoxide. Levels of carbon monoxide were low, averaging less than 2.7 mg/m$^3$ (2.4 ppm) indoors and 4.4–5.6 mg/m$^3$ (3.8–4.9 ppm) outdoors. Spectral time-series analysis was used to evaluate relationships
between environmental exposure and pulmonary effects over time (Robertson & Lebowitz, 1984; Lebowitz et al., 1987). Asthmatics were the most responsive, whereas healthy subjects showed no significant responses. Outdoor ozone, nitrogen dioxide, allergens, meteorology and indoor gas stoves were significantly related to symptoms and peak flow.

8.1.3 Cardiovascular and respiratory response to exercise

The most extensive human studies on the cardiorespiratory effects of carbon monoxide are those involving the measurement of oxygen uptake during exercise. Healthy young individuals were used in most of the studies evaluating the effects of carbon monoxide on exercise performance; healthy older individuals were used in only two studies (Raven et al., 1974a; Aronow & Cassidy, 1975). In all of these studies, oxygen uptake during submaximal exercise for short durations (5–60 min) was not affected by carboxyhaemoglobin levels as high as 15–20%. Under conditions of short-term maximal exercise, however, statistically significant decreases (3–23%) in maximal oxygen uptake ($\dot{V}O_{\text{max}}$) were found at carboxyhaemoglobin levels ranging from 5% to 20% (Pirnay et al., 1971; Ekbloom & Huot, 1972; Vogel & Gleser, 1972; Stewart et al., 1978; Weiser et al., 1978; Klein et al., 1980). In another study by Horvath et al. (1975), the critical level at which carboxyhaemoglobin marginally influenced $\dot{V}O_{\text{max}}$ ($P < 0.10$) was approximately 4.3%. The data obtained by Horvath’s group and others are summarized in Fig. 11. There is a linear relationship between decline in $\dot{V}O_{\text{max}}$ and increase in carboxyhaemoglobin that can be expressed as:

$$\% \text{ decrease in } \dot{V}O_{\text{max}} = 0.91 \times (\% \text{ COHb}) + 2.2 \text{ (US EPA, 1979b; Horvath, 1981).}$$

Short-term maximal exercise duration has also been shown to be reduced (3–38%) at carboxyhaemoglobin levels ranging from 2.3% to 7% (Ekbloom & Huot, 1972; Drinkwater et al., 1974; Raven et al., 1974a,b; Horvath et al., 1975; Weiser et al., 1978).

Numerous studies have demonstrated that an increase in carboxyhaemoglobin is associated with a compensatory increase in brain blood flow. Benignus et al. (1992) conducted two sets of studies on 14 and 12 young healthy men, respectively, measuring brain blood flow by the method of impedance plethysmography. In the first study, subjects were transiently exposed to various concentrations of carbon monoxide. In the second study, the exposure lasted 4 h. The exposures produced carboxyhaemoglobin levels up to 18.4%. The variation of
the brain blood flow response among subjects was large and statistically significant. The authors speculated that changes in carbon monoxide-induced brain blood flow might be related to behavioural effects.

The kinetics of carbon monoxide uptake during the transition phase from rest to exercise was investigated by Kinker et al. (1992). Data from six subjects who switched from rest to constant exercise (at various levels of peak $V_{O_2}$) while breathing carbon monoxide (63 mg/m$^3$ [55 ppm]) show that carbon monoxide uptake increased faster than oxygen uptake at all exercise levels. No significant changes in the diffusing capacity for carbon monoxide were found, suggesting that other factors such as changes in pulmonary blood flow and recruitment of alveoli–capillary surface area might be involved in carbon monoxide uptake.

The work rate-dependent effect of carbon monoxide on minute ventilation ($\dot{V}_E$) during exercise was studied by Koike et al. (1991). Ten healthy subjects were exposed to carbon monoxide to bring the carboxyhaemoglobin levels up to 11% and 20%, respectively. During incremental exercise, $\dot{V}_E$ was not affected by carbon monoxide
breathing at work rates below the lactic acidosis threshold. Above the lactic acidosis threshold, however, as the work load and carboxyhaemoglobin concentration increased, the $\dot{V}_E$ increased as well. The increase in $\dot{V}_E$ correlated positively with carboxyhaemoglobin levels ($r = 0.83$). Such an increase in exercise $\dot{V}_E$ due to carboxyhaemoglobin might restrict work rates above the lactic acidosis threshold and lead to greater lactic acidosis.

Potential effects of hypoxia on muscle deoxygenation during exercise were studied by Maehara et al. (1997). Seven healthy subjects exercised at two constant work loads under various conditions of hypoxic and carbon monoxide-induced hypoxia (15% carboxyhaemoglobin). They found that progressive muscle deoxygenation was accelerated at exercise levels above the lactic acidosis threshold.

It is well recognized that the same decrease in oxygen carrying capacity of blood due to carbon monoxide-induced hypoxia and anaemia will have different physiological effects. Celsing et al. (1987) found in a series of very carefully performed studies in normal subjects that $\dot{V}O_2$ max decreased by 19 ml/min per kilogram per gram per litre change in haemoglobin over a range of haemoglobin concentrations from 13.7 to 17.0 g/dl. This change represents a 2% decrease in $\dot{V}O_2$ max for every 3% decrease in haemoglobin concentration in a well-trained subject. The decrease also corresponds to the decrease in $\dot{V}O_2$ max reported by Ekblom & Huot (1972) and Horvath et al. (1975). However, Ekblom & Huot (1972) found a much more marked effect on maximal work time (i.e., work on a constant load until exhaustion with a duration of about 6 min). An explanation for the marked decrease in maximal work time could be that carbon monoxide has a negative effect on the oxidative enzymatic system, whereas the decrease in work time is due to a combination of a decrease in oxygen capacity and a less efficient oxidative enzymatic system. If the data are extrapolated to lower carboxyhaemoglobin values, a 3% level of carboxyhaemoglobin should decrease the maximal work time by about 20%. However, this decrease is more than the 10% average decrease reported by Klausen et al. (1983), who also found more marked effects in less well-trained subjects compared with well-trained subjects. Additional studies need to be performed to resolve the difference in the maximal work time values reported in these studies.
**8.1.4 Behavioural changes and work performance**

**8.1.4.1 Introduction**

Effects of carboxyhaemoglobin elevation above 20% on behaviour have been unambiguously demonstrated in humans. Below this level, results are less consistent. Based on meta-analysis of Benignus (1994), 18–25% carboxyhaemoglobin levels in healthy sedentary persons would be required to produce a 10% decrement in behaviour. Some of the differences among studies of the effect of carboxyhaemoglobin on the behaviour of humans are apparently due to technical problems in the execution of experiments, because single-blind or non-blind experiments tend to yield a much higher rate of significant effects than do double-blind studies. Even when non-double-blind experiments are eliminated from consideration, however, a substantial amount of disparity remains among results of studies. It is possible that such residual disagreement is due to the action of an unsuspected variable that is not being controlled across experiments. Because at present no data are available on the behavioural changes and work performance of individuals with chronically elevated carboxyhaemoglobin, the subsequent sections discuss only findings of acute studies.

**8.1.4.2 Sensory effects**

1) **Vision**

**Absolute threshold.** In an experiment using four well-trained young subjects, it was demonstrated that visual sensitivity was decreased in a dose-related manner by carboxyhaemoglobin levels of 4.5, 9.4, 15.8 and 19.7% (McFarland et al., 1944). Various aspects of these data were subsequently reported by Halperin et al. (1959) and McFarland (1970). Carboxyhaemoglobin elevations were accomplished by inhalation of boluses of high-concentration carbon monoxide. Visual thresholds were measured repeatedly over a 5-min period at each carboxyhaemoglobin level. Experimenters were not blind to the exposure conditions, and the subjects could have easily deduced the conditions from the experimental design, because no air-only condition was included to control for the effects of the testing scheme itself. Data from only one typical subject were presented. Thresholds were measured at only one level of dark adaptation (0.02 lx).
McFarland (1973), in a scantily documented article, reported that similar threshold shifts occurred at the end of a carbon monoxide exposure period (17% carboxyhaemoglobin) and an air-only session. Thus, it is possible that the effects reported by McFarland et al. (1944) were due to fatigue or some other time-on-task related variable. Von Restorff & Hebisch (1988) found no dark adaptation effects on subjects with carboxyhaemoglobin levels ranging from 9% to 17%. Luria & McKay (1979) found no effect of 9% carboxyhaemoglobin on scotopic visual threshold.

The effect of 17% carboxyhaemoglobin (bolus administration, followed by maintenance carbon monoxide level for 135 min) on the entire dark adaptation curve was studied by Hudnell & Benignus (1989) using 21 young men in a double-blind study. No difference between carbon monoxide and air groups was observed. A power of 0.7 was calculated for the test employed so that the conclusions are reasonably defensible. From the above evidence, it appears that effects on visual sensitivity have not been demonstrated at carboxyhaemoglobin levels up to 17%.

**Temporal resolution.** The temporal resolution of the visual system has been studied in the form of critical flicker frequency. In the critical flicker frequency paradigm, subjects report the frequency at which light flashes begin to appear as a continuous light.

Seppanen et al. (1977) reported dose-ordinal decreases of critical flicker frequency for carboxyhaemoglobin levels of approximately 4.0, 6.1, 8.4, 10.7 and 12.7%. The experiment was conducted with 22 healthy subjects whose ages ranged from 20 to 62 years. Carboxyhaemoglobin was induced by breathing high concentrations of carbon monoxide from a Douglas bag. Subjects were blind as to the condition, but apparently experimenters were informed. Appropriate controls for fatigue were included, and the exposure levels were randomized.

A study was reported by von Post-Lingen (1964) in which carboxyhaemoglobin levels ranging up to 23% were induced in 100 subjects by breathing carbon monoxide-contaminated air from a spirometer for about 7 min in a single-blind procedure. One group of subjects was given an injection of Evipan (sodium hexobarbitone; see Reynolds & Prasad, 1982), a drug previously shown to have produced decreases in critical flicker frequency only if patients had
demonstrable brain damage. In the non-drug group, critical flicker frequency was unaffected until approximately 14% carboxyhaemoglobin. In the drug group, however, effects began at carboxyhaemoglobin levels as low as 6% and were dose proportional up to the highest carboxyhaemoglobin value. When the drug-plus-carbon monoxide study was repeated in a double-blind replication \( n = 15 \), no effects were seen. The latter replication study was given only one paragraph in the report, and thus it is not clear exactly what was done.

Beard & Grandstaff (1970) reported significant effects on critical flicker frequency in an earlier study in which four subjects had been exposed to carbon monoxide levels of 57, 170 or 290 mg/m\(^3\) (50, 150 or 250 ppm) for 1 h. Carboxyhaemoglobin was estimated by the authors to have reached 3.0, 5.0 and 7.5%, respectively, by the end of the exposure. Documentation was extremely sparse, and, with only four subjects, power was probably low. Even though the elevated carboxyhaemoglobin groups had decreased critical flicker frequency, the results were not dose ordinal. There is a comparatively large amount of literature published before the Seppanen et al. (1977) article, in which the effect of elevated carboxyhaemoglobin on critical flicker frequency was tested. In none of the earlier studies was critical flicker frequency found to be affected, even though much higher levels of carboxyhaemoglobin were reached. The studies and their maximum carboxyhaemoglobin levels were Lilienthal & Fugitt (1946), 15.4%; Vollmer et al. (1946), 17.5%; Guest et al. (1970), 8.9%; O’Donnell et al. (1971a), 12.7%; Fodor & Winneke (1972), 7.5%; Ramsey (1973), 11.2%; and Winneke (1974), 10.0%. To be sure, there was much variation in size of the subject group, method and experimental design among the above studies, but no pattern emerges as to why the Seppanen et al. (1977), Beard & Grandstaff (1970) and von Post-Lingen (1964) studies found significant effects when the others did not. It is noteworthy that the studies reporting significant effects were all conducted in a single- or non-blind manner.

**Miscellaneous visual functions.** A number of researchers reported the results of experiments in which visual parameters other than absolute threshold or critical flicker frequency were measured as part of a battery of tests. Many of these experiments studied a large group of subjects.
Beard & Grandstaff (1970) reported a study in which four subjects were exposed to carbon monoxide sufficient to produce estimated (by the authors) carboxyhaemoglobin levels of 3.0, 5.0 and 7.5%. The measurements made were critical flicker frequency (see above), brightness difference thresholds, visual acuity and absolute threshold. Data for the latter variable were unreliable and were not reported. Dose-related impairments in acuity and brightness difference sensitivity were reported. The scant documentation of methods plus the low number of subjects make the results difficult to evaluate.

Five other reports of significant visual function effects by carboxyhaemoglobin elevation are extant. Two of the studies (Bender et al., 1972; Fodor & Winneke, 1972) reported that tachistoscopic pattern detection was impaired by carboxyhaemoglobin levels of 7.3% and 5.3%, respectively. Weir et al. (1973), Ramsey (1972) and Salvatore (1974) reported that brightness discrimination was adversely affected by carboxyhaemoglobin levels of 6–20%.

Tests of visual function after carboxyhaemoglobin elevation conducted by other authors have been uniformly non-significant. Especially noteworthy are studies by Hudnell & Benignus (1989) and Stewart et al. (1975), both of which found no acuity effects as reported by Beard & Grandstaff (1970). Brightness discrimination was similarly not found to be affected (Ramsey, 1973), in contradiction with the reports of others. The latter study is especially interesting in that it represents a failure to replicate an earlier study by the same author (Ramsey, 1972). The earlier study by Ramsey was conducted in a single-blind manner, whereas the later one was double-blind.

The most thorough tests of visual function were performed by Hudnell & Benignus (1989), who tested absolute threshold (see above), acuity and motion detection with carboxyhaemoglobin levels of 17% and found no effects due to carboxyhaemoglobin. The acuity and motion detection were tested at both scotopic and photopic levels.

It would appear that the results of studies on the effects of carboxyhaemoglobin elevation on miscellaneous visual function are not supportive of significant effects. Results that were significant in two studies (Beard & Grandstaff, 1970; Weir et al., 1973) were contradicted by other reports using relatively large groups of subjects under better controlled conditions.
2) Audition

Surprisingly little work has been done concerning the effects of carboxyhaemoglobin on auditory processes. Stewart et al. (1970) reported that the audiogram of subjects exposed to carbon monoxide resulting in up to 12.0% carboxyhaemoglobin was not affected. Haider et al. (1976) exposed subjects to a 105-dB, one-octave bandwidth random noise (centre frequency of 2 kHz) for 15 min while carboxyhaemoglobin level was elevated to 13%. Under continued carboxyhaemoglobin elevation, the temporary threshold shifts were measured after noise cessation. No effects of carboxyhaemoglobin on temporary threshold shift were observed. Guest et al. (1970) tested the effects of elevated carboxyhaemoglobin (8.9%) on auditory flutter fusion and found no significant effect. The flutter fusion test is analogous to critical flicker frequency in vision and was tested by having the subject judge the rate at which an interrupted white noise became apparently continuous. From these data, it would appear that the functioning of the auditory system is not particularly sensitive to carboxyhaemoglobin elevation, but little research has been done.

8.1.4.3 Motor and sensorimotor performance

1) Fine motor skills

In a single-blind study, Bender et al. (1972) found that manual dexterity and precision (Purdue pegboard) were impaired by 7% carboxyhaemoglobin. Winneke (1974) reported that hand steadiness was affected by 10% carboxyhaemoglobin, but no supportive statistical test was presented.

Similar motor functions were evaluated by a number of other investigators and were found not to be affected, even at higher carboxyhaemoglobin levels. Vollmer et al. (1946) reported that 20% carboxyhaemoglobin did not affect postural stability. O’Donnell et al. (1971b) used the Pensacola Ataxia Battery to measure various aspects of locomotion and postural stability. Subjects with 6.6% carboxyhaemoglobin were not affected. Stewart et al. (1970, 1975) tested the ability of subjects to manipulate small parts using the Crawford collar and pin test and screw test, the American Automobile Association hand steadiness test and the Flanagan coordination test. Carboxyhaemoglobin levels up to 15% had no effect on any of the measures. Two subjects were taken to 33% and 40% carboxyhaemoglobin,
however; in these subjects, the collar and pin performance was impaired and the subjects reported hand fatigue. Manual dexterity (Purdue pegboard), rapid precision movement (Purdue hand precision) and static hand steadiness (pen in hole) and tapping tests were not affected by carboxyhaemoglobin levels of approximately 5.3% (Fodor & Winneke, 1972). Wright et al. (1973) reported that hand steadiness was not affected by carboxyhaemoglobin levels of 5.6%. Weir et al. (1973) found no effects of 14% carboxyhaemoglobin on tapping, star tracing and rail walking. Mihevic et al. (1983) discovered no effect on tapping when the task was performed alone or simultaneously with an arithmetic task. Finally, Seppanen et al. (1977) demonstrated that tapping speed was unaffected by 12.7% carboxyhaemoglobin. Most of the above non-significant studies used a moderate to large number of subjects. The overwhelming evidence in the area of fine motor control indicates that carboxyhaemoglobin levels below approximately 20% (the highest level tested) do not produce effects.

2) Reaction time

Of the 12 different experiments that studied reaction time, only 1 reported a significant result (Weir et al., 1973), and that effect occurred only at 20% carboxyhaemoglobin. A number of the non-significant effects were from studies using a large number of subjects. The consistent finding that carboxyhaemoglobin elevation does not affect reaction time is especially impressive because of the wide range of carboxyhaemoglobin levels employed (5.0–41.0%).

3) Tracking

Tracking is a special form of fine motor behaviour and hand–eye coordination that requires a subject to either follow a moving target or compensate for a moving target’s motion by manipulation of a lever, for example. Of the 11 studies on the topic, 4 reported significant effects, and 1 of those found effects only at 20% carboxyhaemoglobin. The matter is more complicated, however, and the literature in the area offers some clues to the reasons for the diversity among the reports.

O’Donnell et al. (1971a,b) used critical instability compensatory tracking in which the task was to keep a meter needle centred. Simultaneous performance of detection tasks was also required in one of the studies. No effects were demonstrated for carboxyhaemoglobin levels as high as 12–13%. The critical instability tracking task was
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also used by Gliner et al. (1983) in conjunction with peripheral light
detection. Carboxyhaemoglobin levels up to 5.8% had no effect on
performance. Pursuit rotor tracking was also reported to be unaffected
at 5.3% carboxyhaemoglobin (Fodor & Winneke, 1972). Weir et al.
(1973) reported that pursuit rotor performance was slightly affected
beginning at 20% carboxyhaemoglobin. In a 1988 study, Bunnell &
Horvath used a two-dimensional tracking task in which the stimulus
was presented on a cathode ray tube and was controlled with a
joystick. No effect of carboxyhaemoglobin or exercise or a combina-
tion of the two was seen for carboxyhaemoglobin levels up to 10.2%.
Schaad et al. (1983) reported that pursuit and compensatory tracking
were not affected by a carboxyhaemoglobin level of 20% even during
simultaneous performance of monitoring tasks.

In a pair of careful studies of different design, Putz et al. (1976,
1979) studied compensatory tracking by having the subject try to keep
a vertically moving spot in the centre of an oscilloscope screen. The
tracking was performed while the subject also did a light brightness
detection task. In both studies, tracking was significantly affected by
carboxyhaemoglobin levels of 5%. The fact that both studies demon-
strated significant results despite differences in experimental design
lends credibility to the finding. Additional credibility was gained
when the Putz et al. (1976) study was replicated with similar results
by Benignus et al. (1987).

The consistency of the compensatory tracking results in the Putz
et al. (1976) protocol was not continued when Benignus et al. (1990a)
tried to demonstrate a dose–effect relationship using the same
experimental design. In the latter study, independent groups were
exposed to carbon monoxide sufficient to produce carboxyhaemoglo-
bin levels of control, 5, 12 and 17%. Carbon monoxide was
administered via Douglas bag breathing, and then carboxyhaemoglo-
in was maintained by low-level carbon monoxide in room air. A
fifth group was exposed to carbon monoxide in the chamber only, and
this group served as a positive control because it was treated in exactly
the same ways as the subjects in Putz et al. (1976) and in Benignus
et al. (1987). No significant effects on tracking were demonstrated in
any group. The means for the tracking error were elevated in a nearly
dose-ordinal manner, but not to a statistically significant extent.
At present, there is no apparent reason for the lack of consistency among the reports of tracking performance. The largest study with the widest dose range (Benignus et al., 1990a) appears to be the strongest indicator of no significant effects of carboxyhaemoglobin elevation. However, it is difficult to ignore the several other studies that were well controlled and did demonstrate significant effects. At this point, the best summary seems to be that carboxyhaemoglobin elevation produces small decrements in tracking that are sometimes significant. The possible reasons for such high variability are unclear.

8.1.4.4 Vigilance

A dependent variable that is possibly affected by elevated carboxyhaemoglobin is the performance of extended, low-demand tasks characterized as vigilance tasks. Because of the low-demand characteristic of vigilance tasks, they are usually of a single-task type. Of the eight reports, four reported significant effects. Despite the seemingly greater unanimity in this area, it is noteworthy that for each report of significant effects, there exists a failed attempt at direct replication.

Horvath et al. (1971) reported a significant vigilance effect at 6.6% carboxyhaemoglobin. A second study, conducted in the same laboratory (Christensen et al., 1977), failed to find significant effects of 4.8% carboxyhaemoglobin on the same task. To be sure, the second study used slightly lower carboxyhaemoglobin levels, but the means left no suggestion of an effect. Roche et al. (1981) from the same laboratory reported that performance of the same task after a bolus exposure was used to produce 5% carboxyhaemoglobin was not affected.

Fodor & Winneke (1972) reported a study in which 5.3% carboxyhaemoglobin significantly impaired performance of a vigilance task. When the same task and protocol were tried again in the same laboratory (Winneke, 1974), no significant effects were found, even for carboxyhaemoglobin levels up to 10%.

Groll-Knapp et al. (1972) reported dose-related significant effects of carboxyhaemoglobin levels ranging from estimated values of 3% to 7.6%. Effects were large, but apparently the study was not blind. Haider et al. (1976) reported similar effects at low carboxyhaemoglobin levels, but not at higher levels. The authors have
twice mentioned failures to replicate the results (Haider et al., 1976; Groll-Knapp et al., 1978). A similar experiment using a different stimulus failed to produce significant effects at 12% carboxyhaemoglobin (Groll-Knapp et al., 1978).

The fact that all replication attempts for each of the reported significant effects of carboxyhaemoglobin on vigilance have failed to verify the original reports is evidence for some unreliability or the operation of unknown and uncontrolled variables. That the non-verifications were conducted by the original researchers, as well as by others, makes the case for unreliability even more convincing. If vigilance is affected by carboxyhaemoglobin elevation, a convincing demonstration remains to be made. Perhaps a case can be made that behavioural effects of carboxyhaemoglobin levels below 20% are present in the exposed population, but they are probably small and, therefore, difficult to demonstrate reliably (Benignus et al., 1990b).

8.1.4.5 Miscellaneous measures of performance

1) Continuous performance

Continuous performance is a category of behaviour that is related to vigilance. The difference is that many tasks that are performed over a long period of time are more demanding and involve more than simple vigilance. Sometimes the continuous performance tasks are not performed for a sufficiently long period of time to involve decrements in vigilance or are interrupted too frequently.

Putz et al. (1976, 1979) reported that monitoring performed simultaneously with tracking was impaired at carboxyhaemoglobin levels as low as 5%. In a replication attempt of the Putz et al. (1976, 1979) studies, Benignus et al. (1987) failed to find any effects of approximately 8% carboxyhaemoglobin. O’Donnell et al. (1971a) also failed to find effects of carboxyhaemoglobin on a monitoring task performed simultaneously with tracking. Schaad et al. (1983) found no effects on monitoring performed simultaneously with tracking even when carboxyhaemoglobin was 20%. Gliner et al. (1983) reported that signal detection was affected by 5.8% carboxyhaemoglobin when performed singly, but not when performed simultaneously with tracking. The latter results are in conflict with those of Putz et al. (1976, 1979).
Insogna & Warren (1984) reported that the total game score on the performance of a multitask video game was reduced by carboxyhaemoglobin levels of 4.2%. Separate task scores were not collected. Schulte (1963) reported that letter, word and colour detection tasks were dose-ordinally impaired by carboxyhaemoglobin levels as low as 5% and ranging up to 20%. Reported carboxyhaemoglobin levels were at considerable variance with values expected from the exposure parameters (Laties & Merigan, 1979). Benignus et al. (1977) reported that 8.2% carboxyhaemoglobin did not affect a numeric monitoring task.

Again, there is disturbing lack of replicability in the literature. The two most credible studies showing effects of carboxyhaemoglobin on continuous performance (Putz et al., 1976, 1979) were not verified by Benignus et al. (1987). In the latter study, the tracking effects of the Putz et al. (1976, 1979) work were verified. Similar studies of monitoring during tracking (O’Donnell et al., 1971a; Gliner et al., 1983; Schaad et al., 1983) also reported no effects of carboxyhaemoglobin, even with levels as high as 20%. It seems necessary to suspend judgement regarding the continuous performance results until further data and understanding are available. Perhaps the best judgement is to hypothesize small effects.

2) Time estimation

In 1967, Beard & Wertheim reported that carboxyhaemoglobin produced a dose-related decrement in single-task time estimation accuracy beginning at 2.7%. Various versions of the same task were tested by others with carboxyhaemoglobin levels ranging up to 20% without effects being demonstrated (Stewart et al., 1970, 1973b, 1975; O’Donnell et al., 1971b; Weir et al., 1973; Wright & Shephard, 1978b). An exact replication, which also did not find significant results, was conducted by Otto et al. (1979). It seems safe to assume that time estimation is remarkably impervious to elevated carboxyhaemoglobin.

3) Cognitive effects

Five of the 11 experiments discussed below that have been reported in the literature found cognitive effects of carboxyhaemoglobin. Bender et al. (1972) reported effects of 7.3% carboxyhaemoglobin on a variety of tasks. Groll-Knapp et al. (1978) reported
memory to be affected after exposure to carbon monoxide during sleep (11% carboxyhaemoglobin), but a very similar study performed by the same group later found no effects of 10% carboxyhaemoglobin (Groll-Knapp et al., 1982). Arithmetic performance was affected slightly in a non-dose-ordinal manner when a simultaneous tapping task was performed (Mihevic et al., 1983). Schulte (1963) reported a dose-ordinal effect on arithmetic performance beginning at 5% and ranging to 20% carboxyhaemoglobin. Carboxyhaemoglobin levels in the latter study were considerably different from values expected from the exposure parameters (Laties & Merigan, 1979). Similar variables were tested by others, sometimes at higher levels of carboxyhaemoglobin and with relatively large groups of subjects, without finding effects (O’Donnell et al., 1971a; Stewart et al., 1975; Haider et al., 1976; Groll-Knapp et al., 1978; Schaad et al., 1983). The conclusions are, at best, equivocal.

A study by Bunnell & Horvath (1988) utilized a wide range of cognitive tasks involving short-term memory, Manikin rotation, Stroop word-colour tests, visual search and arithmetic problems (the latter as part of a divided attention task performed simultaneously with tracking). Carboxyhaemoglobin was formed by bag breathing followed by a carbon monoxide level in room air designed to maintain a constant carboxyhaemoglobin level. Subjects were exercised at 0.35 or 60% of \( \dot{V}_{O_2} \max \) before cognitive tests were performed. The Stroop test performance was slightly but significantly decreased by both 7% and 10% carboxyhaemoglobin by the same amount, but exercise had no effect. The authors suggested that negative transfer effects (difficulty in reversing instructional sets) were responsible for the decrement. Visual searching improved for carboxyhaemoglobin levels both at rest and at medium exercise. At the high exercise level, however, carboxyhaemoglobin produced dose-ordinal impairments in performance. The authors conjectured that hypoxic depression of cortical function interacted with hypoxic stress and exercise stress to produce the effects.

Most of the data on cognitive effects of carboxyhaemoglobin elevation are not sufficiently consistent to consider. The study by Bunnell & Horvath (1988), however, is suggestive of potentially important effects of interactions of carboxyhaemoglobin and exercise. Before any conclusions may be drawn about the results, the study should be replicated and expanded.
8.1.4.6 Automobile driving

Complex behaviour, in the form of automobile driving, has been tested a number of times for effects of carboxyhaemoglobin elevation. Not only is automobile driving potentially more sensitive to disruption because of its complexity, but it is also an inherently interesting variable because of its direct applicability to non-laboratory situations. The well-practised nature of the behaviour, on the other hand, may make performances more resistant to disruption. The complexity of the behaviour also leads to methodological difficulties. Attempting to exhaustively measure the complex behaviours usually leads investigators to measure many dependent variables. Statistically analysing a large number of variables in a defensible way requires many subjects and leads to greater expense.

In an early study by Forbes et al. (1937), using only five subjects, steering accuracy in a simulator was investigated with carboxyhaemoglobin levels of up to 27.8%. No effects were demonstrated. A sparsely documented experiment by Wright et al. (1973), using 50 subjects with 5.6% carboxyhaemoglobin, tested a number of functions of simulator performance but found no effects. Weir et al. (1973) performed an experiment with actual automobile driving on a highway in which many variables were measured and tested. None of the variables was reliably affected until carboxyhaemoglobin exceeded approximately 20%. Wright & Shephard (1978a) failed to find effects of 7% carboxyhaemoglobin on driving (although they reported effects, they had misapplied the chi-square test). The only effect on driving at a lower carboxyhaemoglobin level (7.6%) was reported by Rummo & Sarlanis (1974), who found that the ability to follow another car at a fixed distance was impaired.

The difference between the experiments of Rummo & Sarlanis (1974) and Weir et al. (1973) is troubling. Both measured following distance, but only the experiment employing the lower-level carboxyhaemoglobin found effects. If automobile driving is affected by carboxyhaemoglobin elevation, it remains to be demonstrated in a conclusive manner.

8.1.4.7 Brain electrical activity

Electrical activity of the brain (see review by Benignus, 1984) offers the possibility of testing the effects of carboxyhaemoglobin
without the problem of selecting the most sensitive behavioural dependent variable. It is less dependent upon subject cooperation and effort and may be a more general screening method. The major disadvantage of the measures is the lack of functional interpretability. The area has been plagued with poor quantification and, frequently, a lack of statistical significance testing.

The electroencephalogram is a recording of the continuous voltage fluctuations emitted by the intact brain. The slow-evoked potential originally called the contingent negative variation is computed by averaging over trials and was linked to (among other things) cognitive processes or expectancy (Donchin et al., 1977). The evoked potential is the electrical activity in the brain resulting from sensory stimulation, either auditory or visual. The electroencephalogram, contingent negative variation and evoked potentials have been studied with carboxyhaemoglobin elevation.

Groll-Knapp et al. (1972) reported that the contingent negative variation was decreased in amplitude in a dose-related manner for carboxyhaemoglobin levels ranging from 3% to 7.6%. In a second study, Groll-Knapp et al. (1978) again reported that contingent negative variation amplitude was reduced by 12% carboxyhaemoglobin when subjects missed a signal in a vigilance task. More evidence is required before the functional significance of such an effect can be deduced, but it is a potentially important finding.

Clinical electroencephalograms were analysed by visual inspection by Stewart et al. (1970, 1973a) and Hosko (1970) after exposure to sufficient carbon monoxide to produce carboxyhaemoglobin levels ranging up to 33%. No effects were noticed. Groll-Knapp et al. (1978) reported similar results using spectrum analysis on electroencephalograms from subjects with 12% carboxyhaemoglobin. Haider et al. (1976) reported slight changes in the electroencephalogram spectrum for carboxyhaemoglobin levels of 13%, but no tests of significance were conducted. In view of the above studies, it seems reasonable to assume that no electroencephalogram effects of carboxyhaemoglobin levels below at least 10% should be expected.

O’Donnell et al. (1971b) reported that sleep stages (as determined from the electroencephalogram) were not distributed by carboxyhaemoglobin levels up to 12.4%. Groll-Knapp et al. (1978)
and Haider et al. (1976), however, both reported distributed sleep stages at similar carboxyhaemoglobin levels using electroencephalogram spectra. Groll-Knapp et al. (1982) repeated their earlier study and found essentially the same effects.

The visual evoked potential was not affected consistently by carboxyhaemoglobin elevation below approximately 22%, and usually the lowest level for effects was higher. At higher levels, the effects were dose related (Hosko, 1970; Stewart et al., 1970).

Groll-Knapp et al. (1978) found no effect of carboxyhaemoglobin (8.6%) on click auditory evoked potentials during waking but reported increased positive peak amplitudes when subjects were tested during sleep at approximately 11% carboxyhaemoglobin. The finding was verified by Groll-Knapp et al. (1982). The fact that the data were collected during sleep is potentially important.

Putz et al. (1976) conducted a double-blind study in which 30 persons were exposed to 80 mg carbon monoxide/m³ (70 ppm) for 240 min (5% carboxyhaemoglobin at the end of the session). Among other variables, the auditory evoked potential was measured. The peak-to-peak amplitude of the N₁–P₁ components was increased in a dose-ordinal manner beginning at approximately 3% carboxyhaemoglobin.

Many of the brain electrical activity measures seem to be altered by carboxyhaemoglobin elevation. The functional significance of these changes is not clear. Sometimes an alteration is not an indication of a deleterious effect but merely implies some change in processing. When induced by low levels of carboxyhaemoglobin, however, any change should be viewed as potentially serious.

8.1.5 Adaptation

This section considers whether or not exposure to carbon monoxide will eventually lead to the development of physiological responses that tend to offset some of the deleterious effects. Although there is possibly a temporal continuum in such processes, the term “adaptation” will be used in this review to refer to long-term phenomena, and the term “habituation” will refer to short-term processes. The term “compensatory mechanism” will be used to refer to those
physiological responses that tend to ameliorate deleterious effects, whether in the long-term or short-term case.

### 8.1.5.1 Short-term habituation

Arguments have been made for the possibility that there exist short-term compensatory mechanisms for carbon monoxide exposure. These hypothetical mechanisms have been based upon physiological evidence and have been used to account for certain behavioural findings reported in the literature.

There is physiological evidence for responses that would compensate for the deleterious effects of carbon monoxide in a very short time span. As discussed, carbon monoxide has been demonstrated to produce an increased cerebral blood flow, which is apparently produced by cerebrovascular vasodilation. It has also been shown (Zorn, 1972; Miller and Wood, 1974; Doblar et al., 1977; Traystman, 1978), however, that the tissue $P_{O_2}$ values for various central nervous system sites fall in proportion to carboxyhaemoglobin, despite the increased blood flow. Apparently, the $P_{O_2}$ values would fall considerably more without the increased blood flow. It appears that tissue $P_{O_2}$ falls immediately and continuously as carboxyhaemoglobin rises.

### 8.1.5.2 Long-term adaptation

Adaptation is an all-inclusive term that incorporates all of the acute or chronic adjustments of an organism to a stressor. It does not indicate (or predict) whether the adjustments are initially or eventually beneficial or detrimental. Acclimatization is an adaptive process that results in reduction of the physiological strain produced by exposure to a stressor. Generally, the main effect of repeated, constant exposure to the stressor is considered to result in an improvement of performance or a reduced physiological cost. Both of these phenomena tend to exploit the reserve potential of the organism.

Whether or not adaptation can occur in individuals chronically exposed to various ambient concentrations of carbon monoxide remains unresolved. Concern for carbon monoxide intoxication in England and Scandinavia led to the speculation that adaptational adjustments could occur in humans (Killick, 1940; Grut, 1949). These concerns were directed to situations where high ambient carbon
monoxide concentrations were present. There are only a few available studies conducted in humans.

Killick (1940), using herself as a subject, reported that she developed acclimatization as evidenced by diminished symptoms, slower heart rate and the attainment of a lower carboxyhaemoglobin equilibrium level following exposure to a given inspired carbon monoxide concentration. Interestingly, Haldane & Priestley (1935) had already reported a similar finding as to the attainment of a different carboxyhaemoglobin equilibrium following exposure to a fixed level of carbon monoxide in the ambient air.

Killick (1948) repeated her carbon monoxide exposure studies in an attempt to obtain more precise estimations of the acclimatization effects she had noted previously. The degree of acclimatization was indicated by (1) a diminution in severity of symptoms during successive exposure to the same concentrations of carbon monoxide and (2) a lower carboxyhaemoglobin level after acclimatization than that obtained prior to acclimatization during exposure to the same concentrations of inhaled carbon monoxide.

8.1.6 Carbon monoxide interactions with drugs

There is little direct information on the possible enhancement of carbon monoxide toxicity by concomitant drug use or abuse; however, there are some data suggesting cause for concern. There is evidence that interactions of drug effects with carbon monoxide exposure can occur in both directions; that is, carbon monoxide toxicity may be enhanced by drug use, and the toxic or other effects of drugs may be altered by carbon monoxide exposure.

The effects of combined carbon monoxide exposure and alcohol (ethanol) administration have been the most extensively studied interaction. A study from the Medical College of Wisconsin (1974) found no effects of alcohol doses resulting in blood alcohol levels of about 0.05% and carboxyhaemoglobin levels in the general range of 8–9%, either alone or in combination, on a number of psychomotor behavioural tasks. The lack of sensitivity of these measures to alcohol doses known to affect performance under many other conditions, as well as other problems in the study design, raises the question of the adequacy of this study to detect interactive effects. Rockwell & Weir (1975) studied the interaction of carbon monoxide exposures resulting
in nominal 0, 2, 8 and 12% carboxyhaemoglobin levels with alcohol doses resulting in nominal 0.05% blood alcohol levels for effects on actual driving and driving-related performances in young, non-smoking college students. Dose-related effects of carbon monoxide for perceptual narrowing and decreased eye movement were observed. In addition, effects were observed on some measures by this dose of alcohol alone. An effect-addition model was used to evaluate the alcohol–carbon monoxide interaction. In combination, the effects of carbon monoxide and alcohol were often additive, and there was a supra-additive alcohol–carbon monoxide interaction at 12% carboxyhaemoglobin levels. In a retrospective human study, King (1983) noted that the lethal carbon monoxide level was higher in the presence of ethanol, suggesting that alcohol ingestion prior to carbon monoxide exposure may provide some protection.

Because of a concern that persons exposed to carbon monoxide may not be able to detect odours that would indicate a fire or other hazardous condition, especially when consuming alcohol, Engen (1986) conducted a carefully controlled study of combined carbon monoxide–alcohol exposure in human subject volunteers. The detection of a threshold concentration of the smoky odour of quaiacol was evaluated using signal detection analysis. Although not statistically significant, there was a tendency for both alcohol and carbon monoxide to improve odour detection compared with air only. When alcohol and carbon monoxide were combined, the odour detection was significantly poorer than after either treatment alone, but it was not significantly poorer than the air control.

8.1.7 Combined exposure to carbon monoxide and other air pollutants and environmental factors

In this section, human effects associated with combined exposure to carbon monoxide and other air pollutants and environmental factors are reviewed. Although a number of studies in the literature have tested exposure to combined pollutants, fewer studies have actually been designed to test specifically for interactions between carbon monoxide and the other exposure components. Therefore, this section emphasizes only those studies providing a combined treatment group where pollutant exposure levels are reported.
8.1.7.1 Exposure to other pollutants in ambient air

Photochemical air pollution is usually associated with two or more pollutants, consisting mainly of carbon monoxide, sulfur oxides, ozone, nitrogen oxides, peroxyacyl nitrates and organic peroxides. The gaseous compounds that constitute tobacco smoke are carbon monoxide, hydrogen cyanide and nitric oxide. As urban living, industrial employment and cigarette smoking bring humans into direct contact with carbon monoxide and other pollutants, it seems appropriate to determine if combined exposure to these pollutants has detrimental health effects.

Several studies have been conducted to determine the effects resulting from combined exposure to carbon monoxide and other pollutants. A study by DeLucia et al. (1983) in adults exposed to carbon monoxide plus ozone during exercise showed no synergistic effects on blood carboxyhaemoglobin levels or pulmonary or cardio-respiratory thresholds. Similarly, simultaneous exposure to carbon monoxide plus ozone plus nitrogen dioxide for 2 h produced no consistent changes (synergistic or additive) in pulmonary function indices and physiological parameters in young male subjects (Hackney et al., 1975a,b).

Combined exposure to carbon monoxide and peroxyacyl nitrates exerted no greater effect on the work capacity of healthy men (young and middle-aged smokers and non-smokers) than did exposure to carbon monoxide alone. Increases in blood carboxyhaemoglobin levels of smokers during the carbon monoxide or carbon monoxide plus peroxyacyl nitrate exposures were observed (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975).

Halogenated hydrocarbons, such as the dihalomethanes (e.g., methylene bromide, methylene iodide and methylene chloride), are widely used as organic solvents. These chemicals are metabolized in the body to produce carbon monoxide, which is readily bound to haemoglobin. Therefore, any additional exposure to carbon monoxide, producing higher carboxyhaemoglobin levels, could possibly cause greater health effects. For example, up to 80% of inhaled methylene chloride will be metabolized to carbon monoxide. Inhalation of 1800–3500 mg/m³ (500–1000 ppm), therefore, would result in carboxyhaemoglobin levels of over 14%. Not only can this elevation in carboxyhaemoglobin have a significant effect when combined with
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carbon monoxide exposure, but the carbon monoxide resulting from metabolism generally requires a longer time to dissipate (Kurppa, 1984).

8.1.7.2 Exposure to other environmental factors

1) Environmental heat

Several of the studies (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975) describing the effects of carbon monoxide exposure alone and carbon monoxide combined with peroxyacyl nitrates on exercise performance in healthy adult men also evaluated the effects of heat stress. Subjects were exposed to 57 mg carbon monoxide/m$^3$ (50 ppm) and/or 0.27 ppm peroxyacyl nitrates in environmental exposure chamber conditions of 30% relative humidity at 25 and 30 °C. In these studies, oxygen uptake and exercise duration were assessed during both maximal and submaximal exercise. Heat stress was more effective in reducing maximal exercise performance than exposure to the polluted environments. The combination of heat stress with carbon monoxide exposure was found to be important, however, in producing symptom complaints during submaximal exercise at 35 °C that were not found at 25 °C. Further work in the same laboratory (Bunnell & Horvath, 1989) also demonstrated that subjects experienced significant levels of symptoms, particularly exertion symptoms, associated with elevated carboxyhaemoglobin when exercising in the heat. These studies suggest, therefore, that heat stress may be an important determinant of changes in exercise performance when combined with exposure to carbon monoxide.

2) Environmental noise

An early epidemiological study by Lumio (1948) of operators of carbon monoxide-fuelled vehicles found significantly greater permanent hearing loss than expected after controlling for possible confounding factors. More recently, Sulkowski & Bojarski (1988) studied age-matched workers with similar length of duty employed in foundry, cast iron and cast steel positions where carbon monoxide and noise exposure varied. The group exposed to the combined effects of 95-dB noise and a mean concentration of 47 mg carbon monoxide/m$^3$ (41 ppm) did not experience any greater hearing loss than the groups exposed only to noise (96 dB) or carbon monoxide (52 mg/m$^3$ [45 ppm]). In fact, a permanent threshold shift was significantly
larger in workers exposed to noise alone than in those exposed to the combined influence of carbon monoxide and noise.

8.1.8 Exposure to tobacco smoke

8.1.8.1 Environmental tobacco smoke

A common source of carbon monoxide for the general population is tobacco smoke. Exposure to tobacco smoke not only affects the carboxyhaemoglobin level of the smoker, but, under some circumstances, can also affect non-smokers. For example, acute exposure (1–2 h) to smoke-polluted environments has been reported to cause an incremental increase in non-smokers’ carboxyhaemoglobin of about 1% (Jarvis, 1987).

The carbon monoxide concentration in tobacco smoke is approximately 4.5% (52 000 mg/m$^3$ [45 000 ppm]). A smoker may be exposed to 460–570 mg carbon monoxide/m$^3$ (400–500 ppm) for the approximately 6 min that it takes to smoke a typical cigarette, producing an average baseline carboxyhaemoglobin of 4%, with a typical range of 3–8%. Heavy smokers can have carboxyhaemoglobin levels as high as 15%. In comparison, non-smokers average about 1% carboxyhaemoglobin in their blood. As a result of their higher baseline carboxyhaemoglobin levels, smokers may actually be excreting more carbon monoxide into the air than they are inhaling from the ambient environment. Smokers may even show an adaptive response to the elevated carboxyhaemoglobin levels, as evidenced by increased red blood cell volumes or reduced plasma volumes (Smith & Landaw, 1978a,b).

In addition to being a source of carbon monoxide for smokers as well as for non-smokers, tobacco smoke is also a source of other chemicals with which environmental carbon monoxide could interact. Available data strongly suggest that acute and chronic carbon monoxide exposure attributed to tobacco smoke can affect the cardiopulmonary system, but the potential interaction of carbon monoxide with other products of tobacco smoke confounds the results. In addition, it is not clear if incremental increases in carboxyhaemoglobin caused by environmental exposure would actually be additive to chronically elevated carboxyhaemoglobin levels due to tobacco smoke, because some physiological adaptation may take place.
8.1.8.2 Mainstream tobacco smoke

Acute effects of cigarette smoke on maximal exercise performance appear to be similar to those described in subjects exposed to carbon monoxide. Hirsch et al. (1985) studied the acute effect of smoking on cardiorespiratory function during exercise in nine healthy male subjects who were current smokers. They were tested twice — once after smoking three cigarettes per hour for 5 h and once after not having smoked. The exercise tests were done on a bicycle ergometer with analysis of gas exchange and intra-arterial blood gases and pressures. On the smoking day, $\text{VO}_2\text{max}$ was significantly decreased by 4%, and the anaerobic threshold was decreased by 14%. The rate–blood pressure product was a significant 12% higher at comparable work loads of 100 W on the smoking day than on the non-smoking day. There were no changes due to smoking, however, on the duration of exercise or on the mean work rate during maximal exercise testing. The blood carboxyhaemoglobin level before exercise was 1.8% on the non-smoking day and 6.6% on the smoking day. At peak exercise, the carboxyhaemoglobin was 0.9% and 4.8% on the non-smoking and smoking day, respectively. The authors concluded that the main adverse effect of smoking was due to carbon monoxide, although the increase in rate–blood pressure product also might be the result of the simultaneous inhalation of nicotine. They felt that the magnitude of change in performance indicators corresponded well with earlier reports.

It would be interesting, therefore, to determine if smokers and non-smokers had different responses to carbon monoxide exposure. Unfortunately, smokers and non-smokers were not always identified in many of the studies on exercise performance, making it difficult to interpret the available data. Information derived from studies on cigarette smoke is also sparse. As a result, attempts to sort out the acute effects of carbon monoxide from those due to other components of cigarette smoke have been equivocal. Seppanen (1977) reported that the physical work capacities of cigarette smokers decreased at 9.1% carboxyhaemoglobin levels after either breathing boluses of 1300 mg carbon monoxide/m³ (1100 ppm) or smoking cigarettes. The greatest decrease in maximal work, however, was observed after carbon monoxide inhalation.
Klausen et al. (1983) compared the acute effects of cigarette smoking and inhalation of carbon monoxide on maximal exercise performance. They studied 16 male smokers under three different conditions: after 8 h without smoking (control), after inhalation of the smoke of three cigarettes and after carbon monoxide inhalation. Just before maximal exercise testing, the arterial carboxyhaemoglobin level reached 4.51% and 5.26% after cigarette smoke and carbon monoxide inhalation, respectively, compared with 1.51% for controls. Average $\dot{V_{o2}}$ max decreased by about 7% with both smoke and carbon monoxide. Exercise time, however, decreased 20% with smoke but only 10% with carbon monoxide, suggesting that nicotine, smoke particles or other components of tobacco smoke may contribute to the observed effects. The authors therefore concluded that a specified carboxyhaemoglobin level induced by either smoke or carbon monoxide decreased maximal work performance to the same degree. Of note is the more marked decrease in work time compared with $\dot{V_{o2}}$ max induced by carbon monoxide, a finding that agrees with the Ekblom & Huot (1972) results.

### 8.2 High-risk groups

#### 8.2.1 Effects in individuals with heart disease

Aronow et al. (1972) and Aronow & Isbell (1973) demonstrated that patients with angina pectoris, when exposed to low levels of carbon monoxide (2.5–3% carboxyhaemoglobin), experienced reduced time to onset of exercise-induced chest pain as a result of insufficient oxygen supply to the heart muscle. A study by Anderson et al. (1973) reported similar results at mean carboxyhaemoglobin levels of 2.9% and 4.5%.

In 1981, Aronow reported an effect of 2% carboxyhaemoglobin on time to onset of angina in 15 patients. The protocol was similar to that used in previously reported studies, with patients exercising until onset of angina. Only 8 of the 15 subjects developed 1 mm or greater ischaemic ST-segment depression at the onset of angina during the control periods. This was not significantly affected by carbon monoxide. One millimetre or greater ST-segment depression is the commonly accepted criterion for exercise-induced ischaemia. It is questionable, therefore, as to whether the remaining patients truly met adequate criteria for ischaemia despite angiographically documented
cardiac disease. After breathing 57 mg carbon monoxide/m³ (50 ppm) for 1 h, the patients’ times to onset of angina significantly decreased from a mean of 321.7 ± 96 s to a mean of 289.2 ± 88 s.

The cardiovascular studies by Aronow et al. were severely criticized because the subjective measure of symptoms (angina) was affected by lack of adequate double-blind experimental conditions. There was also a lack of significant objective findings.

In an attempt to improve upon these earlier preliminary studies, the more recent studies placed greater emphasis on electrocardiogram changes as objective measures of ischaemia. Another consideration in the conduct of the newer studies on angina was to better establish the dose–response relationships for low levels of carbon monoxide exposure. Although carboxyhaemoglobin level is accepted as the best measure of the effective dose of carbon monoxide, the reporting of low-level effects is problematic because of inconsistencies in the rigour with which the devices for measuring carboxyhaemoglobin have been validated. The most frequently used technique for measuring carboxyhaemoglobin has been the optical method found in the IL series of CO-Oximeters. Not only is there a lot of individual variability in these machines, but recent comparisons with the gas chromatographic technique of measuring carboxyhaemoglobin have suggested that the optical method may not be a suitable reference technique for measuring low levels of carboxyhaemoglobin. Several additional studies have appeared in the literature to help define the precise carboxyhaemoglobin levels at which cardiovascular effects occur in angina patients. Because the range of carboxyhaemoglobin values obtained with the optical method of analysis may be different from that obtained by gas chromatography, the method used to measure carboxyhaemoglobin will be indicated in parentheses for each of these studies.

Sheps et al. (1987) studied 30 patients aged 38–75 years with ischaemic heart disease and assessed not only symptoms during exercise, but also radionuclide evidence of ischaemia (left ventricular ejection fraction changes). Patients were non-smokers with ischaemia, defined by exercise-induced ST-segment depression, angina or abnormal ejection fraction response (i.e., all patients had documented evidence of ischaemia).
Patients were exposed to carbon monoxide (110 mg/m$^3$ [100 ppm]) or air during a 3-day, randomized double-blind protocol to achieve a post-exposure level of 4% carboxyhaemoglobin (CO-Oximeter measurement). Resting pre-exposure levels were 1.7%, post-exposure levels were 4.1% and post-exercise levels were 3.6% on the carbon monoxide exposure day; thus, the study examined acute elevation of carboxyhaemoglobin levels from 1.7% to an average of 3.8%, or an average increase of 2.2% carboxyhaemoglobin from resting values. Comparing exposure to carbon monoxide with exposure to air, there was no significant difference in time to onset of angina, maximal exercise time, maximal ST-segment depression (1.5 mm for both) or time to significant ST-segment depression. The conclusion of this study was that 3.8% carboxyhaemoglobin produces no clinically significant effects on this patient population.

Interestingly, further analysis of the time to onset of angina data in this paper demonstrated that 3 of the 30 patients experienced angina on the carbon monoxide exposure day but not on the air-control day. These patients had to be deleted from the classical analysis of differences between time to onset of angina that was reported in the publication. However, actuarial analysis of time to onset of angina including these patients revealed a statistically significant ($P < 0.05$) difference in time to onset of angina favouring an earlier time under the carbon monoxide exposure conditions (Bissette et al., 1986). None of the patients had angina only on the air exposure day.

Subsequent work from these same investigators (Adams et al., 1988) focused on repeating the study at 6% carboxyhaemoglobin (CO-Oximeter measurement). Thirty subjects with obstructive coronary artery disease and evidence of exercise-induced ischaemia were exposed to air or carbon monoxide on successive days in a randomized double-blind crossover fashion. Post-exposure carboxyhaemoglobin levels averaged $5.9 \pm 0.1\%$ compared with $1.6 \pm 0.1\%$ after air exposure, representing an increase of $4.3\%$ carboxyhaemoglobin. The mean duration of exercise was significantly longer after air exposure than after carbon monoxide exposure ($626 \pm 50\ s$ for air versus $585 \pm 49\ s$ for carbon monoxide, $P < 0.05$). Actuarial methods suggested that subjects experienced angina earlier during exercise on the day of carbon monoxide exposure ($P < 0.05$). In addition, this study showed that, at a slightly higher level of carbon monoxide exposure, both the level and change in ejection fraction at
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Submaximal exercise were greater on the air day than on the carbon monoxide day. The peak exercise left ventricular ejection fraction, however, was not different for the two exposures.

These results demonstrated earlier onset of ventricular dysfunction and angina and poorer exercise performance in patients with ischaemic heart disease after acute carbon monoxide exposure sufficient to increase carboxyhaemoglobin to 6%. It is of interest that in both the 4% study and the 6% study reported by this group, seven of the patients experienced angina on the carbon monoxide exposure day, but not on the air exposure day. There were no patients who experienced angina in the reverse sequence, providing further support for a significant effect of carbon monoxide exposure on angina occurrence.

Kleinman & Whittenberger (1985) and Kleinman et al. (1989) studied non-smoking male subjects with a history of stable angina pectoris and positive exercise tests. All but 2 of the 26 subjects had additional confirmation of ischaemic heart disease, such as previous myocardial infarction, positive angiogram, positive thallium scan, prior angioplasty or prior bypass surgery. Subjects were exposed for 1 h in a randomized double-blind crossover fashion to either 110 mg carbon monoxide/m³ (100 ppm) or clean air on 2 separate days. Subjects performed an incremental exercise test on a cycle ergometer to the point at which they noticed the onset of angina. For the study group, the 1-h exposure to 110 mg carbon monoxide/m³ (100 ppm) resulted in an increase in carboxyhaemoglobin from 1.4% after clean air to 3% (CO-Oximeter measurement) after carbon monoxide. For the entire study group (n = 26), the 1-h exposure to 110 mg/m³ (100 ppm) resulted in a decrease of the time to onset of angina by 6.9% from 6.5 to 6.05 min (Kleinman & Whittenberger, 1985). This difference was significant in a one-tailed paired t-test (P = 0.03). When using a two-tailed test, the difference loses statistical significance at the P = 0.05 level.

In the published version of results from this study (Kleinman et al., 1989), the two subjects with inconsistencies in their medical records and histories were dropped from the analysis. For this study group (n = 24), the 1-h exposure to 110 mg carbon monoxide/m³ (100 ppm) (3% carboxyhaemoglobin by CO-Oximeter measurement) resulted in a significant decrease of time to onset of angina by 5.9% using a one-tailed, two-factor analysis of variance (P = 0.046). There
was no significant effect on the duration of angina, but oxygen uptake at angina point was reduced 2.7% \( (P = 0.04) \). Only eight of the subjects exhibited depression in the ST-segment of their electrocardiogram traces during exercise. For this subgroup, there was a 10% reduction \( (P < 0.036) \) in time to onset of angina and a 19% reduction \( (P < 0.044) \) in the time to onset of 1-mm ST-segment depression.

A multicentre study of effects of low levels of carboxyhaemoglobin has been conducted in three cities on a relatively large sample \( (n = 63) \) of individuals with coronary artery disease (Allred et al., 1989a,b, 1991). The purpose of this study was to determine the effects of carbon monoxide exposures producing 2.0% and 3.9% carboxyhaemoglobin (gas chromatographic measurement) on time to onset of significant ischaemia during a standard treadmill exercise test. Significant ischaemia was measured subjectively by the duration of exercise required for the development of angina (time to onset of angina) and objectively by the time required to demonstrate a 1-mm change in the ST-segment of the electrocardiogram (time to ST). The time to onset of ST-segment changes was measured to the nearest second, rather than to the nearest minute as in the other studies on angina, a strength of this study. Male subjects aged 41–75 (mean = 62.1 years) with stable exertional angina pectoris and a positive stress test, as measured by a greater than 1-mm ST-segment change, were studied. Further evidence that these subjects had coronary artery disease was provided by the presence of at least one of the following criteria: angiographic evidence of narrowing (\( \geq 70\% \)) of at least one coronary artery, documented prior myocardial infarction or a positive stress thallium test demonstrating an unequivocal perfusion defect. Thus, as opposed to some previous studies reported, this study critically identified patients with documented coronary artery disease.

The protocol for this study was similar to that used in the Aronow studies, because two exercise tests were performed on the same day. The two tests were separated by a recovery period and a double-blind exposure period. On each of the 3 exposure days, the subject performed a symptom-limited exercise test on a treadmill, then was exposed for 50–70 min to carbon monoxide concentrations that were experimentally determined to produce end-exposure carboxyhaemoglobin levels of 2% and 4%. The mean exposure levels and ranges for the test environment were clean air (0 mg carbon
monoxide/m³ (0 ppm), 134 mg carbon monoxide/m³ (117 ppm; range 48–230 mg/m³ [42–202 ppm]) and 290 mg carbon monoxide/m³ (253 ppm; range 160–410 mg/m³ [143–357 ppm]). The subject then performed a second symptom-limited exercise test. The time to onset of angina and the time to 1-mm ST-segment change were determined for each test. The percent changes following exposure at both 2.0% and 3.9% carboxyhaemoglobin (gas chromatographic measurement) were then compared with the same subject’s response to the randomized exposure to room air (less than 2.3 mg carbon monoxide/m³ [2 ppm]).

When potential exacerbation of the exercise-induced ischaemia by exposure to carbon monoxide was tested using the objective measure of time to 1-mm ST-segment change, exposure to carbon monoxide levels producing 2.0% carboxyhaemoglobin resulted in a 5.1% decrease ($P = 0.01$) in the time to attain this level of ischaemia. At 3.9% carboxyhaemoglobin, the decrease in time to the ST criterion was 12.1% ($P \leq 0.0001$) relative to the air-day results; this reduction in time to ST-segment depression was accompanied by a significant ($P = 0.03$) reduction in the heart rate–blood pressure product (double product), an index of myocardial work. The maximal amplitude of the ST-segment change was also significantly affected by the carbon monoxide exposures: at 2% carboxyhaemoglobin, the increase was 11% ($P = 0.002$), and at 3.9% carboxyhaemoglobin, the increase was 17% relative to the air day ($P \leq 0.0001$).

When the individual centre data in the Allred et al. (1989a,b, 1991) study were analysed for covariates that may have influenced the results of this study, only the absolute level of carboxyhaemoglobin was found to have had a significant effect. This finding is not surprising, given the dose–response relationship between carbon monoxide and time to 1-mm ST-segment change. This analysis compared the slopes for each individual subject. The three times to 1-mm ST-segment change were plotted against the three actual carboxyhaemoglobin levels. The 62 individual slopes were then combined to yield a significant ($P < 0.005$) regression model: \textit{Change in time to 1-mm ST-segment change} = (–3.85 ± 0.63) $(\% \text{COHb})$ + (8.01 ± 2.48%). This dose–response relationship indicates that there is a 3.9% decrease in the time to ST criterion for every 1% increase in carboxyhaemoglobin.
The time to onset of angina was also significantly reduced in these subjects. At 2.0% carboxyhaemoglobin, the time to angina was reduced by 4.2% ($P = 0.027$), and at 3.9% carboxyhaemoglobin, the time was reduced by 7.1% ($P = 0.002$). There were no significant changes in the double products at the time of onset of angina in either exposure condition. The regression analysis for the time to angina data also resulted in a significant relationship ($P < 0.025$). The average regression was $\text{Time to angina} = (1.89\% \pm 0.81\%) (\% \text{COHb}) + (1.00\% \pm 2.11\%)$. The lower level of significance and the larger error terms for the angina regression relative to the ST analysis indicate that the angina end-point is more variable. This may be due to the subjective nature of this end-point or the variability in the ability of subjects to clearly recognize the onset of the pain.

The two end-points (time to angina and time to ST change) in the Allred study were also correlated, with a Spearman rank correlation coefficient of 0.49 ($P \#0.0001$). The conclusion of all of the analyses from this multicentre study is that the response of the myocardium in these patients with coronary artery disease is consistent, although the effects are relatively small.

The analysis of the covariates in this multicentre study also provides answers to ancillary questions that have been raised elsewhere in this document. The medication being used by these subjects did not significantly influence the results (i.e., there does not appear to be any drug interaction with the effects of carbon monoxide). The major medications being used in this group were β-blockers (used by 38 of the 63 subjects), nitrates (used by 36 of the 63 subjects) and calcium channel blockers (used by 40 of the 63 subjects). The other major concern was the influence of the severity of the disease. The simplest approach to this was to evaluate the influence of the duration of the exercise, because the subjects with more severe disease were limited in their exercise performance. No significant correlation was found between duration of exercise and the percent change in time to angina or ST criterion. There was also no relationship between the average time of exercise until the onset of angina and either of the end-points. Not was there a relationship between the presence of a previous myocardial infarction and the study end-points.
The duration of exercise was significantly shortened at 3.9% carboxyhaemoglobin but not at 2.0%. This finding must be used cautiously, because these subjects were not exercised to their maximum capacity in the usual sense. The major reason for termination of the exercise was the progression of the angina (306 of 376 exercise tests). The subjects were to grade their angina on a four-point scale; when the exercise progressed beyond level two, they were stopped. Therefore, this significant decrease in exercise time of 40 s at the 3.9% carboxyhaemoglobin level is undoubtedly due to the earlier onset of angina followed by the normal rate of progression of the severity of the angina.

The individual centre data provide insight into the interpretation of other studies that have been conducted in this area. Each of the centres enrolled the numbers of subjects that have been reported by other investigators. The findings reported above were not substantiated in all instances at each centre. When one considers the responses of the group to even 3.9% carboxyhaemoglobin, it is clear why one might not find significance in one parameter or another. For the decrease in ST segment at 3.9%, only 49 of 62 subjects demonstrated this effect on the day tested. The potential for finding significance at this effect rate with a smaller sample size is reduced. Random sampling of this population with a smaller sample could easily provide subjects that would not show significant effects of these low levels of carbon monoxide on the test day.

The recent reports (Allred et al., 1989b, 1991) of the multicentre study, organized and supported by the Health Effects Institute, discuss some reasons for differences between the results of the studies cited above (see Table 16). The studies have different designs, types of exercise tests, inclusion criteria (and, therefore, patient populations), exposure conditions and means of measuring carboxyhaemoglobin. All of the studies have shown an effect of carboxyhaemoglobin elevation on time to onset of angina (see Fig. 12). Results from the Kleinman et al. (1989) study showed a 6% decrease in exercise time to angina at 3.0% carboxyhaemoglobin (CO-Oximeter measurement) measured at the end of exposure. Allred et al. (1989a,b) reported a 5% and 7% decrease in time to onset of angina after increasing carboxyhaemoglobin levels to 3.2% and 5.6% (CO-Oximeter measurement), respectively, at the end of exposure. Although the Sheps et al. (1987) and Adams et al. (1988) studies did not observe statistically
Table 16. Comparison of subjects in studies of the effect of carbon monoxide exposure on occurrence of angina during exercise

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Gender</th>
<th>Medication</th>
<th>Smoking history</th>
<th>Description of disease</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al., 1973</td>
<td>10</td>
<td>male</td>
<td>1 subject took digitalis; drug therapy basis for exclusion</td>
<td>5 smokers (refrained for 12 h prior to exposure)</td>
<td>Stable angina pectoris, positive exercise test (ST changes); reproducible angina on treadmill</td>
<td>mean = 49.9</td>
</tr>
<tr>
<td>Kleinman et al., 1989</td>
<td>24</td>
<td>male</td>
<td>14 on $\beta$-blockers; 19 on nitrates; 8 on calcium channel blockers</td>
<td>No current smokers</td>
<td>Ischaemic heart disease, stable exertional angina pectoris</td>
<td>49–66</td>
</tr>
<tr>
<td>Allred et al., 1989a,b</td>
<td>63</td>
<td>male</td>
<td>38 on $\beta$-blockers; 36 on nitrates; 40 on calcium antagonists</td>
<td>No current smokers</td>
<td>Stable exertional angina and positive exercise test (ST changes) plus one or more of the following: (1) $\geq70%$ lesion by angiography in one or more major vessels, (2) prior myocardial infarction, (3) positive exercise thallium test</td>
<td>41–75</td>
</tr>
<tr>
<td>Sheps et al., 1987</td>
<td>30 (23 with angina)</td>
<td>25 male</td>
<td>26 subjects on medication; 19 on $\beta$-blockers; 11 on calcium channel blockers; 1 on long-acting nitrates</td>
<td>No current smokers</td>
<td>Ischaemia during exercise (ST changes or abnormal ejection fraction response) and one or more of the following: (1) angiographically proven coronary artery disease, (2) prior myocardial infarction, (3) typical angina</td>
<td>36–75</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Gender</td>
<td>Medication</td>
<td>Symptoms</td>
<td>Age (mean)</td>
<td></td>
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<tr>
<td>--------------------</td>
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<td></td>
</tr>
<tr>
<td>Adams et al., 1988</td>
<td>30 (25 with angina)</td>
<td>22 male, 8 female</td>
<td>25 subjects on medication; 13 on $\beta$-blockers + calcium channel blockers; 6 on $\beta$-blockers; 5 on calcium channel blockers; 1 on long-acting nitrates</td>
<td>No current smokers Ischaemia during exercise (ST changes or abnormal ejection fraction response) and one or more of the following: (1) angiographically proven coronary artery disease, (2) prior myocardial infarction, (3) typical angina</td>
<td>36–75 (mean = 58)</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Allred et al. (1989b, 1991).*
Alternative statistical analyses of the Sheps data (Bissette et al., 1986) indicate a significant decrease in time to onset of angina at 4.1% carboxyhaemoglobin if subjects that did not experience exercise-induced angina during air exposure are also included in the analyses.

Fig. 12. The effect of carbon monoxide exposure on time to onset of angina. For comparison across studies, data are presented as mean percent differences between air and carbon monoxide exposure days for individual subjects calculated from each study. Bars indicate calculated standard errors of the mean. Carboxyhaemoglobin levels were measured at the end of exposure; however, because of protocol differences among studies and lack of precision in optical measurements of carboxyhaemoglobin, comparisons must be interpreted with caution (see text and Table 16 for more details) (adapted from Allred et al., 1989b, 1991).

significant changes in time to onset of angina using conventional statistical procedures, the results of these studies are not incompatible with the rest of the studies reporting an effect of carbon monoxide. Both studies reported a significant decrease in time to onset of angina on days when carboxyhaemoglobin levels at the end of exposure were 4.1% and 5.9% (CO-Oximeter measurement), respectively, if the data analysis by actuarial method included subjects who experienced angina on the carbon monoxide day but not on the air day. In addition, the Adams et al. (1988) study reported that left ventricular performance, assessed by radionuclide measurement of the ejection fraction...
fraction, was reduced during submaximal exercise after carbon monoxide exposure compared with air exposure.

Of particular importance in this group of studies was the fact that the multicentre study (Allred et al., 1989a,b, 1991) demonstrated a dose–response effect of carboxyhaemoglobin on time to onset of angina. The only other single study that investigated more than a single target level of carboxyhaemoglobin was that by Anderson et al. (1973), and their results, based on a smaller number of subjects, did not show a dose–response relationship for angina.

The time to onset of significant electrocardiogram ST-segment changes, which are indicative of myocardial ischaemia in patients with documented coronary artery disease, is a more objective indicator of ischaemia than is angina. Allred et al. (1989a,b, 1991) reported a 5.1% and 12.1% decrease in time to ST-segment depression at carboxyhaemoglobin levels of 2.0% and 3.9% (gas chromatographic measurement), respectively, measured at the end of exercise. An additional measurement of the ST change was made by Allred et al. (1989b) to confirm this response — all the leads showing ST-segment changes were summed. This summed ST score was also significantly affected by both levels of carboxyhaemoglobin. The significant finding for the summed ST score indicates that the effect reported for time to 1-mm ST-segment change was not dependent upon changes observed in a single electrocardiogram lead.

The differences between the results of these five studies on exercise-induced angina can largely be explained by differences in experimental methodology and analysis of data and, to some extent, by differences in subject populations and sample size. For example, the Kleinman et al. (1989) study and the Allred et al. (1989a,b, 1991) study used one-tailed $P$ values, whereas the Sheps et al. (1987) and Adams et al. (1988) studies used two-tailed $P$ values. The Allred et al. (1989a,b, 1991) study also used trimmed means (with the two highest and two lowest values deleted) to guard against outliers. If a two-sided $P$ value was utilized on the time to onset of angina variable observed at the lowest carboxyhaemoglobin level in the Allred et al. (1989a,b, 1991) study, it would become 0.054 rather than 0.027, a result that would be considered borderline significant. If a two-sided $P$ value were used in the Kleinman et al. (1989) study, the difference in time to onset of angina would lose significance at the $P = 0.05$ level.
The entry criteria in the Allred et al. (1989a,b, 1991) study were more rigorous than in the other studies. All subjects were required to have stable exertional angina and *reproducible* exercise-induced ST depression and angina. Besides these criteria, all subjects were required to have a previous myocardial infarction, angiographic disease or a positive thallium stress test. In addition, only men were studied. These strict entry criteria were helpful in allowing the investigators to more precisely measure an adverse effect of carbon monoxide exposure. The protocol for the multicentre study, however, was slightly different from some of the protocols previously reported. On each test day, the subject performed a symptom-limited exercise test on a treadmill, then was exposed for approximately 1 h to air or one of two levels of carbon monoxide in air before undergoing a *second* exercise test. Time to onset of ischaemic electrocardiogram changes and time to onset of angina were determined for each exercise test. The percent difference for these end-points from the pre- and post-exposure test was then determined. The results on the 2% target day and then the 4% target day were compared with those on the control day.

The statistical significance reported at the low-level carbon monoxide exposure is present only when the *differences* between pre- and post-exposure exercise tests are analysed. Analysis of only the post-exposure test results in a loss of statistical significance for the 2% carboxyhaemoglobin level. Some of the differences between the results of this multicentre study and previous studies may be related to the fact that the exposure was conducted shortly after patients exercised to angina. The length of time required for resolution of exercise-induced ischaemia is not known. However, exercise treadmill testing of patients with coronary artery disease has been shown to induce regional wall motion abnormalities of the left ventricle that persist for over 30–45 min after exercise when chest pain and electrocardiogram abnormalities are usually resolved (Kloner et al., 1991). In addition, radionuclide studies in these patients have shown metabolic effects of ischaemia to last for more than 1 h after exercise (Camici et al., 1986). Because the effects of ischaemia may have a variable duration, differences between pre- and post-exposure tests may have been due to effects of carbon monoxide exposure on *recovery* from a previous episode of exercise-induced ischaemia rather than detrimental effects only during exercise.
In conclusion, five key studies have investigated the potential for carbon monoxide exposure to enhance the development of myocardial ischaemia during progressive exercise tests. Despite differences between them, it is impressive that all of the studies identified in Fig. 12 show a decrease in time to onset of angina at post-exposure carboxyhaemoglobin levels ranging from 2.9% to 5.9%. This represents incremental increases of 1.5–4.4% carboxyhaemoglobin from pre-exposure baseline levels. Therefore, there are clearly demonstrable effects of low-level carbon monoxide exposure in patients with ischaemic heart disease. The adverse health consequences of these types of effects, however, are very difficult to predict in the at-risk population of individuals with heart disease. There exists a distribution of professional judgements on the clinical significance of small performance decrements occurring with the levels of exertion and carbon monoxide exposure defined in these five studies. The decrements in performance that have been described at the lowest levels (≥3% carboxyhaemoglobin) are in the range of reproducibility of the test and may not be alarming to some physicians. On the other hand, the consistency of the responses in time to onset of angina across the studies and the dose–response relationship described by Allred et al. (1989a,b, 1991) between carboxyhaemoglobin and time to ST-segment changes would strengthen the argument in the minds of other physicians that, although small, the effects could limit the activity of these individuals and affect the quality of their life. In addition, it has been argued by Bassan (1990) that 58% of cardiologists believe that recurrent episodes of exertional angina are associated with a substantial risk of precipitating a myocardial infarction, a fatal arrhythmia or slight but cumulative myocardial damage.

8.2.2 Effects in individuals with chronic obstructive lung disease

Aronow et al. (1977) studied the effects of a 1-h exposure to 110 mg carbon monoxide/m$^3$ (100 ppm) on exercise performance in 10 men, aged 53–67 years, with chronic obstructive lung disease. The resting mean carboxyhaemoglobin levels increased from 1.4% baseline levels to 4.1% after breathing carbon monoxide. The mean exercise time until marked dyspnoea significantly decreased (33%) from 218 s in the air-control period to 147 s after breathing carbon monoxide. The authors speculated that the reduction in exercise performance was due to a cardiovascular limitation rather than respiratory impairment.
Only one other study in the literature, by Calverley et al. (1981), looked at the effects of carbon monoxide on exercise performance in older subjects with chronic lung disease. They evaluated 15 patients with severe reversible airway obstruction due to chronic bronchitis and emphysema. Six of the patients were current smokers, but they were asked to stop smoking for 12 h before each study. The distance walked within 12 min was measured before and after each subject breathed 0.02% (230 mg/m$^3$ [200 ppm]) carbon monoxide in air from a mouthpiece for 20–30 min until carboxyhaemoglobin levels were 8–12% above their initial levels. A significant decrease in walking distance was reported when the mean carboxyhaemoglobin concentration reached 12.3%, a level much higher than most of those reported in studies on healthy subjects.

Thus, although it is possible that individuals with hypoxia due to chronic lung diseases such as bronchitis and emphysema may be susceptible to carbon monoxide during submaximal exercise typically found during normal daily exercise, these effects have not been studied adequately at relevant carboxyhaemoglobin concentrations of less than 5%.

### 8.2.3 Effects in individuals with chronic anaemia

An additional study by Aronow et al. (1984) on the effect of carbon monoxide on exercise performance in anaemic subjects found a highly significant decrease in work time (16%) induced by an increase of 1.24% carboxyhaemoglobin. The magnitude of change seems to be very unlikely, however, even considering the report by Ekblom & Huot (1972). The study was double-blind and randomized, but with only 10 subjects. The exercise tests were done on a bicycle in the upright position with an increase in workload of 25 W every 3 min. However, no measure of maximal performance such as blood lactate was used. The mean maximal heart rate was only 139–146 beats per minute compared with a predicted maximal heart rate of 170 beats per minute for the mean age of the subjects. A subject repeating a test within the same day, which was the case in the Aronow et al. (1984) study, will often remember the time and work load and try to do the same in the second test. Normally, however, some subjects will increase while others will decrease the time. This situation was apparent on the air-control day, with an increase demonstrated in 6 out of 10 subjects, despite the high reproducibility for such a soft, subjective end-point. Also, comparing the control tests
on the air day with the carbon monoxide day, 7 out of 10 subjects increased their work time. After carbon monoxide exposure, however, all subjects decreased their time between 29 and 65 s. These data appear to be implausible given the soft end-point used, when 2–3 of the subjects would be expected to increase their time even if there were a true effect of carbon monoxide.

### 8.2.4 Arrhythmogenic effects

Until recent years, the literature has been confusing with regard to potential arrhythmogenic effects of carbon monoxide.

Davies & Smith (1980) studied the effects of moderate carbon monoxide exposure on healthy individuals. Six matched groups of human subjects lived in a closed, environmental exposure chamber for 18 days and were exposed to varying levels of carbon monoxide. Standard 12-lead electrocardiograms were recorded during five control, eight exposure and five recovery days. P-wave changes of at least 0.1 mV were seen in the electrocardiograms during the carbon monoxide exposure period in 3 of 15 subjects at 2.4% carboxyhaemoglobin and in 6 of 15 subjects at 7.1% carboxyhaemoglobin compared with 0 of 14 at 0.5% carboxyhaemoglobin. The authors felt that carbon monoxide had a specific toxic effect on the myocardium in addition to producing a generalized decrease in oxygen transport to tissue.

Several methodological problems create difficulties of interpretation for this study. The study design did not use each subject as his own control. Thus, only one exposure was conducted for each subject. Half of the subjects were tobacco smokers who were required to stop smoking, and certainly some of the electrocardiogram changes could have been due to the effects of nicotine withdrawal. Although the subjects were deemed to be normal, no screening stress tests were performed to uncover latent ischaemic heart disease or propensity to arrhythmia. Most importantly, no sustained arrhythmias or measurable effects on the conduction system were noted by the authors. If P-wave changes of clinical significance are representative of a toxic effect of carbon monoxide on the atrium, then an effect on conduction of arrhythmias should be demonstrated.

Knelson (1972) reported that 7 of 26 individuals aged 41–60 years had abnormal electrocardiograms after exposure to 110 mg carbon monoxide/m³ (100 ppm) for 4 h (carboxyhaemoglobin levels
of 5–9%). Two of them developed arrhythmias. No further details were given regarding specifics of these abnormalities. Among 12 younger subjects aged 25–36 years, all electrocardiograms were normal.

Hinderliter et al. (1989) reported on effects of low-level carbon monoxide exposure on resting and exercise-induced ventricular arrhythmias in patients with coronary artery disease and no baseline ectopy. They studied 10 patients with ischaemic heart disease and no ectopy according to baseline monitoring. After an initial training session, patients were exposed to air, 110 mg carbon monoxide/m$^3$ (100 ppm) or 230 mg carbon monoxide/m$^3$ (200 ppm) on successive days in a randomized, double-blinded crossover fashion. Venous carboxyhaemoglobin levels after exposure to 110 and 230 mg carbon monoxide/m$^3$ (100 and 200 ppm) averaged 4% and 6%, respectively. Symptom-limited supine exercise was performed after exposure. Eight of the 10 patients had evidence of exercise-induced ischaemia — angina, ST-segment depression or abnormal left ventricular ejection fraction response — during one or more exposure days. Ambulatory electrocardiograms were obtained for each day and were analysed for arrhythmia frequency and severity. On air and carbon monoxide exposure days, each patient had only 0–1 ventricular premature beats per hour in the 2 h prior to exposure, during the exposure period, during the subsequent exercise test and in the 5 h following exercise. The authors concluded that low-level carbon monoxide exposure is not arrhythmogenic in patients with coronary artery disease and no ventricular ectopy at baseline.

The results of low-level carbon monoxide exposure on patients with higher levels of ectopy were reported by the same investigators (Sheps et al., 1990, 1991). The frequency of a single ventricular premature depolarization per hour was significantly greater after carbon monoxide exposure producing 6% carboxyhaemoglobin (167.72 ± 37.99) compared with exposure to room air (127.32 ± 28.22, $P = 0.03$) and remained significant when adjusted for baseline ventricular premature depolarization levels for all subjects regardless of ventricular premature depolarization frequency category. During exercise, the mean number of multiple ventricular premature depolarizations per hour was greater after carbon monoxide exposure producing 6% carboxyhaemoglobin (9.59 ± 3.70) compared with exposure to room air (3.18 ± 1.67, $P = 0.02$) and remained significant after
adjustment for baseline multiple ventricular premature depolarization levels and when all subjects were included regardless of ventricular premature depolarization frequency category. The authors concluded that the number and complexity of ventricular arrhythmias increase significantly during exercise after carbon monoxide exposures producing 6% carboxyhaemoglobin compared with room air exposures, but not after carbon monoxide exposures producing 4% carboxyhaemoglobin. Because statistically significant effects were shown only during the exercise period, however, these reported changes are likely occurring at a lower carboxyhaemoglobin level. In fact, the carboxyhaemoglobin levels during exercise were 1.4% on the air exposure day, 3.7% on the 4% carboxyhaemoglobin target exposure day and 5.3% on the 6% carboxyhaemoglobin target exposure day, reflecting the mean values of the pre- and post-exercise levels. Analysis of dose-response relationships could not be carried out in this study, making it more difficult to determine the strength of the evidence for the effects of carbon monoxide on arrhythmia. In this study, the amount of arrhythmia produced by carbon monoxide exposure was not correlated with measured variables of angina (e.g., time to ST-segment depression and time to angina) or with the clinical descriptors of disease status or medication usage.

Dahms et al. (1993) also studied the effects of low-level carbon monoxide exposure in patients with myocardial ischaemia and a minimum of 30 ventricular ectopic beats over a 20-h period. In total, 28 subjects were exposed in a randomized double-blind fashion to either room air or sufficient carbon monoxide for 1 h to elevate carboxyhaemoglobin levels to 3% and 5%. The frequency of single ventricular ectopic beats at rest was 115 ± 28 in room air, 121 ± 31 at 3% carboxyhaemoglobin and 94 ± 23 at 5% carboxyhaemoglobin. Exposure to carbon monoxide had no additional effect over exercise-induced increases in the frequency of single or multiple ectopic beats. The amount of arrhythmia was not related to the severity of myocardial ischaemia during normal daily activity.

There are important clinical differences in the patients studied by Sheps et al. (1990) and Dahms et al. (1993) that may account for the different results obtained with exercise. In the Dahms et al. (1993) study, the percentage of patients with $50 ventricular ectopic beats per hour was significantly greater and ventricular function of the patients was significantly worse than in the Sheps et al. (1990) study;
however, the myocardial ischaemia, as indicated by exercise-induced angina or ischaemic ST-segment depression, was greater in the patients studied by Sheps et al. (1990), and a greater percentage of them were taking $\beta$-adrenergic blocking drugs.

The effects of low-level carbon monoxide exposure on exercise-induced ventricular arrhythmia in patients with coronary artery disease and baseline ectopy are dependent on their clinical status. In more severely compromised individuals, exposures to carbon monoxide that produce 6% carboxyhaemoglobin (but not lower carboxyhaemoglobin levels) have been shown to significantly increase the number and complexity of arrhythmias.

### 8.2.5 Effects on coronary blood flow

The effects of breathing carbon monoxide on myocardial function in patients with and without coronary heart disease have been examined by Ayres et al. (1969, 1970, 1979). Acute elevation of carboxyhaemoglobin from 0.98% to 8.96% by a bolus exposure using either 1100 mg carbon monoxide/m$^3$ (1000 ppm) for 8–15 min or 57 000 mg/m$^3$ (50 000 ppm) for 30–45 s caused a 20% average decrease in coronary sinus oxygen tension without a concomitant increase in coronary blood flow in the patients with coronary artery disease. Observations in patients with coronary disease revealed that acute elevation of carboxyhaemoglobin to approximately 9% decreased the extraction of oxygen by the myocardium. However, overall myocardial oxygen consumption did not change significantly, because an increase in coronary blood flow served as a mechanism to compensate for a lower overall myocardial oxygen extraction. In contrast, patients with non-coronary disease increased their coronary blood flow with an insignificant decrease in coronary sinus oxygen tension as a response to increased carboxyhaemoglobin. The coronary patients also switched from lactate extraction to lactate production. Thus, because of their inability to increase coronary blood flow to compensate for the effects of increased carboxyhaemoglobin, a potential threat exists for patients with coronary heart disease who inhale carbon monoxide.

Although the coronary sinus $P_{O_2}$ dropped only slightly in this study (reflecting average coronary venous oxygen tension), it is certainly possible that, in areas beyond a significant coronary arterial stenosis, tissue hypoxia might be precipitated by very low tissue $P_{O_2}$. 
values. Tissue hypoxia might be further exacerbated by a coronary-steal phenomenon whereby increased overall coronary flow diverts flow from areas beyond a stenosis to other normal areas. Therefore, the substrate for the worsening of ischaemia and consequent precipitation of arrhythmias is present with carbon monoxide exposure.

8.2.6 Relationship between carbon monoxide exposure and risk of cardiovascular disease in humans

8.2.6.1 Introduction

General population epidemiological studies on the relation between carbon monoxide exposure and ischaemic heart disease are not conclusive. In the USA, early population studies (Goldsmith & Landaw, 1968; Cohen et al., 1969; Hexter & Goldsmith, 1971) suggested an association between atmospheric levels of carbon monoxide and increased mortality from cardiovascular disease in Los Angeles, California, but potential confounders were not effectively controlled. In contrast, a study in Baltimore, Maryland (Kuller et al., 1975), showed no association between ambient carbon monoxide levels and cardiovascular disease or sudden death. A study of emergency room visits for cardiovascular complaints in Denver, Colorado (Kurt et al., 1978), showed a relationship with carbon monoxide exposure levels, but the correlations were relatively weak, and other environmental factors were not evaluated. These early epidemiological data were summarized by Kuller & Radford (1983). They concluded that mortality and morbidity studies have been negative or equivocal in relating carbon monoxide levels to health effects, but studies in human subjects with compromised coronary circulation support an effect of acute exposure to carbon monoxide at blood levels corresponding to a carbon monoxide exposure level of about 20 ppm over several hours. They calculate that, based on health surveys, probably over 10 million subjects in the USA are exposed to potentially deleterious levels of carbon monoxide and that perhaps 1250 excess deaths related to low-dose environmental carbon monoxide exposure occur each year.

8.2.6.2 Daily mortality

More recent time-series studies in North and South America and in Europe have also been equivocal in relating day-to-day variations in carbon monoxide levels with daily mortality. No relationship was
found between carbon monoxide and daily mortality in Los Angeles, California, or Chicago, Illinois (Ito et al., 1995; Kinney et al., 1995; Ito & Thurston, 1996), after adjusting for particulate matter with mass median aerodynamic diameter less than 10μm (PM_{10}). Verhoeff et al. (1996) found no relationship between 24-h average carbon monoxide concentrations and daily mortality in Amsterdam, Netherlands, with or without adjustment for PM_{10} and other pollutants. Saldiva et al. (1994, 1995) found no association between carbon monoxide and daily mortality among children or the elderly in São Paulo, Brazil, after adjusting for nitrogen oxides and PM_{10}, respectively. Three other studies (Touloumi et al., 1994; Salinas & Vega, 1995; Wietlisbach et al., 1996) showed small, statistically significant relationships between carbon monoxide and daily mortality; however, other pollutants (e.g., total suspended particulates, sulfur dioxide, nitrogen dioxide, black smoke) and other environmental variables (e.g., temperature and relative humidity) were also significant. Further studies and analyses will be needed to determine if low-level carbon monoxide exposure is actually increasing mortality, particularly in the elderly population, or if carbon monoxide is a surrogate marker for some other mobile-source pollutant.

Touloumi et al. (1994) investigated the association of air pollution with daily all-cause mortality in Athens, Greece, for the years 1984 through 1988. Daily mean pollution indicators for sulfur dioxide, black smoke and carbon monoxide were averaged over all the available monitoring stations. Auto-regressive models with log-transformed daily mortality as the dependent variable were used to adjust for temperature, relative humidity, year, season, day of week and serial correlations in mortality. Separate models for log(sulfur dioxide), log(smoke) and log(carbon monoxide) produced statistically significant (P < 0.001) coefficients. Air pollution data lagged by 1 day had the strongest association with daily mortality. Multiple regression modelling showed that sulfur dioxide and smoke were independent predictors of mortality, although to a lesser extent than temperature and relative humidity. The inclusion of carbon monoxide in this model did not further improve the association with daily mortality, suggesting that carbon monoxide may be a surrogate marker for other mobile-source pollutants.

Daily mortality results of the European Community multicentre APHEA (Short-term effects of Air Pollution on Health: a European
Approach using epidemiologic time-series data) study (Touloumi et al., 1996) in Athens for the years 1987 through 1991 show that for 8-h carbon monoxide concentrations in ambient air (median 6.1 mg/m$^3$ [5.3 ppm], mean 6.6 mg/m$^3$ [5.8 ppm] and maximum 24.9 mg/m$^3$ [21.7 ppm]) compiled from three fixed monitoring sites, the relative risk (RR) of dying from a 10 mg/m$^3$ (8.7 ppm) increase in the daily carbon monoxide concentration in ambient air is 1.10 (95% confidence interval [CI] = 1.05–1.15). The strongest effect was observed during the winter, when higher levels of sulfur dioxide were observed. This new result has not yet been confirmed in other epidemiological studies. It may be explained by yet unknown health effects of low levels of carbon monoxide, by the presence of highly compromised susceptible groups in the population or by carbon monoxide being merely a surrogate of other combustion-generated air pollutants.

Salinas & Vega (1995) determined the effect of urban air pollution on daily mortality in metropolitan Santiago, Chile, from 1988 to 1991. Data on maximum 8-h average carbon monoxide, maximum hourly ozone, daily mean sulfur dioxide, PM$_{10}$ and PM$_{2.5}$ (particles with diameter <2.5 μm), and meteorological variables were obtained from five monitoring stations. Total and respiratory disease-specific deaths were compared, calculating the risk of death by municipality and month of the year using age-adjusted standardized mortality ratios and controlling for socioeconomic status. Daily counts of deaths were regressed using a Poisson model on the pollutants, controlling for temperature and relative humidity. A clear pattern in the geographic distribution of risk of death was found, both for total mortality and for disease-specific mortality (e.g., pneumonia, chronic obstructive pulmonary disease, asthma), regardless of socioeconomic and living conditions. The number of deaths was significantly associated directly with humidity, carbon monoxide and suspended particles and indirectly with temperature when the model included all days with available data during the 4-year period. The associations remained significant for those days with fine suspended particle levels below 150 μg/m$^3$.

Wietlisbach et al. (1996) assessed the association between daily mortality and air pollution in three Swiss metropolitan areas of Zurich, Basle and Geneva for the period 1984 through 1989. Daily counts were obtained for total mortality, mortality for persons 65 years of age or older and respiratory and cardiovascular disease mortality.
Daily weather variables and pollution data for total suspended particulates, sulfur dioxide, nitrogen dioxide, carbon monoxide and ozone were obtained from the respective reference stations. Daily counts of death were regressed using a Poisson model on the pollutants, controlling for time trends, seasonal factors and weather variables. A positive, statistically significant association was found between daily mortality and total suspended particulates, sulfur dioxide and nitrogen dioxide. The strongest association was observed with a 3-day moving average. Somewhat smaller associations were observed in each city between mortality in persons 65 years of age or older and measured carbon monoxide concentrations (mean = 1.1–2.3 mg/m$^3$ [1–2 ppm]; maximum = 5–8 mg/m$^3$ [4–7 ppm]). Associations with ozone were very weak and inconsistent. When all pollutants were included in the model together, the regression coefficients were unstable and statistically insignificant.

### 8.2.6.3 Hospital admissions

Two recent studies in the USA (Morris et al., 1995; Schwartz & Morris, 1995), a similar study in Canada (Burnett et al., 1997) and one in Greece (Pantazopoulou et al., 1995) have suggested that day-to-day variations in ambient carbon monoxide concentrations are related to cardiovascular hospital admissions, especially for persons 65 years of age or over.

A time-series analysis of ambient levels of gaseous air pollutants (carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone) and Medicare hospital admissions for congestive heart failure was performed for seven US cities (Chicago, Illinois; Detroit, Michigan; Houston, Texas; Los Angeles, California; Milwaukee, Wisconsin; New York, New York; Philadelphia, Pennsylvania) during the 4-year period from 1986 through 1989 by Morris et al. (1995). Maximum daily carbon monoxide levels (mean ± standard deviation [SD]) ranged from 2.1 ± 1.1 mg/m$^3$ (1.8 ± 1.0 ppm) in Milwaukee to 6.4 ± 1.9 mg/m$^3$ (5.6 ± 1.7 ppm) in New York. The relative risk of admissions associated with an 11 mg/m$^3$ (10 ppm) increase in carbon monoxide ranged from 1.10 in New York to 1.37 in Los Angeles. All seven cities showed similar patterns of increasing admissions with increasing ambient carbon monoxide concentrations. Approximately 3250 hospital admissions for congestive heart failure (5.7% of all such admissions) each year can therefore be attributed to the observed association with carbon monoxide levels. It is possible, however, that the observed
association represents the impact of some other, unmeasured pollutant or group of pollutants covarying in time with carbon monoxide.

The association between air pollution and cardiovascular hospital admissions for persons aged 65 years or older was examined in the Detroit, Michigan, metropolitan area during the years 1986 through 1989 by Schwartz & Morris (1995). Air quality data were available for PM$_{10}$ on 82% and for ozone on 85% of possible days. Data were available for sulfur dioxide and carbon monoxide on all days during the study period. The mean PM$_{10}$ was 48.0 : g/m$^3$, the mean ozone was 82.0 : g/m$^3$ (41.0 ppb), the mean sulfur dioxide was 66.0 : g/m$^3$ (25.4 ppb) and the mean carbon monoxide was 2.7 mg/m$^3$ (2.4 ppm). A Poisson auto-regressive model was used to analyse the data with dummy variables for temperature and dew point, month, and linear and quadratic time trends. Daily admissions for ischaemic heart disease were associated with a 32 : g/m$^3$ increase in PM$_{10}$ (RR = 1.018; 95% CI = 1.005–1.032), a 47 : g/m$^3$ (18 ppb) increase in sulfur dioxide (RR = 1.014; 95% CI = 1.003–1.026) and a 1.47 mg/m$^3$ (1.28 ppm) increase in carbon monoxide (RR = 1.010; 95% CI = 1.001–1.018); however, both sulfur dioxide and carbon monoxide became insignificant after controlling for PM$_{10}$, whereas PM$_{10}$ remained significant after controlling for the other pollutants. Daily admissions for heart failure were independently associated with a 1.28 mg/m$^3$ increase in PM$_{10}$ (RR = 1.024; 95% CI = 1.004–1.044) and carbon monoxide (RR = 1.022; 95% CI = 1.110–1.034). Ozone was not a significant risk factor for cardiovascular hospital admissions, and no pollutant was a significant risk factor for dysrhythmia admissions.

A number of issues need to be resolved before the results of Morris et al. (1995) and Schwartz & Morris (1995) can be fully understood. Congestive heart failure is the most common indication for hospitalization among adults 65 years of age or over in the USA; however, elderly patients with heart failure have demonstrated high rates of readmission, ranging from 29% to 47%. Behavioural factors (e.g., non-compliance with medication and diet) and social factors (e.g., isolation) frequently contribute to early readmission, suggesting that many hospital admissions for congestive heart failure could be prevented. Hospital admission for congestive heart failure could also be indicated for severe pulmonary oedema, pneumonia or generalized oedema. Additional information on the admission criteria (e.g., clinical evidence of acute myocardial ischaemia, oxygen saturation or
symptomatic syncope), on cigarette and tobacco use and on indoor carbon monoxide exposures is needed.

The relative risks reported by Morris et al. (1995) are small, ranging from 1.10 to 1.37; the city with the highest carbon monoxide levels (New York) had the lowest relative risk for congestive heart failure admission. Also, the model without any lag provided the strongest association, suggesting that cumulative exposure was not important. The carbon monoxide concentrations measured by stationary monitors are also very low; any carboxyhaemoglobin levels produced by a 1-h exposure to <11 mg carbon monoxide/m³ (<10 ppm), for example, would be difficult to measure. If cumulative exposures were important, even 8 h of exposure to 11 mg carbon monoxide/m³ (10 ppm) with moderate exercise (20 litres/min) would be expected to produce only 1.5% carboxyhaemoglobin. In addition, carbon monoxide data from stationary monitors are not highly correlated with personal exposures, and individuals with coronary heart disease would not be expected to be in locations where carbon monoxide monitors exist. It is possible that carbon monoxide could be a surrogate for automobile pollution, in general. Carbon monoxide is highly correlated with particles during the winter months. Particles (PM₁₀) were found to be correlated in the Schwartz & Morris (1995) study, but were not included in the Morris et al. (1995) analysis. Also, particles have previously been shown to be associated with hospital admissions for both heart failure and ischaemic heart disease in Ontario (Burnett et al., 1995).

Burnett et al. (1997) examined temporal relationships between ambient air pollutants and hospitalizations among the elderly (persons 65 years of age or older) in 10 Canadian cities for the 11-year period from 1981 through 1991. A time-series analysis adjusted for long-term time trends, seasonal and subseasonal variations, and day-of-week effects was used to explore the association between cardiopulmonary illness and the ambient air pollutants carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone and coefficient of haze. After stratifying for months of the year and adjusting for temperature, dew point and other pollutants, the log of the daily 1-h maximum carbon monoxide concentration recorded on the day of admission had the strongest and most consistent statistical association with hospitalization for congestive heart failure. The relative risk was 1.065 (95% CI = 1.028–1.104) for an increase from 1.1 to 3.4 mg carbon monoxide/m³ (1 to 3 ppm, the 25th and 75th percentiles of the
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(continued)

exposure distribution). Except for ozone, the other pollutants were clearly confounded in this analysis; however, carbon monoxide alone accounted for 90% of the daily excess hospitalizations attributable to the entire mix. The authors noted that this relationship may not be causal because of possible misclassification of exposure to carbon monoxide and the likelihood that carbon monoxide may be acting as a surrogate for pollution from transportation sources in general.

Pantazopoulou et al. (1995) studied the daily number of emergency outpatient visits and admissions for cardiac and respiratory causes to all major hospitals in the greater Athens area during 1988. Concentrations of air pollutants (smoke, carbon monoxide and nitrogen dioxide) were obtained from the Ministry of the Environment. Mean levels of carbon monoxide for all available monitoring stations were 4.5 ± 1.6 (SD) mg/m$^3$ (3.9 ± 1.4 ppm) in winter and 3.4 ± 1.0 (SD) mg/m$^3$ (3.0 ± 0.9 ppm) in summer. Multiple linear regression modelling was used to look for statistical relationships, controlling for the potential effects of meteorological and chronological variables, separately for winter and summer. A positive association was found between the daily number of emergency admissions for cardiac and respiratory causes and all measured pollutants during the winter, but not during the summer.

8.2.6.4 Occupational exposures

Early studies of occupational exposure to carbon monoxide (Jones & Sinclair, 1975; Redmond, 1975; Redmond et al., 1979) failed to identify any increased risk of cardiovascular disease associated with carbon monoxide exposure. In a Finnish study (Hernberg et al., 1976; Koskela et al., 1976), the prevalence of angina among foundry workers showed an exposure–response relationship with regard to carbon monoxide exposure, but no such result was found for ischaemic electrocardiogram findings during exercise.

Stern et al. (1981) reported a study performed by NIOSH. They investigated the health effects of chronic exposure to low concentrations of carbon monoxide by conducting a historical prospective cohort study of mortality patterns among 1558 white male motor vehicle examiners in New Jersey, USA. The examiners were exposed to 11–27 mg carbon monoxide/m$^3$ (10–24 ppm). The carboxyhaemoglobin levels were determined in 27 volunteers. The average
carboxyhaemoglobin level before a work shift was 3.3% in the whole group, and the post-shift level was 4.7%; these levels were 2.1% and 3.7%, respectively, in non-smokers only. The death rates were compared with the rates in the US population based on vital statistics. The cohort demonstrated a slight overall increase in cardiovascular deaths, but a more pronounced excess was observed within the first 10 years following employment. The study has several important limitations, however, including the use of historical controls, lack of knowledge about smoking habits and the fact that the individuals’ carboxyhaemoglobin levels were not known.

Stern et al. (1988) investigated the effect of occupational exposure to carbon monoxide on mortality from arteriosclerotic heart disease in a retrospective cohort study of 5529 New York City, New York, USA, bridge and tunnel officers. Among former tunnel officers, the standardized mortality ratio (SMR) was 1.35 (90% CI = 1.09–1.68) compared with the New York City population. Using the proportional hazards model, the authors compared the risk of mortality from arteriosclerotic heart disease among tunnel workers with that of the less exposed bridge officers. They found an elevated risk in the tunnel workers that declined within as few as 5 years after cessation of exposure. The 24-h average carbon monoxide level in the tunnel was around 57 mg/m$^3$ (50 ppm) in 1961 and around 46 mg/m$^3$ (40 ppm) in 1968. However, higher values were recorded during rush hours. In 1971, the ventilation was further improved and the officers were allowed clean air breaks. Although the authors concluded that carbon monoxide exposure may play an important role in the pathophysiology of cardiovascular mortality, other factors must be taken into consideration. Mortality from arteriosclerotic heart disease has a complex multifactor etiology. The presence of other risk factors, such as cigarette smoke, hypertension, hyperlipidaemia, family history of heart disease, obesity, socioeconomic status and sedentary living, can all increase the risk of developing coronary heart disease. In addition, detailed exposure monitoring was not done in this study. The bridge and tunnel workers were exposed not only to carbon monoxide but also to other compounds emitted from motor vehicle exhaust and to the noise and stress of their environment. These other factors could have contributed to the findings.

Hansen (1989) reported the results of a 10-year follow-up study on mortality among 583 Danish male automobile mechanics between
15 and 74 years of age. The number of deaths expected for the automobile mechanics was compared with those for a similar group of Danish men employed as carpenters, electricians and other skilled workers free from occupational exposure to automobile exhaust, petrochemical products, asbestos and paint pigments. The number of deaths observed among the automobile mechanics exceeded the expected number by 21%. Although the increased mortality was not confined to any single cause of death, the author reported a remarkable excess of deaths attributed to ischaemic heart disease where the standardized mortality ratio was 121 and the 95% confidence interval was 102–145. The only other significant category of death was that due to external causes (SMR = 131; 95% CI = 113–153). No significant differences were found among the automobile mechanics for other diseases except for an increase in pancreatic cancer (SMR = 219; 95% CI = 128–351). Exposure to carbon monoxide and polycyclic aromatic hydrocarbons through the inhalation of automobile exhaust and the handling of solvents and oils may have accounted for the difference in ischaemic heart disease deaths between the automobile mechanics and the comparison group; however, other occupational exposures or other lifestyle factors, as indicated above, may also have contributed to the findings.

8.2.6.5 Carbon monoxide poisoning

Intoxication with carbon monoxide that induces carboxyhaemoglobin levels around 50–60% is often lethal; however, even levels around 20% carboxyhaemoglobin have been associated with death, mainly coronary events, in patients with severe coronary artery disease. Balraj (1984) reported on 38 cases of individuals dying immediately or within a few days following carbon monoxide exposures producing 10–50% carboxyhaemoglobin, usually non-lethal levels of carbon monoxide. All of the subjects had coronary artery disease, and 29 of them had severe cases. The author concluded that the carbon monoxide exposure, resulting in carboxyhaemoglobin levels between 10% and 30% in 24 cases, triggered the lethal event in subjects with a restricted coronary flow reserve. Similar associations between carbon monoxide exposure and death or myocardial infarction have been reported by several other authors. Atkins & Baker (1985) reported two cases with 23% and 30% carboxyhaemoglobin, McMeekin & Finegan (1987) reported one case with 45% carboxyhaemoglobin, Minor & Seidler (1986) reported one case with 19% carboxyhaemoglobin and Ebisuno et al. (1986) reported
one case with 21% carboxyhaemoglobin. For a more complete
discussion of carbon monoxide poisoning, see section 8.3.

Forycki et al. (1980) described electrocardiogram changes in
880 patients treated for acute poisoning. Effects were observed in
279 cases, with the most marked changes in cases with carbon
monoxide poisoning. In those, the most common change was a T-
wave abnormality; in six cases, a pattern of acute myocardial
infarction was present. Conduction disturbances were also common
in carbon monoxide poisoning, but arrhythmias were less common.

Elsasser et al. (1995) reported that 78 myocardial infarction
patients with Q-wave infarction had more arrhythmias and higher
creatine kinase levels after acute carbon monoxide exposures that
raised carboxyhaemoglobin levels to 5%. The carboxyhaemoglobin
concentration was measured at admission to the coronary care unit of
a university hospital and 4 h later. The authors concluded that carbon
monoxide was associated with a more severe course of acute myo-
cardial infarction; however, causation could not be determined.

8.2.6.6 Tobacco smoke

The association between smoking and cardiovascular disease is
fully established. Although little is known about the relative
importance of carbon monoxide compared with other components of
tobacco smoke, such as nicotine and polycyclic aromatic hydro-
carbons, most researchers consider all of them to be important. The
nicotine component clearly aggravates the decrease in oxygen
capacity induced by carbon monoxide through an increase in the
oxygen demand of the heart, and polycyclic aromatic hydrocarbons
have been implicated in the atherosclerotic process (Glantz &

Passive smoking exposes an individual to all components in the
cigarette smoke, but the carbon monoxide component dominates
heavily, because only 1% or less of the nicotine is absorbed from
sidestream smoke, compared with 100% in an active smoker (Jarvis,
1987; Wall et al., 1988). Therefore, exposure to sidestream smoke
will be the closest to pure carbon monoxide exposure, even if the
resultant levels of carboxyhaemoglobin are low (about 1–2%) (Jarvis,
1987). The relationship between passive smoking and increased risk
of coronary heart disease is controversial. Early studies on this
relationship were reviewed in the 1986 report of the Surgeon General
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(Surgeon General of the United States, 1986) and by the US National Research Council (NRC, 1986a). Since that time, the epidemiological evidence linking passive smoking exposure to heart disease has rapidly expanded. The available literature, to date, on the relationship between passive exposure to environmental tobacco smoke in the home and the risk of heart disease death in the non-smoking spouse of a smoker consists of 19 published reports (Gillis et al., 1984; Hirayama, 1984; Garland et al., 1985; Lee et al., 1986; Svendsen et al., 1987; Helsing et al., 1988; He, 1989; Hole et al., 1989; Kawachi et al., 1989; Sandler et al., 1989; Humble et al., 1990; Butler, 1991; Dobson et al., 1991; La Vecchia et al., 1993; He et al., 1994; Muscat & Wynder, 1995; Steenland et al., 1996; Kawachi et al., 1997) and 4 review articles (Glantz & Parmley, 1991; Steenland, 1992; Wells, 1994; LeVois & Layard, 1995). All but two of the studies yielded relative risks greater than 1.0; however, six studies in men and eight studies in women had 95% confidence intervals that included 1.0, indicating that the risk of passive smoking for heart disease was not statistically significant. By combining the studies to improve the power to detect an effect, Glantz & Parmley (1991) reported a combined relative risk of 1.3 (95% CI = 1.2–1.4) for 10 studies, Wells (1994) reported a combined relative risk of 1.23 (95% CI = 1.12–1.35) for 12 studies and LeVois & Layard (1995) reported a combined relative risk of 1.29 (95% CI = 1.18–1.41) for 14 studies. Even though it is impossible to rule out an effect of the other components in sidestream smoke, the data suggest an increase in risk of coronary heart disease associated with prolonged exposure to low levels of carbon monoxide.

In a cross-sectional study of 625 smokers aged 30–69, Wald et al. (1973) reported that the incidence of cardiovascular disease was higher in subjects with carboxyhaemoglobin greater than 5% than in subjects with carboxyhaemoglobin below 3%, a relative risk of 21.2 (95% CI = 3.3–734.3). Even if all of the subjects were smokers, the association between carboxyhaemoglobin and cardiovascular disease might be due to the fact that percent carboxyhaemoglobin is a measure of smoke exposure.

Low to intermediate levels of carboxyhaemoglobin might interfere with the early course of an acute myocardial infarction. The increase in carboxyhaemoglobin can be due to recent smoking or environmental exposure. Mall et al. (1985) reported on a prospective
study in smoking and non-smoking patients with an acute myocardial infarction who were separated by their baseline carboxyhaemoglobin levels. Sixty-six patients were studied in total. Thirty-one patients were found to have a carboxyhaemoglobin level of 1.5%, and 35 were found to have a level of 4.5%. In the group with elevated carboxyhaemoglobin, more patients developed transmural infarction, but the difference was not significant. Patients with transmural infarction had higher maximum creatine phosphokinase values when carboxyhaemoglobin was over 2%. During the first 6 h after admission to the hospital, these patients needed an antiarrhythmic treatment significantly more frequently. Differences in rhythm disorders were still present at a time when nicotine, owing to its short half-life, was already eliminated. The authors concluded that moderately elevated levels of carboxyhaemoglobin may aggravate the course of an acute myocardial infarction.

8.2.7 Effects of exposure during pregnancy and early childhood

8.2.7.1 Pregnancy

It is thought that carbon monoxide crosses the placenta by simple diffusion and that the concentration of carboxyhaemoglobin in the fetus is dependent on maternal carboxyhaemoglobin concentrations, the rate of fetal carbon monoxide production, the diffusion capacity of the placenta for carbon monoxide and the relative affinity of the haemoglobin for carbon monoxide (Longo, 1977). Maternal carboxyhaemoglobin levels in non-smokers range between 0.5% and 1.0% and those of fetal blood between 0.7% and 2.5% (Longo, 1970, 1977). Fetal uptake of carbon monoxide takes place more slowly than maternal uptake. Following acute exposure, maternal carboxyhaemoglobin levels reach half the steady-state value in 2 h; in the fetus, on the other hand, steady-state values are not reached until 7 h after the onset of exposure. Final equilibrium is reached 36–48 h after the onset of exposure, and the carboxyhaemoglobin level in fetal blood at this time is 10% higher than maternal levels due to the increased affinity of fetal haemoglobin (Hill et al., 1977; Longo, 1977).

A fairly wide range of neonate and maternal carboxyhaemoglobin levels has been published for humans, probably as a result of wide differences in cigarette smoking patterns prior to and during labour. Maternal smoking during pregnancy exposes the fetus to greater than normal concentrations of carbon monoxide. Mean
concentrations of 2.0–8.3% carboxyhaemoglobin and 2.4–7.6% carboxyhaemoglobin for maternal and fetal blood, respectively, have been reported (Longo, 1970).

In a study by Bureau et al. (1982), the measurement of fetal cord blood in the offspring of cigarette smokers who smoked during labour showed that fetal carboxyhaemoglobin levels were 2.55 times higher than in maternal blood. Cord blood averaged 10.1% carboxyhaemoglobin at delivery, whereas maternal blood averaged 5.6% carboxyhaemoglobin on the mother’s arrival at the hospital and 4.1% carboxyhaemoglobin at delivery. Most of the observations on carbon monoxide exposure in pregnancy are based upon reports of cases of accidental or deliberate maternal carbon monoxide intoxication. These studies provide valuable information on the consequences of high peak carbon monoxide concentrations on pregnancy outcome but say nothing about the effects of short- or long-term low-level exposure to carbon monoxide.

Desclaux et al. (1951) reported a case of carbon monoxide intoxication in the fifth month of pregnancy where the subject was unconscious for 3 days. The child was born at term with a birth weight of 3500 g. Encephalography revealed gross ventricular dilatation, and the child was mentally retarded and had general hypertonia.

Muller & Graham (1995) reviewed eight cases from the literature in which the mother had been intoxicated with carbon monoxide in pregnancy and delivered living offspring. The common features in the offspring were psychomotor disturbances and mental retardation. The authors presented a case of carbon monoxide intoxication shortly before the expected date of delivery. The child was stillborn with cherry red-coloured skin and organs. Fetal blood was 49% saturated with carboxyhaemoglobin.

Copel et al. (1982) reported a case of carbon monoxide intoxication with a maternal blood carboxyhaemoglobin level of 24.5% in the first trimester of pregnancy. Pregnancy was uncomplicated until the 38th week, when amniocentesis revealed a greater than 3:1 lecithin:sphingomyelin ratio and the presence of phosphatidyl glycerol; the amniotic fluid was also meconium-stained. The child was delivered prematurely by caesarean section with a birth
weight of 1950 g. The child developed normally and showed no signs of central nervous system damage at 6 months of age.

The association between carbon monoxide exposure and reduced fetal growth was studied by Astrup et al. (1972). Blood carboxyhaemoglobin was measured in 176 smoking and 177 non-smoking pregnant women. Blood carboxyhaemoglobin levels in 97% of non-smokers and 77% of smokers were below 3%; the mean carboxyhaemoglobin concentration in each group was 0.87% and 1.92%, respectively. The average birth weight of the newborns of smoking women (2990 g) was lower than that of the newborns of non-smoking women (3225 g). No evidence of a dose–effect relationship between maternal blood carboxyhaemoglobin and infant birth weight was presented, but the correlation coefficient between birth weight and the mean carboxyhaemoglobin measurements of each individual was statistically significant ($P < 0.05$). No attempts were made to adjust for other potential growth-retarding factors in cigarette smoke (e.g., nicotine), which may also have effects on birth weight and cannot be disregarded.

There is one case reported in which a 17-year-old healthy female of 37 weeks’ gestation was exposed to carbon monoxide while a passenger in a car. The exposure was for two periods of 3 h each and resulted in headache, nausea, vomiting and chest pain; she became unresponsive while being transferred to hospital. On examination, physical signs were normal except that she was orientated to person and time but not to place. Oxygen partial pressure was 30.5 kPa (229 mmHg), and carboxyhaemoglobin was 47.2%. Results of fetal monitoring were consistent with acute fetal hypoxia. The patient was treated with supplemental oxygen immediately and approximately 2 h after admission to the hospital; hyperbaric oxygen treatment was initiated (100% oxygen at 243 kPa [2.4 atm] absolute for 90 min). After treatment, the subject’s carboxyhaemoglobin was 2.4% (within the normal range for a pregnant female) and fetal heart rate was 140 beats per minute, with normalized beat-to-beat variability. The patient was delivered at term of a health female child (3600 g) with Apgar scores of 9 at 1 min and 10 at 5 min post-delivery. The newborn’s physical condition, including neurological findings, was normal, and mother and child were discharged from hospital 2 days postpartum. Assessment of the child at 2 and 6 months revealed normal growth and development (Van Hoesen et al., 1989).
Koren et al. (1991), in a multicentre prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy, reported on a total of 40 pregnancies, which included 3 twin births, 1 termination of pregnancy and 4 ongoing pregnancies. Exposure to carbon monoxide occurred in the first trimester in 12 pregnancies, the second trimester in 14 pregnancies and the third trimester in 14 pregnancies. The analyses were based on 38 babies. The trimester at the time of carbon monoxide exposure did not affect mean birth weight (3.4 ± 0.5 kg, excluding the twin births and offspring of mothers who smoked 20 cigarettes a day). The exposure was stratified into grades based on clinical symptoms and signs and carboxyhaemoglobin levels where available. Adverse fetal outcome occurred only after grade 4 or 5 poisoning (carboxyhaemoglobin $>21\%$). There were two grade 5 cases; one resulted in stillbirth at 29 weeks of gestation (26% carboxyhaemoglobin, treated with high-flow oxygen), and the second resulted in fetal death at term followed by maternal death. Of the three cases of grade 4 severity (which included the case described by van Hoesen et al., 1989), two were treated with hyperbaric oxygen, and their infants were developing well at 1 year of age. The third case was exposed to carbon monoxide at 23 weeks of gestation and had a carboxyhaemoglobin of 25% 2 h after the exposure. She was treated with high-flow oxygen for 2 h; although she was delivered of a normal infant at term (birth weight 4 kg), the child at 8 months of age had poor head control and developmental delay, which were judged to be compatible with post-anoxic encephalopathy. One patient with grade 2 poisoning at 30 weeks’ gestation (carboxyhaemoglobin 13.8%) was treated with high-flow oxygen for 7 h followed by hyperbaric oxygen for 2 h. She delivered a 3.2-kg infant, who was developing normally at 3 weeks of age. The other grade 2 case was exposed at 20 weeks’ gestation, and the baby, born at 25 weeks, had respiratory distress syndrome and jaundice; at 3 months of age, the infant was developing appropriately. All of the infants of mothers with grade 1 symptoms (10 treated with high-flow oxygen, 19 untreated) developed normally.

In a prospective study designed to assess hyperbaric oxygen tolerance in pregnancy, 44 pregnant women who had been exposed to carbon monoxide were treated with hyperbaric oxygen (203 kPa [2 atm] absolute) for 2 h followed by 4 h of normobaric oxygen within 5.3 ± 3.7 h of the exposure, irrespective of the clinical severity of the intoxication and the stage of the pregnancy. Six patients were lost to
follow-up, two sustained spontaneous abortion and one elected to terminate the pregnancy for reasons unrelated to the intoxication. Thirty-four women gave birth to normal newborns, and one gave birth to a child with Down’s syndrome. There was no evidence that the use of hyperbaric oxygen was implicated in either of the spontaneous abortions. It was concluded that hyperbaric oxygen treatment may be used in pregnant women acutely poisoned with carbon monoxide (Elkharrat et al., 1991).

A prospective study was carried out in Lille, France, in which every pregnant woman admitted to the hyperbaric oxygen unit between January 1983 and December 1989 with carbon monoxide poisoning was evaluated. According to the protocol of the unit, every patient was treated with hyperbaric oxygen. Follow-up data were obtained on 86 of 90 women; when compared with a matched population of carbon monoxide-poisoned non-pregnant women, no difference was observed in source of carbon monoxide, clinical severity, carboxyhaemoglobin or plasma bicarbonate concentrations. Short-term complications were more common in the pregnant women compared with the matched group, but long-term outcome did not differ. In five cases, carbon monoxide intoxication led to fetal death (a fourfold increase in relative risk), 77 women (89.5%) had a successful pregnancy, and the prematurity, fetal hypotrophy and malformation rate were the same as those of the general population. It was concluded that although carbon monoxide intoxication induced an increase in the short-term maternal complication rate and the fetal death rate, the long-term outcome for both the mother and infant where hyperbaric oxygen had been used was not different from that of the general population (Mathieu et al., 1996a).

In summary, carbon monoxide is transferred slowly to the fetus, and fetal haemoglobin has a higher affinity for carbon monoxide than does that of the adult. The oxygen dissociation curve is shifted to the left, making the fetal hypoxia more pronounced than the maternal tissue hypoxia. The severity of fetal intoxication cannot be assessed by the maternal state. There is a difference between the rate of formation of carboxyhaemoglobin in the mother’s and the fetus’s blood. Moreover, in comparison with the mother’s dissociation curve, the curve in the fetus is shifted to the right. These two mechanisms result in a significant delay in elimination of carbon monoxide from the fetus, thus prolonging exposure. High doses of carbon monoxide are
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without doubt able to cause fetal death (Norman & Halton, 1990), developmental disorders and reduced fetal growth. The dose–response functions for these effects are, however, not known, and no safe level of exposure has been defined based upon scientific data. Case reports have generally been based upon high and toxic doses of carbon monoxide. There is a lack of follow-up studies on women with low and chronic carbon monoxide exposure, especially on central nervous system development in their children.

8.2.7.2 Reduced birth weight

Studies relating human carbon monoxide exposure from ambient sources or cigarette smoking to reduced birth weight have frequently failed to take into account all sources of carbon monoxide exposure. Alderman et al. (1987), for example, studied the relationship between birth weight and maternal carbon monoxide exposure based upon neighbourhood ambient carbon monoxide data obtained from stationary air monitoring sites in Denver, Colorado, USA. They failed to show a relationship between these factors, but they also failed to control for maternal cigarette smoking or possible occupational exposures to carbon monoxide. Carboxyhaemoglobin measurements were not made among either the mothers or their offspring to estimate net exposure levels. A similar design problem is found in the study of Wouters et al. (1987), in which cord blood carboxyhaemoglobin and birth weight were correlated. The authors reported a significant correlation between cigarette smoking and reduced birth weight, but no correlation between cord blood carboxyhaemoglobin and birth weight. Such data might be interpreted to mean that carbon monoxide is not the component in cigarette smoke responsible for reduced birth weight. Such a conclusion appears to be unjustified based upon Wouters et al. (1987), because carboxyhaemoglobin is a good estimate of recent carbon monoxide exposure only. Thus, it may indicate only how recently women in this study smoked their last cigarette before delivery of the child rather than estimating smoking rates or history throughout pregnancy.

Other studies have related indirect exposure to smoke in pregnancy with reduced birth weights. Martin & Bracken (1986) showed an association between passive smoking (exposure to cigarette smoke for at least 2 h per day) and reduced birth weight. Unfortunately, sidestream smoke contains significant nicotine as well as
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carbon monoxide, so it is not possible to relate this effect to carbon monoxide exposure.

Mochizuki et al. (1984) attempted to evaluate the role of maternal nicotine intake in reduced birth weight and presented evidence of possibly impaired utero-placental circulation among smokers. These changes were not related specifically to the nicotine content of the cigarettes and failed, moreover, to take into account the possible synergistic effects between reduced perfusion that might have resulted from the vasoconstrictive effects of nicotine and the reduced oxygen availability that might have resulted from carbon monoxide exposure. As noted in the section of this report that deals with the effects of high altitude (section 8.2.8), many of the outcomes of maternal carbon monoxide exposure are also observed in offspring of women living at high altitude. These include reduced birth weight, increased risk of perinatal mortality and increased risk of placental abnormalities. Limited data exist on the possibility of increased risk of carbon monoxide exposure to the fetus being carried at high altitude. Such findings are considered in the section on high altitude.

8.2.7.3 Sudden infant death syndrome

There have been a number of studies linking maternal cigarette smoking with sudden infant death syndrome (Schoendorf & Kiely, 1992; Mitchell et al., 1993; Scragg et al., 1993; Klonoff-Cohen et al., 1995; Blair et al., 1996; Hutter & Blair, 1996), but it is uncertain what the role of carbon monoxide might be in such a relationship.

It has been suggested that carbon monoxide may be a causative factor in sudden infant death syndrome. Hoppenbrouwers et al. (1981) reported a statistical association between the frequency of sudden infant death syndrome and levels of several airborne pollutants, including carbon monoxide, sulfur dioxide, nitrogen dioxide and hydrocarbons. Sudden infant death syndrome was reported more commonly in the winter, at a time when the burning of fossil fuels for heating would be greatest. It is interesting to note that there is a phase lag of approximately 7 weeks between the increase in pollutant levels and the increase of sudden infant death syndrome. Further correlations were obtained between sudden infant death syndrome and the predicted level of carbon monoxide and lead for the child’s birth month and between sudden infant death syndrome and the level of pollution at the reporting station closest to the infant’s home. These
correlations are not compelling without more information on the methods by which other possible risk factors were controlled in making the geographical correlations. Although it is technically difficult, it would be very useful to obtain carboxyhaemoglobin levels close to the time of death in sudden infant death syndrome victims, as this would greatly assist in determining the incidence of elevated carbon monoxide exposure in such cases.

The current data from human children suggesting a link between environmental carbon monoxide exposures and sudden infant death syndrome are weak, but further study should be encouraged.

8.2.7.4 Neurobehavioural effects

Behaviour is an essential function of the nervous system, and abnormalities in this outcome can be diagnostic for particular neurological disorders or for nervous system dysfunction. Because at present no data are available on behavioural changes of children with chronically elevated carboxyhaemoglobin, this section discusses only the findings of acute studies. However, these studies are not adequate for evaluating the dose–effect relationship to be used in ambient air standard setting. Because carboxyhaemoglobin levels are almost always determined at hospital admission time, they will be lower than the carboxyhaemoglobin levels at exposure time. Therefore, except for the confirmation of carbon monoxide inhalation, it is difficult to use these carboxyhaemoglobin levels to estimate severity of poisoning at time of exposure.

Crocker & Walker (1985) reported on the consequences of acute carbon monoxide exposure in 28 children, 16 of which had carboxyhaemoglobin levels over 15% and were considered to have had “potentially toxic” carboxyhaemoglobin levels. These children were between the ages of 8 months and 14 years. The authors reported nausea, vomiting, headache, lethargy and syncope to be the most common signs and symptoms. A very limited follow-up investigation was performed with these children, so no conclusions can be drawn from this work concerning persisting effects. In addition to very large differences in the nature (dose and duration) of exposure, the extreme variability in patient age limits the potential value of the data presented in this work. The absence of any reports from children having carboxyhaemoglobin levels of ≥5% (a very high carboxyhaemoglobin level) is regrettable, because these are the children one
must study to develop an understanding of the relationship between
dose and effect for the purpose of setting standards for ambient air.

Klees et al. (1985) conducted a more comprehensive study of the
consequences of childhood carbon monoxide exposure on subsequent
behavioural development. They reported that the age at which
exposure occurred, its severity and also the child’s intellectual level
at the time of exposure also play a role in the outcome.

The authors suggested that the severity of neurobehavioural
effects depends on the exposure period when it occurs at a critical
time of the development of certain neurobehavioural functions.
Subjects who had higher intellectual function prior to accidental
exposure also appeared to fare better after carbon monoxide exposure.
However, the authors stressed that long-term perceptual and
intellectual consequences of carbon monoxide exposure may occur
that are not well identified in short-term cursory examinations,
because certain invisible visuo-spatial disorders persisting for years
may seriously impair adaptive functioning of the child. Because of the
difficulty of interpreting carboxyhaemoglobin levels on hospital
admission, the authors adopted the following criteria to evaluate
intensity of intoxication: (1) light: hypotonia, vertigo, vomiting, etc.;
(2) medium: loss of consciousness (short period); (3) severe: any of
the previous symptoms followed by coma. Of 14 children followed up
for 2–11 years after intoxication, only 1 (medium) showed no sequelae
(despite carboxyhaemoglobin levels of 42% on admission to hospital
at the age of 9 years 10 months). Seven children (four light, three
medium) had impairment of visual memory and concentration, but
normal IQ scores. Six children (two light, one medium, three severe)
who had serious learning disorders did not have more severe carbon
monoxide exposures as judged from their carboxyhaemoglobin levels.
They include several cases where exposures did occur at a young age
and children who had psychological difficulties prior to carbon
monoxide exposure. This study leaves some question concerning the
relative vulnerability of children to carbon monoxide as a function of
their age, because several of the youngest children did make full
recovery, whereas others did not. It seems likely that the child’s age
may have an influence, as well as the promptness of hospitalization
and efficacy of treatment. Further study of the outcomes of childhood
carbon monoxide exposures will be useful in determining whether
there are differences with respect to vulnerability to carbon monoxide
level.
Venning et al. (1982) reported on a case of acute carbon monoxide poisoning in a 13-week-old baby who had profoundly elevated carboxyhaemoglobin levels (60% 2 h after removal from the automobile in which she had been accidentally exposed to carbon monoxide). Her parents had much lower carboxyhaemoglobin values, although this may reflect differences in concentration of carbon monoxide inhaled. The child was reported to be unconscious for 48 h, to go through convulsions over the next 18 days, but to show recovery from “minor neurological abnormalities” by 6 weeks later.

8.2.8 High-altitude effects

8.2.8.1 Introduction

Although there are many studies comparing and contrasting inhaling carbon monoxide with exposure to altitude, there are relatively few reports on the effects of inhaling carbon monoxide at altitude. There are data to support the possibility that the effects of these two hypoxia episodes are at least additive. These data were obtained at carbon monoxide concentrations that are too high to have much significance for regulatory concerns. There are also data that indicate decrements in visual sensitivity and flicker fusion frequency in subjects exposed to carbon monoxide (5–10% carboxyhaemoglobin) at higher altitudes. These data, however, are somewhat controversial.

There are even fewer studies of the long-term effects of carbon monoxide at high altitude. These studies generally indicate few changes at carbon monoxide concentrations below 110 mg/m³ (100 ppm) and altitudes below 4570 m. A provocative study by McDonagh et al. (1986) suggests that the increase in ventricular capillarity seen with altitude exposure may be blocked by carbon monoxide. The fetus may be particularly sensitive to the effects of carbon monoxide at altitude; this is especially true with the high levels of carbon monoxide associated with maternal smoking.

Precise estimates of the number of people exposed to carbon monoxide at high altitude are not readily available. As of 1980, however, more than 4.2 million people (T.K. Lindsey, letter to Dr. J. McGrath dated 4 July 1989, Forestville, Maryland, USA) were living at altitudes in excess of 1525 m. Moreover, estimates obtained from several US states with mountainous regions (i.e., California, Nevada,
Hawaii and Utah) indicate that more than 35 million tourists may sojourn in high-altitude areas during the summer and winter months.

The potential effects on human health of inhaling carbon monoxide at high altitudes are complex. Whenever carbon monoxide binds to haemoglobin, it reduces the amount of haemoglobin available to carry oxygen. People at high altitudes already live in a state of hypoxaemia, however, because of the reduced $P_{O_2}$ in the air. Carbon monoxide, by binding to haemoglobin, intensifies the hypoxaemia existing at high altitudes by further reducing transport of oxygen to the tissues. Hence, the effects of carbon monoxide and high altitude are usually considered to be additive.

This consideration does not take into account the fact that within hours of arrival at high altitude, certain physiological adjustments begin to take place. Haemoconcentration occurs, and the increased haemoglobin concentration offsets the decreased oxygen saturation and restores oxygen concentration to pre-ascent levels. Consequently, the simple additive model of carboxyhaemoglobin and altitude hypoxaemia may be valid only during early altitude exposure.

The visitor newly arrived to higher altitudes may be at greater risk from carbon monoxide than the adapted resident, however, because of a non-compensated respiratory alkalosis from hyperventilation, lower arterial haemoglobin saturation without a compensatory absolute polycythaemia (therefore greater hypoxaemia) and hypoxia-induced tachycardia.

Several factors tend to exacerbate ambient carbon monoxide levels at high altitude (Kirkpatrick & Reeser, 1976). For example, carbon monoxide emissions from automobiles are likely to be higher in mountain communities. Early studies on automobile emissions showed that automobiles tuned for driving at 1610 m emit almost 1.8 times more carbon monoxide when driven at 2440 m. Automobiles tuned for driving at sea level emit almost 4 times more carbon monoxide when driven at 2440 m. Moreover, automobile emissions are increased by driving at reduced speeds, along steep grades and under poor driving conditions. Therefore, large influxes of tourists driving automobiles tuned for sea level conditions into high-altitude resort areas may drastically increase pollutant levels in general, and carbon monoxide levels in particular (NRC, 1977).
Although emission data comparing sea level and high-altitude conditions for the current automobile fleet are not yet available, newer automobile engine technologies should significantly reduce carbon monoxide emissions in general, as well as carbon monoxide emissions at high altitude. Heating devices (space heaters and fireplaces) used for social effect, as well as warmth, are a second factor contributing to carbon monoxide emissions in mountain resort areas. Finally, population growth in mountain areas is concentrated along valley floors; this factor, combined with the reduced volume of air available for pollutant dispersal in valleys, causes pollutants, including carbon monoxide, to accumulate in mountain valleys.

8.2.8.2 Carboxyhaemoglobin formation

The effects of high altitude on carboxyhaemoglobin formation have been considered in a theoretical paper by Collier & Goldsmith (1983). Transforming and rearranging the CFK equation (Coburn et al., 1965), these workers derived an equation expressing carboxyhaemoglobin in terms of endogenous and exogenous sources of carbon monoxide. According to this relationship, a given partial pressure of carbon monoxide will result in a higher percent carboxyhaemoglobin at high altitudes (where \( P_{O_2} \) is reduced). Thus, Collier & Goldsmith (1983) calculated an incremental increase in carboxyhaemoglobin at altitude even in the absence of inhaled carbon monoxide that is most likely due to endogenous production of carbon monoxide (see Table 17).

8.2.8.3 Cardiovascular effects

There are studies comparing the cardiovascular responses to carbon monoxide with those to high altitude, but there are relatively few studies of the cardiovascular responses to carbon monoxide at high altitude. Forbes et al. (1945) reported that carbon monoxide uptake increased during 6 min of exercise of varying intensity on a bicycle ergometer at an equivalent altitude of 4875 m. The increased carbon monoxide uptake was caused by altitude hyperventilation stimulated by decreased arterial oxygen tension and not by diminished barometric pressure.

Pitts & Pace (1947) reported that pulse rate increased in response to the combined stress of high altitude and carbon monoxide. The subjects were 10 healthy men who were exposed to simulated altitudes
Table 17. Calculated equilibrium values of percent carboxyhaemoglobin and percent oxyhaemoglobin in humans exposed to ambient carbon monoxide at various altitudes\(^{a,b}\)

<table>
<thead>
<tr>
<th>Ambient CO</th>
<th>Sea level</th>
<th>1530 m</th>
<th>3050 m</th>
<th>3660 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/m(^3)</td>
<td>ppm</td>
<td>% COHb</td>
<td>% O(_2)Hb</td>
<td>% COHb</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td>97.3</td>
<td>0.26</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>0.8</td>
<td>96.8</td>
<td>0.9</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>1.4</td>
<td>96.2</td>
<td>1.6</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>2.1</td>
<td>95.6</td>
<td>2.3</td>
</tr>
<tr>
<td>18</td>
<td>16</td>
<td>2.7</td>
<td>95.1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

\(^{a}\) The table is for unacclimatized, sedentary individuals at one level of activity (oxygen uptake of 500 ml/min).

\(^{b}\) Adapted from Collier & Goldsmith (1983).
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of 2135, 3050 and 4570 m and inhaled 3400 or 6900 mg carbon monoxide/m³ (3000 or 6000 ppm) to obtain carboxyhaemoglobin levels of 6% or 13%, respectively. The mean pulse rate during exercise and the mean pulse rate during the first 5 min after exercise were correlated with and increased with the carboxyhaemoglobin concentration and simulated altitude. The authors concluded that the response to a 1% increase in carboxyhaemoglobin level was equivalent to that obtained by raising a normal group of men 100 m in altitude. This relationship was stated for a range of altitudes from 2135 to 3050 m and for increases in carboxyhaemoglobin up to 13%.

Weiser et al. (1978) studied the effects of carbon monoxide on aerobic work at 1610 m in young subjects rebreathing from a closed-circuit system containing a bolus of 100% carbon monoxide until carboxyhaemoglobin levels reached 5%. They reported that this level of carboxyhaemoglobin impaired exercise performance at high altitude to the same extent as that reported at sea level (Horvath et al., 1975). Because these subjects were Denver, Colorado, USA, residents and were fully adapted to this altitude, however, they would have had an arterial oxygen concentration the same as at sea level (about 20 ml oxygen/dl). Hence, 5% carboxyhaemoglobin would lower arterial oxygen concentration about the same amount at both altitudes and impair work performance at altitude to the same extent as at sea level. In the Weiser et al. (1978) study, breathing carbon monoxide during submaximal exercise caused small but significant changes in cardiorespiratory function; the working heart rate increased, and post-exercise left ventricular ejection time did not shorten to the same extent as when filtered air was breathed. Carbon monoxide exposure lowered the anaerobic threshold and increased minute ventilation at work rates heavier than the anaerobic threshold due to increased blood lactate levels.

Wagner et al. (1978) studied young smokers and non-smokers who exercised at 53% of $\dot{V}_O_2\text{max}$ at 101.3 and 69.7 kPa (760 and 523 torr). Carboxyhaemoglobin levels were raised to 4.2%. While at altitude with these elevated carboxyhaemoglobin levels, non-smokers increased their cardiac output and decreased their arterial–mixed venous oxygen differences. Smokers did not respond in a similar manner. Smokers, with their initial higher haemoglobin concentrations, may have developed some degree of adaptation to carbon monoxide and/or high altitude.
In a complex study involving four altitudes ranging from sea level up to 3050 m and four ambient carbon monoxide concentrations (up to 170 mg/m$^3$ [150 ppm]), Horvath et al. (1988a,b) evaluated carboxyhaemoglobin levels during a maximal aerobic capacity test. They concluded that $\bar{V}_{O_2}$ max values determined in men and women were only slightly diminished as a result of increased ambient carbon monoxide. Carboxyhaemoglobin concentrations attained at maximum were highest at 55 m (4.42%) and lowest at 3050 m (2.56%) while breathing 170 mg carbon monoxide/m$^3$ (150 ppm). This was attributed to the reduced partial pressure of carbon monoxide at high altitude. No additional effects that could be attributed to the combined exposure to high altitude and carbon monoxide were found. Independence of the altitude and carbon monoxide hypoxia was demonstrated under the condition of performing a maximum aerobic capacity test. The reductions in $\bar{V}_{O_2}$ max due to high altitude and to the combined exposure of ambient carbon monoxide and high altitude were similar.

Horvath & Bedi (1989) studied 17 non-smoking young men to determine the alterations in carboxyhaemoglobin during exposure to ambient carbon monoxide at 0 or 10 mg/m$^3$ (0 or 9 ppm) for 8 h at sea level or an altitude of 2135 m. Nine subjects rested during the exposures, and eight exercised for the last 10 min of each hour at a mean ventilation of 25 litres (at body temperature, barometric pressure, saturated conditions). All subjects performed a maximal aerobic capacity test at the completion of their respective exposures. At the low carbon monoxide concentrations studied, the CFK equation estimated carboxyhaemoglobin levels to be 1.4% (Peterson & Stewart, 1975). Carboxyhaemoglobin concentrations fell in all subjects during their exposures to 0 mg carbon monoxide/m$^3$ (0 ppm) at sea level or 2135 m. During the 8-h exposures to 10 mg carbon monoxide/m$^3$ (9 ppm), carboxyhaemoglobin levels rose linearly from approximately 0.2% to 0.7%. No significant differences in uptake were found whether the subjects were resting or intermittently exercising. Levels of carboxyhaemoglobin were similar at both altitudes. A portion of the larger estimate of carboxyhaemoglobin determined by the CFK equation could be accounted for by the use of an assumed blood volume. Maximal aerobic capacity was reduced approximately 7–10% consequent to altitude exposure during 0 mg carbon monoxide/m$^3$ (0 ppm). These values were not altered following 8-h exposure to 10 mg carbon monoxide/m$^3$ (9 ppm) in either resting or exercising individuals.
In a study of patients with coronary artery disease, Leaf & Kleinman (1996) performed exercise stress tests after random exposures to either carbon monoxide or clean air at sea level or a simulated 2.1-km-high altitude. The carbon monoxide and high-altitude conditions were each selected to reduce the percentage of oxygen saturation of arterial blood by 4%. Levels of carboxyhaemoglobin were increased from an average of 0.62% after clean air exposure to 3.91% after carbon monoxide exposure. The average incidence of exercise-induced ventricular ectopy was approximately doubled after exposure to carbon monoxide or high altitude compared with clean air exposures (from 10 to approximately 20 premature ventricular contractions). There was also a significant trend of increased ectopy with decreased oxygen saturation. No effects were observed in subjects who were free from ectopy. These results indicate that individuals having coronary artery disease and baseline ectopy are susceptible to increased levels of hypoxaemia resulting from either hypoxic or carbon monoxide exposures.

Exposure to carbon monoxide from smoking may pose a special risk to the fetus at altitude. Moore et al. (1982) reported that maternal smoking at 3100 m was associated with a two- to threefold greater reduction in infant birth weight than has been reported at sea level. Moreover, carboxyhaemoglobin levels of 1.8–6.2% measured in all pregnant subjects were inversely related to infant birth weight. Earlier, Brewer et al. (1970, 1974) reported that the mean carboxyhaemoglobin level in smokers at altitude is higher than in smokers at sea level, and that subjects who smoked had greater oxygen affinities than non-smokers. Moreover, cessation of smoking by polycythaemic individuals at altitude results in a marked reduction in carboxyhaemoglobin and a decrease in oxygen–haemoglobin affinity to values less than those reported for normal individuals at sea level.

8.2.8.4 Neurobehavioural effects

The neurobehavioural effects following carbon monoxide exposure are controversial and should, therefore, be interpreted with extreme caution. Those neurobehavioural studies specifically concerned with carbon monoxide exposure at altitude are reviewed briefly in this section.

McFarland et al. (1944) reported changes in visual sensitivity occurring at a carboxyhaemoglobin concentration of 5% or at a
simulated altitude of approximately 2430 m. Later, McFarland (1970) expanded on the original study and noted that a pilot flying at 1830 m breathing 0.005% (57 mg/m$^3$ [50 ppm]) carbon monoxide in air is at an altitude physiologically equivalent to approximately 3660 m. McFarland (1970) stated that sensitivity of the visual acuity test was such that even the effects of small quantities of carbon monoxide absorbed from cigarette smoke were clearly demonstrable. In subjects inhaling smoke from three cigarettes at 2285 m, there was a combined loss of visual sensitivity equal to that occurring at 3050–3355 m. Results from the original study were confirmed by Halperin et al. (1959), who also observed that recovery from the detrimental effects of carbon monoxide on visual sensitivity lagged behind elimination of carbon monoxide from the blood.

Lilienthal & Fugitt (1946) reported that combined exposure to altitude and carbon monoxide decreased flicker fusion frequency (i.e., the critical frequency in cycles per second at which a flickering light appears to be steady). Whereas mild hypoxia (that occurring at 2745–3660 m) alone impaired flicker fusion frequency, carboxyhaemoglobin levels of 5–10% decreased the altitude threshold for onset of impairment to 1525–1830 m.

The psychophysiological effects of carbon monoxide at altitude are a particular hazard in high-performance aircraft (Denniston et al., 1978). Acute ascent to altitude increases ventilation via the stimulating effects of a reduced $P_{O_2}$ on the chemoreceptors. The increased ventilation causes a slight increase in blood pH and a slight leftward shift in the oxyhaemoglobin dissociation curve. Although such a small shift would probably have no physiological significance under normal conditions, it may take on physiological importance for aviators required to fly under a variety of operational conditions and to perform tedious tasks involving a multitude of cognitive processes. The leftward shift of the oxyhaemoglobin dissociation curve may be further aggravated by the persisting alkalosis caused by hyperventilation resulting from anxiety. The potential for this effect has been reported by Pettyjohn et al. (1977), who found that respiratory minute volume may be increased by 110% during final landing approaches requiring night vision devices. Thus, the hypoxia-inducing effects of carbon monoxide inhalation would accentuate the cellular hypoxia caused by stress- and altitude-induced hyperventilation.
8.2.8.5 Compartmental shifts

The shift of carbon monoxide out of the blood has been demonstrated in studies (Horvath et al., 1988a,b) conducted on both men and women undergoing maximal aerobic capacity tests at altitudes of 55, 1525, 2135 and 3060 m and carbon monoxide concentrations of 0, 57, 110 and 170 mg/m$^3$ (0, 50, 100 and 150 ppm). Carbon monoxide at maximum work shifted into extravascular spaces and returned to the vascular space within 5 min after exercise stopped.

8.3 Carbon monoxide poisoning

Carbon monoxide is responsible for more than half of the fatal poisonings that are reported all over the world each year (National Safety Council, 1982; Faure et al., 1983; Cobb & Etzel, 1991; Mathieu et al., 1996a). At sublethal levels, carbon monoxide poisoning occurs in a small but important fraction of the population. Certain conditions exist in both the indoor and outdoor ambient environments that cause a small percentage of the population to become exposed to dangerous levels of carbon monoxide. Outdoors, concentrations of carbon monoxide are highest near intersections, in congested traffic, near exhaust gases from internal combustion engines and from industrial combustion sources, and in poorly ventilated areas such as parking garages and tunnels. Indoors, carbon monoxide concentrations in the workplace or in homes that have faulty appliances or downdrafts and backdrafts have been measured in excess of 110 mg/m$^3$ (100 ppm), resulting in carboxyhaemoglobin levels of greater than 10% for 8 h of exposure. In addition, carbon monoxide is found in the smoke produced by all types of fires. Of the 6000 deaths from burns in the USA each year, more than half are related to inhalation injuries where victims die from carbon monoxide poisoning, hypoxia and smoke inhalation (Heimbach & Waeckerle, 1988). Despite efforts in prevention and in public and medical education, this intoxication remains frequent, severe and too often overlooked (Barret et al., 1985).

Carbon monoxide poisoning is not new, although more attention has been focused on this problem recently in the scientific literature as well as in the popular media. The first scientific studies of the hypoxic effects of carbon monoxide were described by Bernard in 1865. The attachment of carbon monoxide to haemoglobin, producing carboxyhaemoglobin, was evaluated by Douglas et al. (1912),
providing the necessary tools for studying human response to carbon monoxide. During the next half century, numerous studies were conducted, with the principal emphasis being on high concentrations of carboxyhaemoglobin. Carbon monoxide poisoning as an occupational hazard (Grut, 1949) received the greatest attention owing to the increased use of natural gas and the potential for leakage of exhaust fumes in homes and industry. Other sources of carbon monoxide have become more important and more insidious. The clinical picture of carbon monoxide poisoning, as described by Grut (1949), relates primarily to the alterations in cardiac and central nervous system function as a result of the extreme hypoxia induced.

Mortality from carbon monoxide exposure is high. In 1985, 1365 deaths due to carbon monoxide exposure were reported in England and Wales (Meredith & Vale, 1988). In the USA, more than 3800 people die annually from carbon monoxide (accidental and intentional), and more than 10,000 individuals seek medical attention or miss at least 1 day of work because of a sublethal exposure (US Centers for Disease Control, 1982). The per capita mortality and morbidity statistics for carbon monoxide are surprisingly similar for the Scandinavian countries and for Canada as well. However, not all instances of carbon monoxide poisoning are reported, and complete up-to-date data are difficult to obtain. In some places, continuous surveillance by recording all cases hospitalized for every hospital in the region covered has been set up by a poison centre that gives annual epidemiological reports at the local level (Mathieu et al., 1996a). Often the individuals suffering from carbon monoxide poisoning are unaware of their exposure, because symptoms are similar to those associated with the flu or with clinical depression. This may result in a significant number of misdiagnoses by medical professionals (Grace & Platt, 1981; Fisher & Rubin, 1982; Barret et al., 1985; Dolan et al., 1987; Heckerling et al., 1987, 1988; Kirkpatrick, 1987). Therefore, the precise number of individuals who have suffered from carbon monoxide intoxication is not known, but it is certainly larger than the mortality figures indicate. Nonetheless, the reported literature available for review indicates the seriousness of this problem.

The symptoms, signs and prognosis of acute poisoning correlate poorly with the level of carboxyhaemoglobin measured at the time of arrival at the hospital (Klees et al., 1985; Meredith & Vale, 1988). Carboxyhaemoglobin levels below 10% are usually not associated
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with symptoms. At the higher carboxyhaemoglobin saturations of 10–30%, neurological symptoms of carbon monoxide poisoning can occur, such as headache, dizziness, weakness, nausea, confusion, disorientation and visual disturbances. Exertional dyspnoea, increases in pulse and respiratory rates, and syncope are observed with continuous exposure producing carboxyhaemoglobin levels in excess of 30–50%. When carboxyhaemoglobin levels are higher than 50%, coma, convulsions and cardiorespiratory arrest may occur. There are numerous tables giving symptom-associated carboxyhaemoglobin levels and the corresponding carbon monoxide concentrations in the atmosphere (Ellenhorn & Barceloux, 1988). Examples are given in Table 18.

Different individuals experience very different clinical manifestations of carbon monoxide poisoning and, therefore, have different outcomes even under similar exposure conditions. Norkool & Kirkpatrick (1985) found that carboxyhaemoglobin levels in individuals who had never lost consciousness ranged from 5% to 47%. In individuals who were found unconscious but regained consciousness at hospital arrival, the range was 10–64%; for those remaining unconscious, carboxyhaemoglobin levels ranged from 1% to 53%. The large differences in carboxyhaemoglobin levels found in these individuals most likely resulted from differences in time elapsing from exposure to carbon monoxide and admission to the hospital. Considerable differences in exposure duration may also be responsible for the lack of correlation between blood carboxyhaemoglobin and the clinical severity of carbon monoxide poisoning (Sokal, 1985; Sokal & Kralkowska, 1985). These data clearly indicate that carboxyhaemoglobin saturations correlate so poorly with clinical status that they have little prognostic significance.

The level of carbon monoxide in the tissues may have an equal or greater impact on the clinical status of the patient compared with the level of carbon monoxide in the blood (Broome et al., 1988). The extent of tissue toxicity, which becomes significant under hypoxic conditions or with very high levels of carbon monoxide, is likely determined by the length of exposure. For example, a short exposure to carbon monoxide at high ambient concentrations may allow insufficient time for significant increases in tissue levels of carbon monoxide to occur. The syncope observed in individuals with carbon monoxide poisoning who were exposed in this manner may be the
Table 18. Symptoms associated with varying levels of carbon monoxide poisoning*

<table>
<thead>
<tr>
<th>CO in the atmosphere</th>
<th>COHb in blood</th>
<th>Physiological and subjective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>% mg/m³</td>
<td>ppm</td>
<td>(%)</td>
</tr>
<tr>
<td>0.007</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>0.01</td>
<td>140</td>
<td>120</td>
</tr>
<tr>
<td>0.02</td>
<td>250</td>
<td>220</td>
</tr>
<tr>
<td>0.035–0.052</td>
<td>400–600</td>
<td>350–520</td>
</tr>
<tr>
<td>0.080–0.122</td>
<td>900–1400</td>
<td>800–1220</td>
</tr>
<tr>
<td>0.195</td>
<td>2200</td>
<td>1950</td>
</tr>
</tbody>
</table>

* Adapted from Winter & Miller (1976).

result of simple hypoxia with rapid recovery despite high carboxyhaemoglobin levels. On the other hand, prolonged exposure to carbon monoxide prior to hospital arrival may allow sufficient uptake of carbon monoxide by tissues to inhibit the function of intracellular compounds such as myoglobin. This effect, in combination with the existing reduction in tissue oxygen, may cause irreversible central nervous system or cardiac damage.

Complications occur frequently in carbon monoxide poisoning. Immediate death from carbon monoxide is most likely cardiac in origin, because myocardial tissue is most sensitive to hypoxic effects of carbon monoxide. Severe poisoning results in marked hypotension and lethal arrhythmias, which may be responsible for a large number of pre-hospital deaths. Rhythm disturbances include sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions, ventricular tachycardia and fibrillation. Other documented electrocardiographic changes include decrease in the
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magnitude of the R-wave, ST elevation, T-wave inversion and heart block. Coronary underperfusion can lead to myocardial infarction, especially if coronary arteries are previously narrowed. Pulmonary oedema is a fairly common feature that makes routine chest X-ray mandatory in each carbon monoxide-poisoned patient (Mathieu & Wattel, 1990). Rhabdomyolysis and its consequence, renal failure, as well as pancreatitis, are also complications that may be seen in carbon monoxide poisoning.

Neurological manifestations of acute carbon monoxide poisoning include disorientation, confusion, coma, cogwheel rigidity, opisthotonic posturing, extremity flaccidity or spasticity, and extensor plantar response. Perhaps the most insidious effect of carbon monoxide poisoning is the delayed development of neuropsychiatric impairment. Within 1–3 weeks of poisoning, 15–40% of patients will manifest inappropriate euphoria, impaired judgement, poor concentration and relative indifference to obvious neurological deficits. Computed axial tomography can show low density in the area of globus pallidus in some patients with poor neurological outcome (Sawday et al., 1980), but this feature is not specific for carbon monoxide poisoning.

Observed ocular effects from case reports on acute carbon monoxide poisoning range from retinal haemorrhages (Dempsey et al., 1976; Kelley & Sophocleus, 1978) to blindness (Duncan & Gumpert, 1983; Katafuchi et al., 1985). In addition, Trese et al. (1980) described a case report of a 57-year-old woman having peripheral neuropathy and tortuous retinal vessels after chronic, intermittent exposure to low levels of carbon monoxide over a 16-month period. These authors speculated that increased blood flow from low-level, chronic exposure to carbon monoxide may lead to the development of a compensatory retinal vascular tortuosity. With high-level, acute exposures to carbon monoxide, the compensation will not take place, and localized vascular haemorrhages result.

Management of carbon monoxide-poisoned patients first consists of removing the patient from exposure to the toxic atmosphere and supplying pure oxygen to accelerate the elimination of carbon monoxide and improve tissue oxygenation. Respiratory and circulatory conditions are assessed rapidly, and resuscitative measures are performed if needed. Evaluation includes neurological status of conscious level, motor response and reflectivity, and a complete
physical examination looking for complications, associated trauma or intoxication, and previous disease. Laboratory exams should include a blood gas analysis to look for acidosis and a carboxyhaemoglobin measurement. Carboxyhaemoglobin levels over 5% in a non-smoker and over 10% in a smoker confirm the diagnosis but not the severity of intoxication (Ilano & Raffin, 1990).

Patients with carbon monoxide poisoning respond to treatment with 100% oxygen (Pace et al., 1950). If available, treatment with hyperbaric oxygen at 2.5–3 times atmospheric pressure for 90 min is preferable (Myers, 1986), but the precise conditions requiring treatment have been a topic of debate in the literature (Mathieu et al., 1985; Norkool & Kirkpatrick, 1985; Broome et al., 1988; Brown et al., 1989; James, 1989; Raphael et al., 1989; Roy et al., 1989; Thom & Keim, 1989; Van Hoesen et al., 1989). It has been suggested that if carboxyhaemoglobin is above 25%, hyperbaric oxygen treatment should be initiated (Norkool & Kirkpatrick, 1985), although treatment plans based on specific carboxyhaemoglobin saturations are not well founded (Thom & Keim, 1989). Most hyperbaric centres treat patients with carbon monoxide intoxication when they manifest loss of consciousness or other neurological signs and symptoms (excluding headache), regardless of the carboxyhaemoglobin saturation at presentation (Piantadosi, 1990). The first European Consensus Conference on hyperbaric medicine has concluded that hyperbaric oxygen is highly recommended in every comatose patient, every patient who had lost consciousness during exposure, every patient with abnormal neuropsychological manifestation and every pregnant woman (Mathieu et al., 1996b).

The half-time elimination of carbon monoxide while breathing air is approximately 320 min; when breathing 100% oxygen, it is 80 min; and when breathing oxygen at 304 kPa (3 atm), it is 23 min (Myers et al., 1985). In the case of normobaric oxygen treatment, length of oxygen administration is also controversial, but it appears that it must be long enough to ensure total carbon monoxide detoxication. Proposed durations are often between 12 and 48 h.

Successful removal of carbon monoxide from the blood does not ensure an uneventful recovery with no further clinical signs or symptoms. Neurological problems may develop insidiously weeks after recovery from the acute episode of carbon monoxide poisoning.
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(Meredith & Vale, 1988). These late neurological sequelae include intellectual deterioration, memory impairment and cerebral, cerebellar and midbrain damage. Smith & Brandon (1973) published a study in which they found 10% of cases with immediate gross neurological sequelae, but also 33% with delayed personality deterioration and 43% with memory disturbances. In a literature review, Ginsberg & Romano (1976) found between 15% and 40% of late cases with neurological sequelae. The explanation for neurological problems may lie in misdiagnosis (30% in a French Poison Control Center study; Mathieu et al., 1985), inadequate therapy (40% of the patients of Smith & Brandon, 1973, did not receive any oxygen in the emergency treatment) or delayed therapy. Complete recovery is obtained in more cases if oxygen is applied in less than 6 h (Barois et al., 1979).

Mathieu et al. (1996a) conducted a study on the long-term consequences of carbon monoxide poisoning and treatment by hyperbaric oxygen therapy on 774 patients, who were divided into five groups: group zero, in which patients suffered only from headache or nausea; group I, with abnormality in neurological examination; group II, where patients had lost consciousness regardless of their clinical state of admission; group III, in which patients were comatose (Glasgow coma scale 6); and group IV, where patients were deeply comatose. Group zero received only normobaric pure oxygen, while groups I, II, III and IV received hyperbaric oxygen. At 1 year only, 4.4% of patients suffered from persistent manifestation, and only 1.6% had major functional impairment. However, persistent neurological manifestations occurred only in patients from groups I and IV.

As in the previous study (Mathieu et al., 1996a) and in accordance with the Klees et al. (1985) conclusions, neither the clinical status nor the carboxyhaemoglobin level on hospital admission can predict the development of delayed neuropsychological changes. Thus, the authors advocate the use of hyperbaric oxygen in every carbon monoxide-poisoned patient who has suffered loss of consciousness during carbon monoxide exposure, who has a neurological abnormality upon clinical examination or who remains comatose upon admission. These results are in accordance with those obtained by Myers et al. (1981).

In conclusion, carbon monoxide poisoning remains frequent and severe with a relatively high risk of immediate death, complications
and late sequelae; furthermore, it is too often overlooked. The human data from cases of accidental high-dose carbon monoxide exposures are not adequate for evaluating the relationship between dose and effect and identifying a LOEL and a NOEL, or for setting carbon monoxide standards in ambient air, because of the small number of cases reviewed and problems in documenting levels of exposure. Nevertheless, they suggest that in some circumstances and meteorological conditions, acute poisoning can always occur in a chronic situation. This possibility has to be taken into account in defining standards. As well, such data, if systematically gathered and reported, could be useful in identifying possible ages of special sensitivity to carbon monoxide and cofactors or other risk factors that might identify sensitive subpopulations.
9. EVALUATION OF HEALTH RISKS

9.1 Introduction

Most of the critical information on the human health effects of carbon monoxide discussed in this document has been derived by consideration of data from two carefully defined population groups — young, healthy adults and patients with diagnosed coronary artery disease. In addition to laboratory studies, supporting evidence has been obtained from epidemiological and clinical studies as well as reports of accidental exposures. On the basis of the known effects described, patients with reproducible exercise-induced ischaemia appear to be a well-defined sensitive group within the general population that is at increased risk for experiencing health effects (i.e., decreased exercise duration due to exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient carbon monoxide exposure concentrations that result in carboxyhaemoglobin levels down to 3%. A smaller sensitive group of healthy individuals experiences decreased exercise duration at similar levels of carbon monoxide exposure, but only during short-term maximal exercise. Decrements in exercise duration in the healthy population, therefore, would be mainly of concern to competing athletes rather than to ordinary people carrying out the common activities of daily life.

From both clinical and theoretical work and from experimental research on laboratory animals, certain other groups in the population are identified as being at probable risk from exposure to carbon monoxide. These probable risk groups include (1) fetuses and young infants, (2) pregnant women, (3) the elderly, especially those with compromised cardiopulmonary or cerebrovascular functions, (4) individuals with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease, (5) individuals with congestive heart failure, (6) individuals with peripheral vascular or cerebrovascular disease, (7) individuals with haematological diseases (e.g., anaemia) that affect oxygen carrying capacity or transport in the blood, (8) individuals with genetically unusual forms of haemoglobin associated with reduced oxygen carrying capacity, (9) individuals with chronic obstructive lung diseases, (10) individuals using medicinal or recreational drugs having effects on the brain or cerebrovasculature, (11) individuals exposed to other pollutants (e.g., methylene chloride) that increase endogenous formation of carbon monoxide and
(12) individuals who have not been adapted to high altitude and are exposed to a combination of high altitude and carbon monoxide.

Little empirical evidence is currently available by which to specify health effects associated with ambient or near-ambient carbon monoxide exposures for most of these probable risk groups. Whereas the previous chapters dealt with documented evidence of carbon monoxide exposure through controlled or natural laboratory investigations, in this chapter an effort will be made to determine the anticipated effects of carbon monoxide in special subpopulations that form a significant proportion of the population at large.

As well, guideline values for ambient air carbon monoxide exposure and recommendations for further research and protection of human health are provided in this chapter.

9.2 Age, gender and pregnancy as risk factors

The fetus and newborn infant are theoretically susceptible to carbon monoxide exposure for several reasons. Fetal circulation is likely to have a higher carboxyhaemoglobin level than the maternal circulation as a result of differences in uptake and elimination of carbon monoxide from fetal haemoglobin. Because the fetus also has a lower oxygen tension in the blood than adults, any further drop in fetal oxygen tension owing to the presence of carboxyhaemoglobin could have a potentially serious effect. The newborn infant with a comparatively high rate of oxygen consumption and lower oxygen transport capacity for haemoglobin than most adults would also be potentially susceptible to the hypoxic effects of increased carboxyhaemoglobin. Newer data from laboratory animal studies on the developmental toxicity of carbon monoxide suggest that prolonged exposure to high levels (>110 mg/m\(^3\) [>100 ppm]) of carbon monoxide during gestation may produce a reduction in birth weight, cardiomegaly and delayed behavioural development. Human data are scant and more difficult to evaluate, but further research is warranted. Additional studies are therefore needed to determine if chronic exposure to carbon monoxide, particularly at low, near-ambient levels, can compromise the already marginal conditions existing in the fetus and newborn infant.
The effects of carbon monoxide on maternal–fetal relationships are not well understood. In addition to fetuses and newborn infants, pregnant women also represent a susceptible group, because pregnancy is associated with increased alveolar ventilation and an increased rate of oxygen consumption that serves to increase the rate of carbon monoxide uptake from inspired air. Perhaps a more important factor is that pregnant women experience haemodilution as a result of the disproportionate increase in plasma volume compared with erythrocyte volume. This group, therefore, should be studied to evaluate the effects of carbon monoxide exposure and elevated carboxyhaemoglobin levels.

Changes in metabolism with age may make the aging population particularly susceptible to the effects of carbon monoxide. Maximal oxygen uptake declines steadily with age. The rate of decline in the population is difficult to determine, however, partly because of the wide range of values reported in the cross-sectional and longitudinal studies published in the literature, and partly because of confounding factors such as heredity, changes in body weight and composition, and level of physical activity.

By the time an average healthy, non-smoking male reaches the age of 65 years, the maximal oxygen uptake will be about 23 ± 5 ml/kg body weight per minute. At 75 years of age, the maximal oxygen uptake will be about 17 ± 5 ml/kg body weight per minute. The decline in maximal oxygen uptake with age seems to be the same in females, as well. However, because females have about 20–25% lower maximal oxygen uptake, the corresponding values will occur about 5–8 years earlier in females. In physically active individuals, the corresponding values will occur about 10–15 years later than in the average sedentary person.

### 9.3 Risk of carbon monoxide exposure in individuals with pre-existing disease

#### 9.3.1 Subjects with coronary artery disease

Coronary heart disease is one of the major causes of death and disability in the world, especially in industrialized societies. In a 1996 WHO estimate, 7.2 million deaths globally were caused by coronary heart disease, which ranked first in leading causes of death (WHO,
Although deaths from coronary heart disease constitute only about 14% of the global total number of deaths, they are responsible for about one-third of all deaths in industrialized societies. The coronary heart disease epidemic began in industrialized societies in the early decades of the 20th century. Its death rates peaked in the 1960s and early 1970s and have since declined dramatically. On the other hand, coronary heart disease is now increasing in developing countries as their populations age and adopt unhealthy habits and behaviours. The world’s highest coronary heart disease mortality rates are now found in eastern and central Europe.

According to data compiled by the American Heart Association (1989), persons with diagnosed coronary artery disease numbered 5 million in 1987 and 7 million in 1990, the latter being about 3% of the total US population (Collings, 1988; US Department of Health and Human Services, 1990). These persons have myocardial ischaemia, which occurs when the heart muscle receives insufficient oxygen delivered by the blood. For some, exercise-induced angina pectoris can occur. In all patients with diagnosed coronary artery disease, however, the predominant type of ischaemia, as identified by ST-segment depression, is asymptomatic (i.e., silent). In other words, patients who experience angina usually have more ischaemic episodes that are asymptomatic. Unfortunately, some individuals in the population have coronary artery disease but are totally asymptomatic. It has been estimated that 5% of middle-aged men develop a positive exercise test, one of the signs of ischaemia. A significant number of these men will have angiographic evidence of coronary artery disease (Cohn, 1988; Epstein et al., 1988, 1989). For example, in the USA, more than 1 million heart attacks occur each year, half of them being fatal (American Heart Association, 1989). About 10–15% of all myocardial infarctions are silent (Kannel & Abbott, 1984; Epstein et al., 1988). Of the 500 000 survivors of hospitalized myocardial infarction, about 10% are asymptomatic but have signs of ischaemia. Thus, many more persons, as many as 3–4 million Americans (American Heart Association, 1989), are not aware that they have coronary heart disease and may constitute a high-risk group.

Persons with both asymptomatic and symptomatic coronary artery disease have a limited coronary flow reserve and therefore will be sensitive to a decrease in oxygen carrying capacity induced by carbon monoxide exposure. In addition, carbon monoxide might exert
a direct effect on vascular smooth muscle, particularly in those individuals with an already damaged vascular endothelium. Naturally occurring vasodilators like acetylcholine cause a release of endothelium-derived relaxing factor that precedes the onset of vascular smooth muscle relaxation. Oxyhaemoglobin and oxymyoglobin will antagonize these smooth muscle relaxant effects. Although no clinical studies have been done, *in vitro* studies suggest that carbon monoxide may inhibit the effects of oxyhaemoglobin on the action of acetylcholine. Carbon monoxide exposure in patients with a diseased endothelium, therefore, could accentuate acetylcholine-induced vaso-spasm and aggravate silent ischaemia.

9.3.2 *Subjects with congestive heart failure*

Congestive heart failure is a major and growing public health problem. Because the prevalence of heart failure is known to increase with age, improvements in the average life expectancy of the general population would be expected to increase the magnitude of the problem over the next few decades. It was reported that about 75% of patients with heart failure are above the age of 60 years in the USA (Brody et al., 1987).

Worldwide morbidity and mortality data for heart failure are not available. In the USA, about 400,000 new cases of heart failure are diagnosed every year, resulting in about 1.6 million hospitalizations. The mortality rate is high, between 15% and 60% per year. The onset of death is often sudden, and, because about 65% of heart failure patients have serious arrhythmias, this sudden death is thought to be due to arrhythmia (Brody et al., 1987).

Patients with congestive heart failure have a markedly reduced circulatory capacity and therefore may be very sensitive to any limitations in oxygen carrying capacity. Thus, exposure to carbon monoxide will certainly reduce their exercise capacity and will even be dangerous, especially because of its arrhythmogenic activity. The etiology of heart failure is diverse, but the dominating disease is coronary artery disease. The large portion of heart failure patients with coronary artery disease, therefore, might be even more sensitive to carbon monoxide exposure.
9.3.3 Subjects with other vascular diseases

Vascular disease including cerebrovascular disease is present in both the male and female population and is more prevalent above 65 years of age. Both of these conditions are often found in subjects with coronary artery disease. Both conditions are also associated with a limited blood flow capacity and therefore should be sensitive to carbon monoxide exposure. It is not clear, however, how low levels of exposure to carbon monoxide will affect these individuals. Only one study has been reported on patients with peripheral vascular disease.

9.3.4 Subjects with anaemia and other haematological disorders

Clinically diagnosed low levels of haemoglobin, characterized as anaemia, are a relatively prevalent condition throughout the world. If the anaemia is mild to moderate, an inactive person is often asymptomatic. However, owing to the limitation in the oxygen carrying capacity resulting from the low haemoglobin levels, an anaemic person should be more sensitive to low-level carbon monoxide exposure than a person with normal haemoglobin levels. If anaemia is combined with other prevalent diseases, such as coronary artery disease, the individual will also be at an increased risk from carbon monoxide exposure. Anaemia is more prevalent in women and in the elderly, already two potentially high-risk groups. An anaemic person will also be more sensitive to the combination of carbon monoxide exposure and high altitude.

Individuals with haemolytic anaemia often have higher baseline levels of carboxyhaemoglobin, because the rate of endogenous carbon monoxide production from haem catabolism is increased. One of the many causes of anaemia is the presence of abnormal haemoglobin in the blood. For example, in sickle-cell disease, the average life span of red blood cells with abnormal haemoglobin S is 12 days compared with an average of 88 days in healthy individuals with normal haemoglobin (haemoglobin A). As a result, baseline carboxyhaemoglobin levels can be as high as 4%. In subjects with haemoglobin Zurich, where affinity for carbon monoxide is 65 times that of normal haemoglobin, carboxyhaemoglobin levels range from 4% to 7%.
9.3.5 Subjects with obstructive lung disease

Chronic obstructive pulmonary disease is a prevalent disease, especially among smokers, and a large number (>50%) of these individuals have limitations in their exercise performance, demonstrated by a decrease in oxygen saturation during mild to moderate exercise. In spite of their symptoms, many of them (~30%) continue to smoke and already may have carboxyhaemoglobin levels of 4–8%. Subjects with hypoxia are also more likely to have a progression of the disease, resulting in severe pulmonary insufficiency, pulmonary hypertension and right heart failure. Studies suggest that individuals with hypoxia due to chronic lung disease such as bronchitis and emphysema may be susceptible to carbon monoxide during submaximal exercise typically found during normal daily activity.

Hospital admissions for asthma have increased considerably in the past few years, particularly among individuals less than 18 years of age. Because asthmatics can also experience exercise-induced airflow limitation, it is likely that they would also be susceptible to hypoxia. It is not known, however, how exposure to carbon monoxide would affect these individuals.

9.4 Subpopulations at risk from combined exposure to carbon monoxide and other chemical substances

9.4.1 Interactions with drugs

There is almost a complete lack of data on the possible toxic consequences of combined carbon monoxide exposure and drug use. Because of the diverse classes of both cardiovascular and psychoactive drugs, and because many other classes have not been examined at all, it must be concluded that this is an area of concern for which it is difficult at the present time to make recommendations that will have an effect on air quality guidelines.

Because data are generally lacking on carbon monoxide–drug interactions, it should be useful to speculate on some of the mechanisms by which carbon monoxide might be expected to alter drug effects, or vice versa, and discuss possible populations at risk because of these potential interaction effects.
9.4.2 Interactions with other chemical substances in the environment

Besides direct ambient exposure to carbon monoxide, there are other chemical substances in the environment that can lead to increased carboxyhaemoglobin saturation when inhaled. Halogenated hydrocarbons used as organic solvents undergo metabolic breakdown by cytochrome P-450 to form carbon monoxide and inorganic halide. Possibly the greatest concern regarding potential risk in the population comes from exposure to one of these halogenated hydrocarbons, methylene chloride, and some of its derivatives.

9.5 Subpopulations exposed to carbon monoxide at high altitudes

For patients with coronary artery disease, restricted coronary blood flow limits oxygen delivery to the myocardium. Carbon monoxide also has the potential for compromising oxygen transport to the heart. For this reason, such patients have been identified as the subpopulation most sensitive to the effects of carbon monoxide. A reduction in the partial pressure of oxygen in the atmosphere, as at high altitude, also has the potential for compromising oxygen transport. Therefore, patients with coronary artery disease who visit higher elevations might be unusually sensitive to the added effects of atmospheric carbon monoxide.

It is important to distinguish between the long-term resident of high altitude and the newly arrived visitor from low altitude. Specifically, the visitor will be more hypoxaemic than the fully adapted resident.

One would postulate that the combination of high altitude with carbon monoxide would pose the greatest risk to persons newly arrived at high altitude who have underlying cardiopulmonary disease, particularly because they are usually older individuals. Surprisingly, this hypothesis has never been tested adequately.

It is known that low birth weights occur in both infants born at altitudes above 1830 m as well as infants born near sea level whose mothers had elevated carboxyhaemoglobin levels as a result of cigarette smoking. It has also been shown that carboxyhaemoglobin levels in smokers at high altitude are higher than in smokers at sea
level. Although it is probable that the combination of hypoxic hypoxia and hypoxia resulting from ambient exposure to carbon monoxide could further reduce birth weight at high altitude and possibly modify future development, no data are currently available to support this hypothesis.

9.6 Carbon monoxide poisoning

The majority of this document deals with the relatively low concentrations of carbon monoxide that induce effects in humans at or near the lower margin of detection by current medical technology. Yet the health effects associated with exposure to this pollutant range from the more subtle cardiovascular and neurobehavioural effects at low ambient concentrations, as identified in the preceding sections, to unconsciousness and death after acute exposure to high concentrations of carbon monoxide. The morbidity and mortality resulting from the latter exposures are described briefly here to complete the picture of carbon monoxide exposure in present-day society.

Carbon monoxide is reported to be the cause of more than half of the fatal poisonings that are reported in many countries. Fatal cases are also grossly under-reported or misdiagnosed by medical professionals. Therefore, the precise number of individuals who have suffered from carbon monoxide intoxication is not known. In the USA, the National Center for Health Statistics (1986) estimates that between 700 and 1000 deaths per year are due to accidental carbon monoxide poisoning.

The symptoms, signs and prognosis of acute poisoning correlate poorly with the level of carboxyhaemoglobin measured at the time of hospital admission; however, because carbon monoxide poisoning is a diagnosis frequently overlooked, the importance of the early symptoms (headache, dizziness, weakness, nausea, confusion, disorientation and visual disturbances) has to be emphasized, especially if they recur with a certain periodicity or in certain circumstances. Complications occur frequently in carbon monoxide poisoning. Immediate death is most likely cardiac in origin, because myocardial tissues are most sensitive to the hypoxic effects of carbon monoxide. Severe poisoning results in marked hypotension and lethal arrhythmias and other electrocardiographic changes. Pulmonary oedema is a fairly common feature. Neurological manifestation of
Acute carbon monoxide poisoning includes disorientation, confusion and coma. Perhaps the most insidious effect of carbon monoxide poisoning is the delayed development of neuropsychiatric impairment within 1–3 weeks and the neurobehavioural consequences, especially in children. Carbon monoxide poisoning during pregnancy results in high risk for the mother, by increasing the short-term complication rate, and for the fetus, by causing fetal death, developmental disorders and chronic cerebral lesions.

In conclusion, carbon monoxide poisoning occurs frequently, has severe consequences, including immediate death, involves complications and late sequelae and is often overlooked. Efforts in prevention in public and medical education should be encouraged.

9.7 Recommended guideline values

9.7.1 Environmental sources

Carbon monoxide comes from both natural and anthropogenic processes. About half of the carbon monoxide is released at the Earth’s surface, and the rest is produced in the atmosphere. About 60% of the carbon monoxide is from human activities, whereas natural processes account for the remaining 40%. Recent reports showed that global carbon monoxide concentrations started to decline rapidly from 1988 to 1993. Since 1993, the downward trend in global carbon monoxide has levelled off, and it is not clear if carbon monoxide concentrations will continue to decline.

9.7.2 Environmental concentrations

The natural background carbon monoxide concentrations in remote areas of the southern hemisphere are around 0.05 mg/m³ (0.04 ppm), primarily as a result of natural processes. In the northern hemisphere, background concentrations are 2–3 times higher because of a greater human population density.

Carbon monoxide concentrations in ambient air monitored from fixed-site stations are generally below 10 mg/m³ (9 ppm, 8-h average). The annual mean carbon monoxide concentrations are less than 10 mg/m³ (9 ppm). However, short-term peak carbon monoxide concentrations occur in traffic environments; carbon monoxide concentrations up to 57 mg/m³ (50 ppm) are reported on heavily...
travelled roads. Air quality data from fixed-site monitoring stations seem to underestimate the short-term peak carbon monoxide level in traffic environments. Personal monitoring data from pedestrians and street workers showed that the carbon monoxide level could reach 10–16 mg/m³ (9–14 ppm) and 11–57 mg/m³ (10–50 ppm), respectively.

Indoor and in-transit concentrations of carbon monoxide may be significantly different from ambient carbon monoxide concentrations. The carbon monoxide levels in homes are usually lower than 10 mg/m³ (9 ppm); however, the peak value in homes with gas stoves could be higher than 10 mg/m³ (9 ppm) and up to 21 mg/m³ (18 ppm) in the kitchen, from 1.1 to 34 mg/m³ (1 to 30 ppm) with wood combustion and from 2.3 to 8 mg/m³ (2 to 7 ppm) with a kerosene heater. A report from homes with unvented gas-fired water heaters showed that the indoor carbon monoxide levels range from less than 11 mg/m³ (10 ppm) to more than 110 mg/m³ (100 ppm).

The carbon monoxide concentrations inside motor vehicles are generally around 10–29 mg/m³ (9–25 ppm) and occasionally over 40 mg/m³ (35 ppm). Carbon monoxide levels in parking garages, tunnels and ice skating rinks are higher than in common indoor environments.

The differences between indoor and outdoor air quality and the different amounts of time people spend indoors and outdoors explain why using ambient air quality measurements alone will not provide accurate estimates of population exposure. The measurement of carbon monoxide from personal monitors more accurately reflects the real exposure.

Occupational exposure levels are generally below 34 mg/m³ (30 ppm). Workers exposed to vehicle exhaust may have peak exposures over 230 mg/m³ (200 ppm).

9.7.3 Carboxyhaemoglobin concentrations in the population

Carbon monoxide diffuses rapidly across the alveolar and capillary membrane and more slowly across the placental membrane. Approximately 85% of the absorbed carbon monoxide binds with haemoglobin to form carboxyhaemoglobin, which is a specific biomarker of exposure in blood. The remaining 15% is distributed
extravascularly. During an exposure to a fixed ambient concentration of carbon monoxide, the carboxyhaemoglobin concentration increases rapidly at the onset of exposure, starts to level off after 3 h and approaches a steady state after 6–8 h of exposure. An 8-h value would be representative of any longer continuous exposure value. In real-life situations, the prediction of individual carboxyhaemoglobin levels is difficult because of large spatial and temporal variations in both indoor and outdoor levels of carbon monoxide. Typical carboxyhaemoglobin concentrations in the non-smoking population range from 0.5% to 2.0%; levels are slightly higher in pregnant women.

A common source of carbon monoxide for the general population is tobacco smoke. Exposure to tobacco smoke not only increases carboxyhaemoglobin concentrations in smokers, but under some circumstances can also affect non-smokers. In many of the studies currently cited to justify the formulation of exposure limits, neither the smoking habits of the subjects nor their exposure to passive smoking has been taken into account. In addition, as the result of higher baseline carboxyhaemoglobin levels, smokers may actually be excreting more carbon monoxide into the air than they are inhaling from the ambient environment. Smokers may even show an adaptive response to the elevated carboxyhaemoglobin levels, as evidenced by increased red blood cell volumes and reduced plasma volumes. As a consequence, it is not clear if incremental increases in carboxyhaemoglobin caused by environmental exposure would actually be additive to the chronically elevated carboxyhaemoglobin levels due to tobacco smoke. Thus, the exposure limits are recommended primarily for the protection of non-smokers.

9.7.4 General population exposure

The environmental health criteria used in arriving at a recommendation for an exposure limit for the general population were mainly those data obtained from the exposure of non-smoking subjects with coronary artery disease to carbon monoxide while exercising and potential effects in fetuses of non-smoking pregnant mothers exposed to ambient sources of carbon monoxide. The principal cause of carbon monoxide-induced effects at low levels of ambient exposure is thought to be increased carboxyhaemoglobin formation. Therefore, the primary exposure limits are derived on the basis of carboxyhaemoglobin.
In order to protect non-smoking population groups with documented or latent coronary artery disease from acute ischaemic heart attacks and to protect fetuses of non-smoking pregnant mothers from untoward hypoxic effects, a carboxyhaemoglobin level of 2.5% should not be exceeded.

9.7.5 Working population exposure

Non-smoking people in certain occupations (e.g., car, bus and taxi drivers, policemen, firemen, traffic wardens, street workers, garage and tunnel workers, mechanics) can have long-term carboxyhaemoglobin levels up to 5%. On the basis of present knowledge, the Task Group unanimously agreed on maintaining carboxyhaemoglobin levels not exceeding 5%, because working populations comprise individuals who are assumed to be healthy, physiologically resilient and under regular supervision.

9.7.6 Derived guideline values for carbon monoxide concentrations in ambient air

It is important, wherever possible, to have both biological and environmental assessments of human exposure to pollutants. Although the biological measurements may be more relevant in relation to effects in population groups, they may be more difficult to use in practice. For carbon monoxide, the relationship between concentrations in air and carboxyhaemoglobin levels is affected by several physiological and environmental variables, including exposure time. The appropriate carbon monoxide guidelines are based on the CFK exponential equation, which takes into account all known physiological variables affecting carbon monoxide uptake (see chapter 6).

The following guideline values (ppm values rounded) and periods of time-weighted average exposures have been determined in such a way that the carboxyhaemoglobin level of 2.5% is not exceeded, even when a normal subject engages in light or moderate exercise:

- $100 \text{ mg/m}^3$ (87 ppm) for 15 min
- $60 \text{ mg/m}^3$ (52 ppm) for 30 min
- $30 \text{ mg/m}^3$ (26 ppm) for 1 h
- $10 \text{ mg/m}^3$ (9 ppm) for 8 h
It should be emphasized that analyses of carbon monoxide in air and of carboxyhaemoglobin in blood are complementary and should be in no way regarded as alternative methods of monitoring. Obviously, air monitoring has its uses in the planning and implementation of control measures and for warning purposes, but such measurements have limited value in estimating the actual human exposure defined by carboxyhaemoglobin levels. It must also be recognized that complete protection of all persons, at all times, cannot reasonably be sought by ambient environmental control.

9.8 Recommendations

9.8.1 Further research

Further research is needed to:

- evaluate the effects of long-term carbon monoxide exposure on pregnant women and newborns;
- study the health effects of chronic exposure to low-level carbon monoxide, with emphasis on the fetus and newborn infant;
- determine the effects of carbon monoxide exposure on patients with asthma, chronic obstructive pulmonary disease, anaemia and haematological disorders;
- study the interactions of carbon monoxide and other outdoor and indoor environmental pollutants;
- study the interactions of carbon monoxide and medication;
- study the influence of environmental factors, including high altitude and heat stress, on health effects from exposure to carbon monoxide, both in the general population and in high-risk groups, including the elderly, children and those suffering from cardiorespiratory diseases;
- identify the biomarkers for delayed neurological sequelae of carbon monoxide exposure and for epidemiological studies;
• study the mechanism of carbon monoxide toxicity at cellular and subcellular levels;

• study factors influencing endogenous carbon monoxide production; and

• improve estimates of population exposure to carbon monoxide, especially by the use of personal exposure monitors.

9.8.2 Protection of human health

For protection of human health, it is desirable to:

• educate the general population, especially those with cardiovascular and respiratory diseases, about the risk of carbon monoxide exposure;

• improve monitoring of carbon monoxide in the workplace and in public places (streets, shops, restaurants, car parks);

• increase awareness of health risks from carbon monoxide exposure for those potentially exposed to high peak carbon monoxide levels from internal combustion engines used in enclosed environments;

• increase efforts to reduce carbon monoxide emissions from combustion engines;

• encourage the development of better methods for carbon monoxide detection and promotion of the use of carbon monoxide detectors; and

• improve the awareness of medical professionals, as well as the general population, of the dangers of carbon monoxide exposure during pregnancy.
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