Environmental Health Criteria 13

Carbon monoxide

Executive Summary

Issued by the World Health Organization
in conjunction with the
United Nations Environment Programme

NOTE TO THE READER

In response to a number of World Health Assembly resolutions, and taking into consideration the recommendations of the United Nations Conference on the Human Environment held in Stockholm in 1972, and of the Governing Council of the United Nations Environment Programme (UNEP), an integrated and expanded programme on the assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, is implemented with the support of the Environment Fund of UNEP. In 1980, the Environmental Health Criteria Programme was incorporated into the more comprehensive International Programme on Chemical Safety (IPCS), jointly sponsored by the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The results of the programme are a series of criteria documents.

Each criteria document comprises an extensive scientific review concerning a specific environmental pollutant or group of pollutants, with information ranging from sources and exposure levels to a detailed account of the available evidence concerning their effects on human health. Drafts of these documents are prepared for WHO by individual experts or national institutions. They are then extensively reviewed by the approximately 25 Member States participating in this Programme and by one or more international groups of experts (*task groups*). A major objective of this programme is to assess existing information on the relationship between exposure to environmental pollutants (or other physical and chemical factors) and man's health and *to provide guidelines for setting exposure limits consistent with the protection of public health.*

To facilitate the application of these guidelines in national environmental protection programmes, WHO decided to prepare "executive summaries" highlighting the information contained in the documents for those who need to know the health issues at hand, but not the scientific details.

The executive summaries contain the exposure guidelines specified in the criteria documents as developed by the task group, together with the major supporting information on health effects. Every effort has been made not to deviate from the information presented in the criteria documents themselves. For some criteria documents, particularly those published three or four years ago, this means that any new data published since the meetings of the task groups have not been included. Such information will be considered when the criteria documents and the summaries are reviewed and revised.

It would be appreciated if the reader would draw the attention of WHO to any difficulties encountered in using the information contained in the summary documents. Comments regarding this document should be addressed to:

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CARBON MONOXIDE*

1. Introduction

Carbon and oxygen combine to form either carbon monoxide (CO) (incomplete combustion) or carbon dioxide (CO_2) (complete combustion). Whereas carbon dioxide is inert, carbon monoxide is a potent poison owing to its ability to form strong bonds with the blood pigment, haemoglobin. Carbon monoxide is produced naturally, but the major man-made source is the motor vehicle — especially petrol-driven cars. Cigarette smokers subject themselves to further exposure by inhaling CO in the smoke.

2. Characteristics

Carbon monoxide is an odourless, tasteless, colourless gas under normal ambient conditions, and is emitted into the environment from both natural and man-made sources. Natural sources of CO include the oceans, the oxidation of atmospheric methane, volcanoes, forest fires and electrical storms. There is some doubt about the amounts of carbon monoxide produced globally by natural sources. However, man-made sources are currently estimated to yield approximately 600 million tonnes per year. Over half of this comes from petrol-driven motor vehicles and a third from stationary sources such as coal and oil combustion, industry and the burning of refuse. Indoor sources of CO include kitchen stoves and certain types of heater. On occasion, high levels of CO have been measured inside cars and buses.

Human exposure to carbon monoxide can be estimated either by the measurement of the CO concentration in the air or by the measurement of carboxyhaemoglobin (HbCO) in the blood. In ambient air, it can be monitored continuously and automatically by non-dispersive infrared spectrometers or semi-continuously by gas chromatographic methods. Both these techniques can detect CO

*Summary of *Carbon monoxide*. Geneva, World Health Organization, 1979 (Environmental Health Criteria No. 13), 125 pages.

levels as low as 0.02–1.0 mg/m³ of air. Portable detector tubes are also used for less accurate estimations and their limit of detection is about 5 mg/m³. The carboxyhaemoglobin levels in blood are measured by analysing venous blood by automated spectrophotometry or by gas chromatography. In this summary, carboxyhaemoglobin concentrations in blood that are expressed in percentages indicate the proportion of haemoglobin that is saturated with carbon monoxide.

3. Environmental concentrations

Urban CO concentrations vary with the density of petrol-driven vehicles and most cities have CO peak levels that coincide with morning and evening rush hours. Variations in these levels are also influenced by the topography of the streets and buildings as well as the weather. The variability in ambient concentrations is only slowly reflected in the HbCO levels in humans as it takes from 4 hours to 12 hours for equilibrium to occur between air levels and blood levels. Thus, environmental concentrations tend to be expressed in terms of 8-hour average concentrations. The presentation of such data as moving 8-h averages over the day rather than as 3 consecutive non-overlapping periods has the advantage that it presents a picture approximating to the human body response. For example, in 1973 8-h averages in the USA ranged from less than 10 mg/m³ to 58 mg/m³, with most of the values being less than 30 mg/m³, while in Japan, averages rarely exceeded 23 mg/m³. In Los Angeles, the daily 8-h average ranged from 7 to 49 mg/m³ in 1973.

Carbon monoxide is widely generated indoors by heating and cooking appliances, particularly if they are operated in poorly ventilated rooms. However, most exposures from indoor sources are lower than those produced by smoking cigarettes. Some individuals may also be exposed to CO in the course of their work. Persons likely to be exposed include traffic policemen or wardens, garage workers, employees at metallurgical, petroleum, gas or chemical plants, and fire fighters.

Such occupational exposure can be considerable. For example, levels of CO in garages have been shown to reach levels as high as 600

mg/m³ and workers in such places may exhibit HbCO levels up to five times higher than normal. Highway inspectors have been shown to exhibit HbCO concentrations from 4% to 7.6% (smokers) and 1.4% to 3.8% (nonsmokers) during a day's work. By contrast, HbCO levels in the general population rarely exceed 1%, although a study of 18 urban areas in North America showed that 45% of non-smokers exposed to ambient CO had HbCO levels exceeding 1.5%. When considering such "background" levels it is important to remember that humans themselves produce CO during normal metabolic processes. Such endogenous production probably accounts for about 0.1-1% of the total HbCO in blood.

4. Effects of exposure

The most important biological characteristic of CO is its affinity for haemoglobin, the oxygen-carrying pigment of red blood cells. This results in the formation of carboxyhaemoglobin (HbCO) which is over two hundred times more stable than oxyhaemoglobin (HbO_2). The relatively slow breakdown of HbCO results in the prolonged exclusion of such red cell pigment molecules from oxygen-carrying duties, and this can have serious, even fatal, consequences for the poisoned organism. In addition, muscle metabolism and intra-cellular enzyme function may be impaired by similar stable CO bonding. This aspect of CO toxicity may be minor in healthy humans but can be of crucial importance in someone suffering from pre-existing heart muscle malformation or poor peripheral blood circulation

The effects of CO in man appear to vary depending on the pre-existing state of health. Some fat people seem capable of tolerating HbCO levels as high as 40% for short periods, but persons with heart or lung disease may succumb to HbCO levels of 5–10%. The effects of high concentrations of CO on the central nervous system and cardiovascular system are well known. However, the response of healthy people to lower levels of CO, especially for long periods, is less clear. For example, the performance of vigilance tasks — those involving the ability of an individual to detect small changes in his environment taking place at unpredictable times and demanding continuous attention may — be impaired by HbCO levels below 10% and

even as low as 5%. (This is roughly equivalent to CO levels in air of 80 and 35 mg/m^3 respectively.) Such effects are less noticeable in smokers, presumably because they are habitually exposed to similar concentrations in cigarette smoke.

Studies on healthy volunteers exercising as hard as possible (maximal oxygen uptake studies) show that collapse may occur at HbCO levels of 50%. Lighter work, at 70% maximal levels for 5–60 minutes, is not impaired by HbCO levels of 33%, but the heart rate is disproportionately elevated. Longer-term studies of 4 hours' work at HbCO levels of 5–6% show similar heart rate effects but little else. Results seem to indicate that, for nonsmokers at least, a linear relationship does exist between HbCO and decreased maximum oxygen capacity.

Although high levels of CO can cause blood pressure changes, accelerated heart rate, abnormal heart rhythm, heart failure, and peripheral blood vessel damage, data on the cardiovascular effects of low-level CO exposure are sparse. The known association of smoking with increased risk of coronary heart disease suggests that CO may be playing a part in the genesis of such disease. (Heavy smokers not uncommonly have HbCO levels as high as 15%.) Nevertheless, it has not yet been proven that carbon monoxide, *per se,* causes heart or lung disease but its ability to impair oxygen transport in the human body has serious implications for persons with pre-existing heart or lung pathology. Epidemiological studies of cardiac morbidity or mortality by area and ambient CO concentrations are difficult to interpret. However, chest pain when making a physical effort certainly seems to occur earlier in patients exposed to CO concentrations of 60 mg/m^3, resulting in HbCO levels of approximately 5%.

Although pregnant women and their fetuses have elevated endogenous CO production, additional exogenous exposure may lower the tissue oxygenation and placental function, leading to babies with a lower birth weight. This may explain why women who smoke heavily have babies of lower than normal birth weight. Two other aspects of the health effects of CO are worth noting. First, in animals it seems possible that adaptation to CO can occur, as shown by their ability to tolerate, with apparent ease, acute exposure to higher concentrations; this, however, needs confirmation. Second, in relation to occupational exposures to CO, a disturbing new development is the

realization that at least one halogenated hydrocarbon, methylene chloride (dichloromethane), can cause elevated HbCO levels due to its metabolism in the body following absorption. As this compound belongs to a group of solvents introduced into industry to replace highly toxic materials like carbon tetrachloride, clearly a reappraisal of their occupational safety is required.

5. Evaluation of health risks

The task group convened by WHO to review and revise the criteria document and to prepare the evaluation were well aware of the limitations of the exposure data outlined in section 4 (above). They were concerned about the lack of corroborative data on low-level, long-term exposures to carbon monoxide and about the conflicting data on behavioural effects at such low levels.

Regarding exposure, the task group emphasized the complementary nature of carbon monoxide in air determinations and carboxyhaemoglobin estimations in blood. Neither was a substitute for the other and as both were relatively easy to measure, both should be recorded. Interpretation of HbCO levels are, however, dependent on a number of factors including time, length and quantity of CO exposure, smoking habits, ventilation rate and blood volume.

The main sequelae of CO exposure are found in its effects on the cardiovascular and central nervous systems. There is no incontrovertible evidence at present that CO can cause heart disease but some well designed volunteer studies provide reliable evidence that pre-existing cardiovascular disease symptoms are exacerbated by CO exposure. Behavioural disorders probably occur at HbCO levels below 20% but a no-observed-adverse-effect[a] level has not been established. Work capacity is affected by CO exposure, and limitation probably starts at HbCO levels of 4%. Although maximal work effort is not diminished at 2.5–4.0%, the length of time that such effort can be maintained is shortened.

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[a] "No observed adverse effect" refers to the absence of biological change in an organism, organ, or tissue.

As smoking is a major contributor to the HbCO levels of smokers, recommendations for exposure limits are designed to protect non-smokers. An HbCO level of 2.5–3.0% is the tentative maximum suggested by the task group for the protection of the general public, including those with impaired health. For occupationally exposed groups, the HbCO level should not exceed 5%.

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of either the World Health Organization or the United Nations Environment Programme

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

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ENVIRONMENTAL HEALTH CRITERIA FOR CARBON MONOXIDE

A WHO Task Group on Environmental Health Criteria for Carbon Monoxide met in Geneva from 11 to 17 October 1977. Dr V.B. Vouk, Chief, Control of Environmental Pollution and Hazards, opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the second draft of the criteria document and made an evaluation of the health risks from exposure to carbon monoxide.

The first and second drafts were prepared by Dr S.M. Horvath of the Institute of Environmental Studies, University of California, Santa Barbara, USA. The comments on which the second draft was based were received from the national focal points for the WHO Environmental Health Criteria Programme in Bulgaria, Canada, Czechoslovakia, France, Netherlands, Poland, USSR, and USA and from the International Labour Organisation (ILO), Geneva, the Food and Agriculture Organization of the United Nations (FAO), Rome, the United Nations Educational, Scientific and Cultural Organization (UNESCO), Paris, the United Nations Industrial Development Organization (UNIDO), Vienna, the Permanent Commission and International Association on Occupational Health, the Commission on Atmospheric Environment, International Union of Pure and Applied Chemistry (IUPAC), and from the Pan American Sanitary Engineering Center (CEPIS).

The collaboration of these national institutions, international organizations and WHO collaborating centres is gratefully acknowledged. Without their assistance this document would not have been completed. The Secretariat wishes to thank, in particular, Professor P.J. Lawther and Mr R.E. Waller of the Medical Research Council Toxicology Unit, St Bartholomew's Hospital Medical College, London, and Dr G. Winneke of the Institute for Air Hygiene and Silicosis Research, Düsseldorf, for their help in the scientific editing of the document.

This document is based primarily on original publications listed in the reference section. However, several recent publications broadly reviewing health aspects of carbon monoxide have also been used including those of the Commission of the European Communities (1974), NAS/NRC (1977), US Department of Health, Education and Welfare (1970, 1972), and Committee on the Challenges of Modern Society (1972).

Details of the WHO Environmental Health Criteria Programme, including some of the terms frequently used in the documents, may be found in the introduction to the publication "Environmental Health Criteria 1—Mercury" published by the World Health Organization, Geneva, 1976, and now available as a reprint.

The following conversion factors[a] have been used in this document:

carbon monoxide	1 ppm = 1145 μg/m³	1 mg/m³ = 0.873 ppm
methylene chloride	1 ppm = 3480 μg/m³	1 mg/m³ = 0.288 ppm
nitrogen dioxide	1 ppm = 1880 μg/m³	1 mg/m³ = 0.532 ppm
ozone	1 ppm = 2000 μg/m³	1 mg/m³ = 0.500 ppm
peroxyacetyl nitrate	1 ppm = 5000 μg/m³	1 mg/m³ = 0.200 ppm

1 Torr = 1.333×10^2 pascals = 1 mmHg

[a] All conversion factors for atmospheric pollutants refer to 25 °C and 101 kPa (1 atm) pressure.

1. SUMMARY AND RECOMMENDATIONS FOR FURTHER STUDIES

1.1 Summary

1.1.1 Properties and analytical methods

Carbon monoxide (CO) is a colourless, odourless, tasteless gas that is slightly less dense than air. It is a product of incomplete combusion of carbon-containing fuels and is also produced by some industrial and biological processes. Its health significance as a contaminant of air is largely due to the fact that it forms a strong coordination bond with the iron atom of the protohaem complex in haemoglobin forming carboxyhaemoglobin (HbCO) and thus impairs the oxygen-carrying capacity of the blood. The dissociation of oxyhaemoglobin is also altered by the presence in blood of carboxyhaemoglobin so that the supply of oxygen to tissues is further impaired. The affinity of haemoglobin for carbon monoxide is roughly 240 times that of its affinity for oxygen; the proportions of carboxyhaemoglobin and oxyhaemoglobin in blood are largely dependent on the partial pressures of carbon monoxide and oxygen. Carbon monoxide is absorbed through the lungs and the concentration[a] of carboxyhaemoglobin in the blood at any time will depend on several factors. When in equilibrium with ambient air, the carboxyhaemoglobin content of the blood will depend mainly on the concentrations of inspired carbon monoxide and oxygen. However, if equilibrium has not been achieved, the carboxyhaemoglobin concentration will also depend on the time of exposure, pulmonary ventilation, and the carboxyhaemoglobin originally present before inhalation of the contaminated air. Formulae exist by which these estimates can be made. In addition to its reaction with haemoglobin, carbon monoxide combines with myoglobin, cytochromes, and some enzymes; the health significance of these reactions is not clearly understood but is likely to be of less importance than that of the reaction of the gas with haemoglobin.

Methods available for the measurement of carbon monoxide in ambient air[b] range from fully automated methods using the non-dispersive infrared technique and gas chromatography to very simple semiquantitative manual methods using detector tubes. Since the formation of carboxyhaemoglobin

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[a] Throughout the document, the word concentration refers to mass concentration, unless otherwise stated.

[b] *Selected Methods of Measuring Air Pollutants*, WHO Offset Publication No. 24 (1976) published under the joint sponsorship of the United Nations Environment Programme and the World Health Organization, Geneva.

in man is dependent on many factors including the variability of ambient air concentrations of carbon monoxide, carboxyhaemoglobin concentrations should be measured rather than calculated. Several relatively simple methods are available for determining carbon monoxide either by analysis of the blood or of alveolar air that is in equilibrium with the blood. Some of these methods have been validated by careful comparative studies.

1.1.2 Sources of environmental pollution

At present, the significance of natural sources of carbon monoxide for man is uncertain. Estimates of man-made carbon monoxide emissions vary from 350 to 600 million tonnes per annum. By far the most important source of carbon monoxide at breathing level is the exhaust of petrol-powered motor vehicles. The emission rate depends on the type of vehicle, its speed, and its mode of operation. Other sources include heat and power generators, some industrial processes such as the carbonization of fuel, and the incineration of refuse. Faulty domestic cooking and heating appliances may be important sources that are often overlooked.

1.1.3 Environmental levels

Natural background levels of carbon monoxide are low (0.01–0.9 mg/m^3 or 0.01–0.8 ppm). Carbon monoxide concentrations in urban areas are closely related to motor traffic density and to weather and vary greatly with time and distance from the sources. The configuration of buildings is important and concentrations fall sharply with increasing distance from the street.

There are usually well-marked diurnal patterns with peaks corresponding to the morning and evening "rush hours". Data from Japan and the USA show that 8-h mean concentrations of carbon monoxide are generally less than 20 mg/m^3 (17 ppm). However, maximum 8-h mean concentrations of up to 60 mg/m^3 (53 ppm) have occasionally been recorded. Much higher relatively transient peaks may be observed in still weather where there is traffic congestion, and high concentrations can be found in confined spaces such as tunnels, garages, and loading bays in which vehicles operate and in vehicles with faulty exhaust systems. There may be relatively high pollution by carbon monoxide in workplaces and in some homes with cooking and heating appliances that are faulty or do not have flues.

By far the commonest cause of high carboxyhaemoglobin concentrations in man is the smoking of tobacco and the inhalation of the products by the smoker.

1.1.4 Effects on experimental animals

Many experiments on animals have yielded valuable information about the effects of carbon monoxide. There is general agreement that most animals die when carboxyhaemoglobin levels exceed about 70% and that the rate of administration of the gas is important in determining the outcome. It is also agreed that carboxyhaemoglobin levels exceeding 50% are often associated with damage to organs including the brain and the heart. When animals are exposed to lower concentrations, the effects are more difficult to discern and may be manifested as changes in metabolism and biochemistry, alterations in the blood, or changes in behaviour. There is evidence that some animals adapt to exposure to comparatively low concentrations of carbon monoxide. As might be expected, the variability of reported results of experiments increases as the effects become less marked and the need for scrupulous experimental design and technique becomes more important. Of particular importance is the interpretation of the claims of some workers that continuous intermittent exposure of animals to concentrations resulting in carboxyhaemoglobin levels of 10–20% can produce demonstrable histological changes in the myocardium, blood vessels, and central nervous system. There are claims that such exposures affect cholesterol uptake in the aorta and the coronary arteries. The relevance of these findings, if accepted as real, are obvious for the aetiology of cardiovascular diseases in man and, therefore, must be assessed with great caution. It is also important to study carefully the reports of research workers who have failed to find evidence of damage.

1.1.5 Effects on man

The effects on man of exposure to high concentrations of carbon monoxide are well documented and the diagnosis, treatment, and sequelae of acute carbon monoxide poisoning are adequately dealt with in standard texts. Recently much attention has been paid to the possible effects on function and structure of exposure to carbon monoxide concentrations resulting in carboxyhaemoglobin levels of 10% or less. Carbon monoxide acts primarily by interfering with oxygen transport and as the central nervous system is more sensitive to hypoxia than the other systems of the body, much work has been done on the impairment of vigilance, perception, and the performance of fine tasks following exposure to concentrations of carbon monoxide too low to produce clinical signs or symptoms. Many common drugs, beverages, food, and fatigue can alter alertness, efficiency, and dexterity and reported observed effects of low concentrations of carbon monoxide are difficult, if not impossible, to interpret when no account is

given of precautions taken in the experimental design to eliminate or assess the separate effects of other stresses. Again, great attention must be paid to reports of impeccable experiments that have failed to reproduce effects already reported. There would seem to be some justification for accepting the possibility that concentrations of carboxyhaemoglobin exceeding 2.5% might be associated with some impairment of vigilance and other modes of perception. However, it cannot be emphasized too strongly that when assessing the significance (health and social) of this, the effects that many other commonly acceptable factors might have on the tests should be taken into account. It is possible, even likely, that the damaged heart and respiratory system are more prone to impairment by carbon monoxide than the intact brain. Skeletal muscle is sensitive to hypoxia and obviously its sensitivity is enhanced by arterial disease. However, of much greater importance is the effect of carbon monoxide on the ischaemic myocardium which is especially vulnerable to additional hypoxia. Evidence has been reported of changes in cardiac function and the time of onset of angina pectoris on exercise when carboxyhaemoglobin levels exceed 2.5%. Changes in oxygen uptake and transfer are theoretically possible at or below these levels, and thus there will be some patients whose cardiac function is so impaired that any further hypoxic stress from carbon monoxide or from other factors, will be intolerable. Similarly, the gross hypoxia of all tissues seen in cases of severe respiratory disease renders the body even more susceptible to the effects of low concentrations of carbon monoxide. It follows that there is reason to regard carbon monoxide in this sense as a pollutant for which the "threshold" is that concentration which would be in equilibrium with the carboxyhaemoglobin produced endogenously by the breakdown of blood pigments. However, it must be realized that at these extremes of illness other usually trivial stresses, such as ambient and body temperatures, infection, noise, and anxiety, may be of much greater importance.

In addition to patients with diseases of the heart and the lungs, it is likely that other groups, such as the anaemic, elderly, postoperative patients, or those with cerebrovascular arteriosclerosis may be at special risk. The effects on the fetus *in utero* of carbon monoxide, especially that derived from maternal smoking, are of special interest. The effects of carbon monoxide on people living at high altitudes are greater than on those living at sea level and this added risk must be assessed. There is a distinct possibility that healthy man may adapt to the mild hypoxia caused by carboxyhaemoglobin levels of about 3–5% (or to even higher values) as he does to high altitude. Many workers in industry, and even more smokers, repeatedly have carboxyhaemoglobin values such as these and there have been few attempts to correlate symptoms or pathological findings specifically with

these levels of carboxyhaemoglobin. There is little evidence that exposure to comparatively low concentrations of carbon monoxide causes disease though it is suspected of being an etiological factor in the association of heart disease with smoking.

1.1.6 Evaluation of health risk

There can be no doubt that the assessment of risk of exposure to the lower concentrations of carbon monoxide in inspired air in populations containing the sick and the fit, the smoker and nonsmoker, the very young and the very old, would be a complex, if not impossible, task, even if the ambient concentration of carbon monoxide remained constant in time and place. Rough guidance, therefore, is all that is possible in the light of available evidence derived from sound scientific work. Those responsible for the welfare of specially susceptible groups must refer critically to the evidence from published works and to that reviewed in this document and make their special decisions. There is general agreement that any individual should be protected from exposure to carbon monoxide that would result in carboxyhaemoglobin levels of 5% for any but transient periods, and that especially susceptible persons ought not to be subjected to concentrations giving carboxyhaemoglobin levels exceeding 2.5%. Advice concerning such subjects must depend on individual assessment of their clinical status and of other environmental factors including the demands of the tasks they have to perform (persons engaged in driving, monotonous tasks, keeping watch, etc., though healthy, might require special consideration). The real possibility that adaptation occurs makes consideration of the smoker and industrially exposed worker difficult; ethical as well as health factors might affect action but it would seem reasonable to have the same limit of 5% carboxyhaemoglobin for industrial workers as for the rest of the healthy population. The smoker inflicts high carboxyhaemoglobin values on himself, by choice; he ought to be told of the evidence that this habit might be harmful and then be subject to the levels of protection recommended above.

1.2 Recommendations for Further Studies

(*a*) Though some would maintain that there are enough data on levels of carbon monoxide in urban air, there is a need for further surveys of air and blood levels so that some more precise correlations may be established. Various populations in various places should be studied properly to assess the magnitude of the problem posed by carbon monoxide in the air of towns, houses, and workplaces.

(*b*) Opinions concerning levels of carbon monoxide below which no adverse effects are seen and above which impairment of mental or bodily functions seems to occur are based on comparatively few data. These have been obtained from experiments concerning vigilance tests and other tests of perception and performance, or the effects of carbon monoxide on exercising cardiac and skeletal muscle and on symptoms in patients with cardiovascular disease. There is an obvious need to provide further data concerning larger numbers of subjects in soundly designed experiments, the results of which should be properly analysed. By such means it is hoped that dose-response and concentration-response relationships may be established. The continued refinement and application of epidemiological techniques must complement experimental work.

(*c*) There are few data for assessing the possible consequences of exposure of man to long-term, low concentrations of carbon monoxide. There is a need to evaluate the possible effects of such exposures and to determine the role of adaptation.

(*d*) Evidence that carbon monoxide plays a role in the observed deleterious effects of smoking has been produced by experiments on animals but more work is needed to confirm and extend these findings. The hazards to the fetus of maternal smoking need to be evaluated and the susceptibility of the fetus to carbon monoxide from whatever source needs to be studied.

(*e*) The effects of comparatively low levels of carboxyhaemoglobin on such skills as driving, and on perception in other tasks, need further careful investigation. Not only must the possibility of the enhancement of effects of carbon monoxide by other commonly occurring factors be assessed, but there is a need to compare the effects of carbon monoxide on vigilance and performance with the effects of such common agents as therapeutic drugs, alcohol, fatigue, and food. Attention is drawn to the difficulties inherent in the design of such tests as well as to the problems involved in the assessment of the health and social significance of the results.

(*f*) The possible effects of carbon monoxide on people living and working at high altitudes (including aircraft pilots) have received too little attention. There is a need for further work on this subject.

2. CHEMISTRY AND ANALYTICAL METHODS

2.1 Physical and Chemical Properties

Carbon monoxide (CO) is a colourless, odourless, and tasteless gas which is commonly formed during the incomplete combustion of carbonaceous material. It is slightly lighter than air and only slightly soluble in water. Carbon monoxide absorbs electromagnetic radiation in the infrared region with the main absorption band centred at 4.67 μm; this property is used for the measurement of carbon monoxide concentrations in air. Some other physical properties of carbon monoxide are listed in Table 1.

While carbon monoxide is chemically inert under normal conditions of temperature and pressure (25 °C; 1 atm (101 kPa)), it becomes reactive at higher temperatures and can act as a strong reducing agent. At 90 °C, it reacts with iodine pentoxide to produce iodine vapour. At 150 °C, it also releases mercury vapour from mercury(II) oxide. Both reactions are used in the analytical chemistry of carbon monoxide. The oxidation of carbon monoxide to carbon dioxide (CO_2) is accelerated by metallic catalysts such as palladium on silica gel, or by a mixture of manganese and copper oxides (Hopcalite).

In forming carboxyhaemoglobin (HbCO), carbon monoxide reacts with the iron in protohaem—a constituent of haemoglobin—and forms strong co-ordination bonds. Thus carboxyhaemoglobin is toxic because it is about 200 times more stable than oxyhaemoglobin (HbO_2). Carbon monoxide also combines reversibly with myoglobin and cytochromes, including P-450.

Table 1. Physical properties of carbon monoxide

Relative molecular mass	28.01
Critical point	−140.2 °C at 34.5 atm (3.5 MPa)
Melting point	−205.1 °C
Boiling point	−191.5 °C
Density, at 0 °C, 1 atm	1.250 g/litre
at 25 °C, 1 atm	1.145 g/litre
Specific gravity relative to air	0.967
Solubility in water at 0 °C, 1 atm	3.54 ml/100 ml
at 25 °C, 1 atm	2.14 ml/100 ml
at 37 °C, 1 atm	1.83 ml/100 ml[a]
Conversion factors:	
at 0 °C, 1 atm	1 mg/m³ = 0.800 ppm[b]
	1 ppm = 1.250 mg/m³
at 25 °C, 1 atm	1 mg/m³ = 0.873 ppm
	1 ppm = 1.145 mg/m³

[a] Value obtained by graphic or calculated interpolation (Altman et al., 1971).
[b] Parts per million by volume.

The environmental chemistry of carbon monoxide is discussed in section 4.2.

2.2 Methods of Measuring Carbon Monoxide in Ambient Air

Three methods are most commonly used for the routine estimation of carbon monoxide in air. These are the continuous analysis method based upon nondispersive infrared absorption spectroscopy (NDIR); the semi-continuous analysis method using gas chromatographic techniques and a semiquantitative method employing detector-tubes. Other methods include catalytic oxidation, electrochemical analysis, mercury displacement, and the dual isotope technique (WHO, 1976).

In the NDIR method, infrared radiation is divided into two beams that are directed through a reference and a sample cell, respectively. Any carbon monoxide introduced into the sample cell will absorb radiation at the characteristic band centred at 4.67 μm, causing the detector to produce an output signal proportional to the concentration of carbon monoxide in the sample cell. NDIR analysers are produced by several manufacturers in the form of continuous, automated instruments. Good commercial instruments have a detection limit of about 1 mg/m^3 (0.87 ppm). Carbon dioxide and water vapour interfere but there are several techniques to minimize this interference.

In chromatographic methods, carbon monoxide is first separated from water vapour, carbon dioxide, and hydrocarbons. It is then catalytically reduced to methane and passed through a flame ionization detector, the output signal of which is proportional to the carbon monoxide concentration in the air sample. The most common concentration range in commercial instruments is from about 1 to 350 mg/m^3 (1–300 ppm) but others are available with a range of about 0.02 to 1.00 mg/m^3 (0.017–0.87 ppm). Gas chromatography is particularly suitable, when low concentrations of carbon monoxide have to be measured with a high degree of specificity.

The detector tube method is very simple and can be used for estimating concentrations above 5 mg/m^3. Air is drawn through specially manufactured tubes containing a chemical agent that changes colour if carbon monoxide is present and can be used to estimate concentrations. The advantages and limitations of detector tubes are further discussed in a WHO manual (WHO, 1976).

A well known method is based on the measurement of the temperature rise caused by the catalytic oxidation of carbon monoxide. The limit of detection is about 1 mg/m^3. Most hydrocarbons will interfere unless

removed (NAS/NRC, 1977). For measurements in ambient air, the sensitivity may not always be sufficient.

Electrochemical analysers (Hersch, 1964, 1966) are based on the liberation by carbon monoxide of iodine from iodine pentoxide (at 150 °C), which is then reduced at the cathode of a galvanic cell. The current developed is a measure of the carbon monoxide concentration present in the air sample.

A further highly sensitive method is based on the reduction of mercury(II) oxide by carbon monoxide at a temperature between 170 and 210 °C. Mercury vapour generated during this reaction is determined by absorption spectrophotometry at 253.7 nm. This method, as modified by Seiler & Junge (1970), has a reported detection limit of about 3 $\mu g/m^3$.

The slight difference in the fluorescence spectra of ^{16}CO and ^{18}CO is used for carbon monoxide determination by the so-called dual isotope fluorescence method. Instruments using this principle are available with ranges of 0–20 mg/m^3 (0–17.5 ppm) and 0–200 mg/m^3 (0–175 ppm) with a reported detection limit of about 0.2 mg/m^3 (0.17 ppm). Other pollutants present cause very little interference (McClatchie et al., 1972).

An important part of any carbon-monoxide measurement procedure is the calibration technique. Many publications deal with this topic and the Deutsche Industrienormen Ausschuss (DIN) and the International Standard Organization (ISO) have special groups for establishing suitable calibration standards.

2.3 Biological Monitoring

Blood carboxyhaemoglobin can be satisfactorily determined in a venous blood sample, which should be collected in a closed container containing an anticoagulant (dry sodium heparin or di-sodium ethylene-diaminotetracetic acid, EDTA). Blood samples may be preserved for several days prior to analysis if kept cold (4 °C) and in the dark. Complete mixing of blood must be attained if carbon monoxide and haemoglobin are to be measured separately. Total haemoglobin is conveniently determined by conversion to cyanmethaemoglobin (Van Kampen & Zijlstra, 1961), which is then determined spectrophotometrically (Drabkin & Austin, 1935).

Various methods are available for the determination of carboxyhaemoglobin by spectrophotometry or by the liberation of carbon monoxide (WHO, 1976). One method consists of measuring the absorbance at 4 wavelengths in the Soret region (390–440 nm) of a blood sample diluted to about 1:70 with an aqueous solution of ammonia (Small et al., 1971). Carboxyhaemoglobin and methaemoglobin are estimated from absorbance

values, and oxyhaemoglobin is obtained from the difference. The method is precise at low carboxyhaemoglobin concentrations (up to 25% saturation). A very convenient method is the automated differential spectrophotometer (Malenfant et al., 1968), which is available commercially as CO-oximeter. Simultaneous absorbance measurements are made to determine the three component system (reduced haemoglobin, oxyhaemoglobin and carboxyhaemoglobin) contained in a haemolysed blood sample. The signals are processed and displayed in a digital form as haemoglobin (g/100 ml) and the percentage of oxyhaemoglobin and carboxyhaemoglobin. A method has recently been described (Rossi-Bernardi et al., 1977) for the simultaneous determination of four haemoglobin derivatives (deoxyhaemoglobin, oxyhaemoglobin, methaemoglobin, carboxyhaemoglobin) and total oxygen contents of 10 µl of whole blood. The spectrophotometric method of Commins & Lawther (1965), which has been validated by Lily et al. (1972), has the advantage of requiring only 0.01 ml blood obtained from a finger prick sample.

Gas chromatography on molecular sieves with a suitable detection system is probably the most satisfactory procedure for the measurement of carbon monoxide liberated from carboxyhaemoglobin. Carbon monoxide liberation is achieved through acidification. The method described by Sotnikov (1971) requires only 0.1 ml of blood and has a limit of detection of 0.01 ml of carbon monoxide per 100 ml of blood. Dahms & Horvath (1974) have proposed a very accurate method for estimating low concentrations of

Table 2. Comparison of techniques for the analysis of carboxyhaemoglobin in blood[a]

Detection method	Sample volume (ml)	Resolution[b] (ml/dl)	Sample analysis time (min)	CV[c] (%)	Reference
Gasometric					
Van Slyke	1.0	0.3	15	6	Horvath & Roughton (1942)
syringe-capillary	0.5	0.02	30	2–4	Roughton & Root (1945)
Optical					
spectrophotometric	2.0	0.006	30	1.8	Coburn et al. (1964)
spectrophotometric	0.1	0.08	10		Small et al. (1971)
spectrophotometric	0.4	0.10	3		Maas et al. (1970)
spectrophotometric	0.01	0.10	20		Commins & Lawther (1965)
Chromatographic					
thermal conductivity	1.0	0.005	20[d]	1.8	McCredie & Jose (1967)
flame ionization	0.1	0.002	20	1.8	Collison et al. (1968)
thermal conductivity	1.0	0.001	30	2.0	Ayres et al. (1966)
thermal conductivity	0.25	0.006	3	1.7	Dahms & Horvath (1974)

[a] Adapted from: Dahms & Horvath (1974).
[b] Smallest detectable difference between duplicate determinations.
[c] Coefficient of variation based on samples containing less than 2.0 ml of carbon monoxide per decilitre.
[d] Best estimate.

carboxyhaemoglobin. Table 2 compares some techniques for the analysis of carboxyhaemoglobin in blood.

Another approach to the estimation of exposure to carbon monoxide is by the analysis of expired air. The subject takes a deep breath and holds it for 20 sec. The first 350–500 ml of expired air (dead air space) is discarded and the remaining gas (alveolar air) is collected in an aluminized mylar bag for analysis, using an NDIR instrument. The value of the alveolar technique, pioneered by Sjöstrand (1948), is based on the assumption that, during breath-holding, the lung is a closed vessel in which blood carboxyhaemoglobin equilibrates with lung gas and that Haldane's relationship (see section 6) applies. Theoretically, the slope of the straight line relating % carboxyhaemoglobin to alveolar pCO in ppm should be approximately 0.155 at sea level for % carboxyhaemoglobin values equivalent to a carbon monoxide concentration between 0 and 50 ppm, and progressively lower for higher concentrations (Coburn et al., 1965). Values approximating to this theoretical ratio have been found experimentally (Forbes et al., 1945; Malenfant et al., 1968). Although the alveolar air method is less precise than the direct measurement of carboxyhaemoglobin in blood, it can be used in epidemiological studies and for general monitoring (McFarland, 1973) but cannot be used on persons with chronic pulmonary disease.

3. SOURCES OF CARBON MONOXIDE IN THE ENVIRONMENT

3.1 Natural Occurrence

The amount of carbon monoxide produced globally by natural sources is at present uncertain. Several investigators have estimated that natural sources (primarily oxidation of methane in the atmosphere and emissions from the oceans) produce about ten times as much carbon monoxide as man-made sources (Spedding, 1974). On the other hand, a recent study concluded that the natural production of carbon monoxide was much smaller and might be somewhat less than the emissions from man-made sources (Seiler, 1975). If this is the case, man-made emissions of carbon monoxide may play an important role in the global carbon monoxide cycle.

Several estimates of the production of carbon monoxide by atmospheric reactions have been made. Stevens et al. (1972) estimated that in the northern hemisphere alone, more than 3×10^9 metric tonnes of carbon monoxide are produced annually by the oxidation of methane and other organic constituents. McConnell et al. (1971) considered that biologically produced methane could be the source of approximately 2.5×10^9 metric tonnes of carbon monoxide annually. Subsequently, it was calculated, by Weinstock & Nicki (1972), that the oxidation of methane alone could produce twenty-five times the quantity of carbon monoxide generated by man's activities. Estimates by Levy (1972) indicated that the oxidation of methane was a much larger source of carbon monoxide that man-made sources.

The surface layers of the ocean are a second major natural source of carbon monoxide. Linnenbom et al. (1973) calculated an upper limit of 220×10^6 metric tonnes of carbon monoxide emitted from the oceans. Using a model of the flux of gases across the air-sea interface, Liss & Slater (1974) estimated a total ocean flux of carbon monoxide of 43×10^6 metric tonnes per year.

Among other natural sources of carbon monoxide are forest and grass fires, volcanoes, marsh gases, and electric storms. Some carbon monoxide is also formed in the upper atmosphere (above 75 km) by the photodissociation of carbon dioxide (Altshuller & Bufallini, 1965; Bates & Witherspoon, 1952). Another natural source of carbon monoxide is rainwater, where production of carbon monoxide in the clouds is tentatively attributed to the photochemical oxidation of organic matter or the slight dissociation of carbon dioxide induced by electrical discharges or both (Swinnerton et al., 1971). Some carbon monoxide is also formed during

germination of seeds and seedling growth (Siegel et al., 1962; Wilks, 1959), by the action of microorganisms on plant flavonoids (Westlake et al., 1961), and in higher plants (Delwiche, 1970). Kelp may be a significant source of carbon monoxide. Chapman & Tocher (1966) reported that some float cells of kelp contained carbon monoxide concentrations as high as 916 mg/m^3 (800 ppm).

Carbon monoxide is produced in measurable quantities in man and animals as a by-product of haem catabolism.

3.2 Man-Made Sources

According to Jaffe (1973), global emissions of man-made carbon monoxide in 1970 amounted to 360 million tonnes. Seiler (1975) calculated the carbon monoxide emissions for 1973 as 600 million tonnes. A breakdown of Jaffe's estimate according to the type of source is shown in Table 3. The motor vehicle was by far the largest contributor accounting for 55% of total emissions. Other transportation sources, certain industrial processes, waste disposal and miscellaneous burning activities were responsible for the remaining carbon monoxide emissions.

The tremendous increase in the number and use of motor vehicles during the past 30 years has been accompanied by a rapid increase in carbon monoxide emissions. In the USA for example, the emission of carbon monoxide rose from approximately 73 million tonnes in 1940 to about 100 million tonnes in 1970 (US Environmental Protection Agency, 1973a). In 1968, the upward trend was reversed because of the initial impact of motor vehicle emission controls. The rate at which carbon monoxide is emitted

Table 3. Estimated global man-made emissions of carbon monoxide, 1970[a]

Source	Emissions (10^6 metric tonnes)
Mobile	
Motor vehicles: gasoline	197
diesel	2
Aircraft	5
Watercraft	18
Railroads	2
Other (nonhighway) motor vehicles	26
Stationary	
Coal combustion	4
Oil combustion	1
Industrial processes	41
Refuse disposal	23
Miscellaneous	41
Total	360

[a] From: Jaffe (1973).

from motor vehicles varies not only with vehicle but also with the mode of operation of the vehicle. The emissions of carbon monoxide by other mobile sources are comparatively small; however, the emissions from locomotives, boats, and aircraft may create local problems.

Among the stationary sources, the burning of waste material and certain industrial processes generate substantial amounts of carbon monoxide. Petroleum refineries, iron foundries, kraft-pulp mills, carbon-black plants, and sintering processes are the major sources. Emission rates for some of these processes are given in Table 4. The burning of refuse, either in incinerators or openly, is an important source of carbon monoxide. If uncontrolled, the emission rate of carbon monoxide from incinerators is about 17.5 kg per tonne of refuse burned. If burned openly, the emission rates can vary from about 25 to 60 kg per tonne, depending upon the type of refuse (US Environmental Protection Agency, 1973b). The combustion of fossil fuels in electric generating plants, industries, and the home, while resulting in the emission of smaller quantities of carbon monoxide individually, may constitute a major source when combined.

Any industrial process or operation, where incomplete combusion of carbonaceous material occurs, may easily be of importance as far as occupational exposure to carbon monoxide is concerned. Smelting of iron ore, gas production works, gasworks and coke ovens, distribution and use of both natural gas and coal gas, automobile manufacturing, garages, and service stations are among the most important sources for occupational exposure to carbon monoxide (Ministry of Labour, 1965).

It should also be emphasized that tobacco smoke is a most significant source of man-made carbon monoxide in a closed environment and that the carboxyhaemoglobin levels found in smokers are consistently higher than those in nonsmokers.

Table 4. Emission rates for carbon monoxide in selected industrial processes[a]

Source	Emissions (uncontrolled)
Petroleum refineries	
Fluid catalytic cracking units	39.2 kg/10^3 litre
Moving bed catalytic cracking units	10.8 kg/10^3 litre
Steel mills	
Blast furnaces— ore charge	875 kg/tonne
Sintering	22 kg/tonne
Basic oxygen furnace	69.5 kg/tonne
Gray iron foundries	
Cupola	72.5 kg/tonne
Carbon black	
Channel process	16 750 kg/tonne
Thermal process	negligible
Furnace process	2650 kg/tonne

[a] From: US Environmental Protection Agency (1973b).

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Atmospheric Transport and Diffusion

The ambient air concentrations of carbon monoxide at locations removed from man-made sources are low and variable. Junge et al. (1971) reported that background levels of carbon monoxide in the lower atmosphere may range from 0.01 to 0.23 mg/m^3 (0.009–0.2 ppm). Concentrations have been reported of 0.025 to 0.9 mg/m^3 (0.022–0.8 ppm) in North Pacific marine air; 0.04 to 0.9 mg/m^3 (0.036–0.8 ppm) in rural areas of California; 0.07 to 0.30 mg/m^3 (0.06–0.26 ppm) at Point Barrow, Alaska; 0.06 to 0.8 mg/m^3 (0.05–0.7 ppm) in Greenland; and about 0.07 mg/m^3 (0.06 ppm) in the South Pacific (Cavanagh et al., 1969; Goldman et al., 1973; Robbins et al., 1968; Robinson & Robbins, 1970). Seiler & Junge (1969) observed similar average concentrations over the North and South Atlantic Ocean (0.20 mg/m^3 and 0.06 mg/m^3 (0.18 and 0.05 ppm) respectively). Background levels of carbon monoxide are influenced by the origin of the air masses and vertical distributions of carbon monoxide have been reported by Seiler & Junge (1969, 1970). They found consistent carbon monoxide concentrations of 0.15 mg/m^3 (0.13 ppm) at an altitude of 10 km in both northern and southern hemispheres. In the troposphere, average concentrations of 0.11 mg/m^3 (0.10 ppm) were observed, while, in the stratosphere, the concentrations ranged from 0.03 to 0.06 mg/m^3 (0.027–0.05 ppm). A recent study (Goldman et al., 1973) showed that a gradual decrease in carbon monoxide concentrations occurred with increasing altitude ranging from approximately 0.09 mg/m^3 (0.08 ppm) at 4 km to 0.05 mg/m^3 (0.04 ppm) at 15 km.

4.2 Environmental Absorption and Transformation

The residence time of carbon monoxide in the atmosphere is believed to be approximately 0.2 years. Background levels do not appear to be increasing, indicating the presence of various scavenging and removal mechanisms (sinks). Oxidation in the atmosphere and take-up by the soil, vegetation, and inland fresh waters have been identified as the major removal mechanisms.

The oceans act as reservoirs for carbon monoxide, since considerable quantities are dissolved in the water. Because of the equilibrium that exists, carbon monoxide is dissolved or released according to conditions depending

on the partial pressure of carbon monoxide in the atmosphere and on the water temperature.

The carbon monoxide produced at the earth's surface migrates by diffusion and eddy currents to the troposphere and stratosphere where it is oxidized to carbon dioxide (CO_2) by the hydroxyl (OH) radical. This process, however, can account for only a portion of the carbon monoxide oxidation. Calvert (1973) suggested several possible reactions of carbon monoxide with other pollutants also involving the hydroxyl radical and Westberg et al. (1971) demonstrated that carbon monoxide can accelerate both the oxidation of nitric acid (NO) to nitrogen dioxide (NO_2) and the rate of ozone formation.

Microorganisms can metabolize carbon monoxide and large quantities of these organisms are present in the soil. Ingersoll et al. (1974) showed that desert soils took up carbon monoxide at the lowest rates and tropical soils at the highest. Cultivated soils had a lower carbon monoxide uptake rate than uncultivated soils, presumably because there is less organic matter in the surface layer.

It has been reported that some plant species can remove carbon monoxide from the atmosphere by oxidation to carbon dioxide or by conversion to methane (Bidwell & Fraser, 1972). However, Ingersoll et al. (1974) could not measure carbon monoxide removal by any plants tested in an artificial atmosphere containing a carbon monoxide concentration of 115 mg/m^3 (100 ppm). The process of plant respiration as a carbon monoxide sink still requires considerable further study.

It is believed that inland fresh waters may remove some carbon monoxide from the atmosphere. Rainwater contains appreciable quantities of carbon monoxide and the runoff into the lakes and rivers may account for additional removal.

5. ENVIRONMENTAL LEVELS AND EXPOSURES

5.1 Ambient Air Concentrations and Exposures

Carbon monoxide concentrations in the ambient air have been measured in many large urban areas for a number of years. Although a substantial body of data is now available, it is still not possible to assess the overall human exposure to carbon monoxide adequately. Both the extreme temporal and spatial variability of carbon monoxide concentrations and the small number of monitoring stations in each urban area make the assessment of human exposure difficult. The available data, however, provide some indication of the patterns and trends of urban carbon monoxide concentrations.

Concentrations in urban areas usually follow a very pronounced diurnal pattern, and, although influenced by factors such as location and meteorological conditions, their values are closely correlated with the amount of motor vehicle traffic. Thus, although the exact shape of the curve representing the temporal variation in carbon monoxide concentrations over a day, varies with the situation, it usually shows two peaks, corresponding to the morning and evening traffic rush hours. Such curves have been established by many authors (Colucci & Begeman, 1969; Göthe et al., 1969; Waller et al., 1965), by means of continuous carbon monoxide monitoring. In general, an initial peak is detected between 07h00 and 09h00 coinciding with heavy morning traffic, and another, in the late afternoon, as illustrated in Fig. 1. However, there may be exceptions to this typical pattern, as shown in Fig. 2, which presents data from a monitoring station in New York City (Martin & Stern, 1974). In this case, the traffic conditions were such that carbon monoxide concentrations remained high during most of the day. Because of changes in traffic patterns, the carbon monoxide concentrations are usually lower at weekends than on weekdays and follow a different diurnal pattern.

At any location, the concentration of carbon monoxide due to motor vehicle traffic depends on the following specific variables:

(*a*) number of vehicles operating;

(*b*) engine characteristics of the operating vehicles (capacity, gasoline or diesel, use of emission control devices);

(*c*) speed of traffic and gradient;

(*d*) temperature (as it affects the operating efficiency of the engine).

More general variables include the meteorological conditions (including wind speed and direction, and temperature gradients) and the geometry of locality (shape and height of buildings, width of street, etc.).

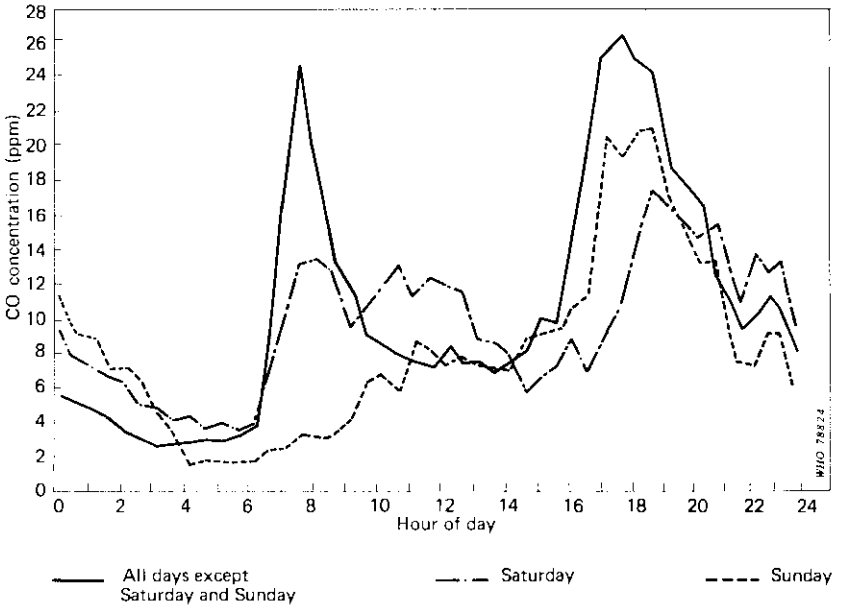

Fig. 1. Average diurnal concentration of carbon monoxide in Wiesbaden, Federal Republic of Germany (From: Göthe et al., 1969). Carbon monoxide 1 ppm = 1145 μg/m³.

Carbon monoxide concentrations are normally reported in terms of 8-h average concentrations. This averaging time has been used because it takes from 4 to 12 h for the carboxyhaemoglobin levels in the human body to reach equilibrium with the ambient carbon monoxide concentrations. Two types of approaches have been used for calculating the 8-h average (McMullen, 1975). One approach is to examine all possible 8-h intervals and calculate a moving 8-h average (24, 8-h averages each day). The other approach is to examine three consecutive, nonoverlapping, 8-h intervals per day. It would appear that the moving average approach offers some advantages in that it approximates the human body's integrating response to cumulative carbon monoxide exposure. In addition to the 8-h averages, carbon monoxide concentrations are also reported in terms of other averaging times and frequency distributions.

Carbon monoxide concentrations in the ambient air vary considerably, not only among urban areas but within cities as well. The maximum 8-h mean concentrations measured at more than 200 monitoring stations in the USA in 1973 ranged from less than 10 mg/m³ to 58 mg/m³ (8.7–51 ppm) with most of the values being less than 30 mg/m³ (26 ppm) (Martin & Stern, 1974). The highest 8-h mean concentration of 59 mg/m³ was observed at a monitoring station in New York City. Data from a 38 station network in

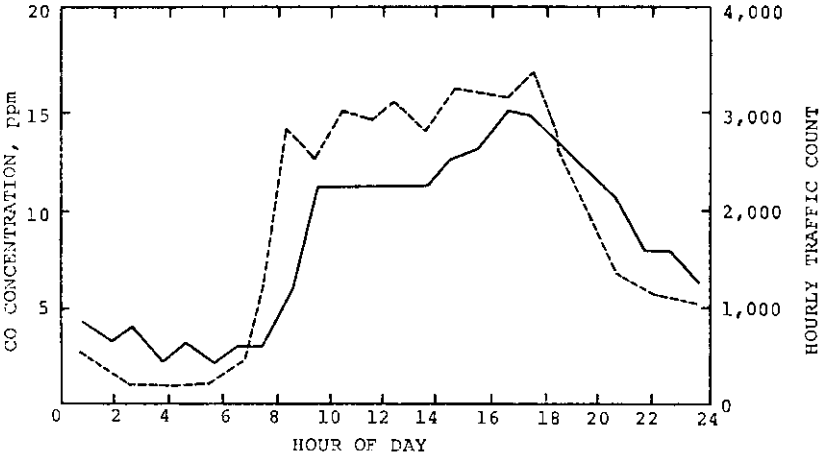

Fig. 2. Average carbon monoxide concentrations and traffic count at a site in Manhattan, New York City (From: Martin & Stern, 1974). Carbon monoxide 1 ppm = 1145 μg/m³.

Japan showed that the 8-h standard of 23 mg/m³ (20 ppm) was not exceeded (Environment Agency, 1973). That carbon monoxide concentrations are extremely variable within an urban area is illustrated by the maximum 8-h means observed at monitoring stations in the metropolitan Los Angeles area in 1973. They ranged from 7 mg/m³ (6 ppm) in the outlying areas to 49 mg/m³ (42.6 ppm) near the centre of the city. The maximum 1-h mean concentrations exhibit a similar variability ranging from less than 10 mg/m³ (8.7 ppm) in some areas to over 90 mg/m³ (78.3 ppm) in others. The highest 1-h mean concentration observed in 1973 was 92 mg/m³ (80 ppm) at a monitoring station in Philadelphia; at more than 80% of the stations the maximum 1-h concentration was below 50 mg/m³ 43.5 ppm). In Japan the maximum 1-h concentrations ranged from 5 mg/m³ to 48 mg/m³ (4.3–41.8 ppm).

Although the data presented above refer to measurements carried out in the USA and Japan, it is indicated that very similar conditions are prevalent in many parts of the world.

Annual average concentrations of carbon monoxide are not of much value for assessing human exposure, although they do provide an indication of the long-term trends. Annual average concentrations of carbon monoxide in most locations fall well below 10 mg/m³ (8.7 ppm) (Stewart et al., 1976).

Usually, the monitoring stations are located so that they can provide representative information of air pollution within the community. However, in certain areas, such as loading platforms and underpasses, the concentrations found are much higher than those in city streets. At Chicago post office loading platforms (Conlee et al., 1967), ambient carbon monoxide concentrations ranged from 10 to 88 mg/m³ at various locations.

Wright et al. (1975) determined the levels of carbon monoxide encountered by pedestrians and street workers in Toronto. They reported carbon monoxide levels ranging from 11 to 57 mg/m^3, with much higher concentrations in poorly ventilated underpasses and underground garages.

Industry also contributes to the pollution of the ambient air. Gas generator plants (Nowara, 1975), smelters (Morel & Szemberg, 1971), steelworks (Butt et al., 1974; Maziarka et al., 1974); plastics works (Argirova, 1974, unpublished data)[a], electric generating plants (Grigorov et al., 1968), and mines (Notov, 1959) have all been suggested, among other industrial activities, as sources of environmental carbon monoxide pollution. Rural work places, especially those involving intensive livestock production facilities, can provide high ambient levels of carbon monoxide. Concentrations up to 136 mg/m^3 (119 ppm) have been found in these conditions, with high levels of carboxyhaemoglobin in both animals and workers (Long & Donham, 1973).

5.2 Indoor Concentrations and Exposure

Carbon monoxide is widely generated indoors by heating, cooking, and tobacco smoking. According to Yocom et al. (1971), gas heating systems did not appear to affect indoor carbon monoxide concentrations, but gas stoves, water heaters, and automobile activity in attached garages could be major sources. These authors also reported that carbon monoxide concentrations were generally unrelated to outdoor levels. Obviously, peak concentrations in the kitchen were observed during meal times, Sofoluwe (1968) reported extremely high concentrations of carbon monoxide in Nigerian dwellings, where firewood was used for cooking. During the preparation of meals, average carbon monoxide concentrations were reported to be over 1000 mg/m^3 (870 ppm) with peak levels as high as 3400 mg/m^3 (2960 ppm). Sidorenko et al. (1970) found an indoor level of carbon monoxide of 32.3mg/m^3 (28 ppm) some two and a half hours after domestic gas combustion began, when there was no ventilation, but only 13.4 mg/m^3 (11.6 ppm) when ventilation was provided. The use of improved stoves resulted in better conditions (Sidorenko et al., 1972).

Rench & Savage (1976) have also investigated winter levels of carbon monoxide in the home. Outdoor concentrations were lower than those found indoors. Age of building, type of appliance, heating sources, and socio-economic status were statistically significantly related to indoor levels of

[a] Argirova, M. [Atmospheric air pollution by a plant processing plastics.] In: *Proceedings of the First National Conference on Sanitary Chemistry of the Air, Sofia, Bulgaria, 26–27 November, 1974* (in Bulgarian).

carbon monoxide, higher levels occurring in the kitchens of old houses and in homes belonging to families in lower income groups. Levels were also higher in kitchens with space wall heaters compared with those with forced air, gravity feed, or hot water heating systems. Places of recreation may be problem areas. Excessive levels of carbon monoxide were found in ice-skating areas where ice-resurfacing machines were used. Levels as high as 348 mg/m^3 (304 ppm) were found in such an arena after complaints of illness among children skating there were reported to the local health department (Johnson et al., 1975). Improperly regulated space heaters in such premises could also produce high concentrations of carbon monoxide. This was recently reported to have occurred in an Alaskan ice-skating arena.

That outdoor concentrations of carbon monoxide can sometimes strongly influence indoor levels was illustrated in a study conducted in New York City (Lee, 1972). As shown in Fig. 3, the concentrations inside and outside an apartment building followed the same general pattern and were closely related to nearby traffic flows.

Relatively high concentrations of carbon monoxide have also been observed inside the passenger compartment of motor vehicles (Borst, 1970). Carbon monoxide may enter the compartment from faulty or damaged

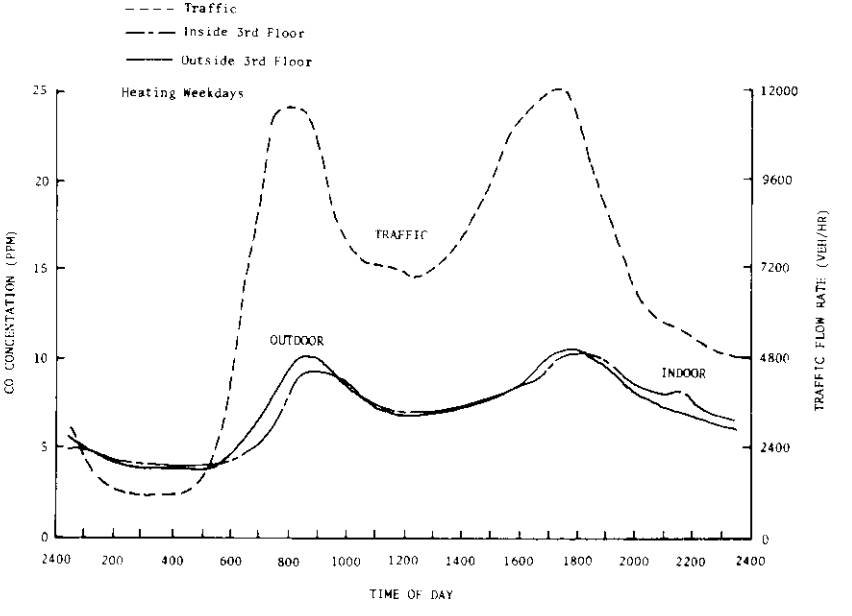

Fig. 3. Indoor–outdoor concentrations in a city (From: Lee, 1972). Carbon monoxide 1 ppm = 1145 μg/m^3.

Table 5. Percentage carboxyhaemoglobin levels in smokers and nonsmokers[a]

Description	Nonsmokers		Smokers	
	mean	range	mean	range
UK pregnant women	1.1		3.6	
Meat porters	1.6		5.1	
Office workers	1.3		6.2	
London office workers	1.12	0.1–2.7	5.5	2.2–13.0
29 000 USA blood donors	1.39	0.4–6.9	5.57	0.8–11.9
3311 California longshoremen	1.3		5.9	
Munich population	2.36		7.38	
Rural Bavarians	1.03		6.06	

[a] From: Wakeham (1976).

exhaust systems or from the surrounding air, in road traffic. The carbon monoxide level in the compartment is often higher than that found outside the vehicle. Haagen-Smit (1966) found an average concentration in a vehicle passenger compartment of 42 mg/m^3 (36.5 ppm) on a Los Angeles freeway during the rush hour traffic (higher concentrations have been reported by Aronow et al. (1972).

It should be emphasized that cigarette smoking is the most common source of carbon monoxide for the general population (Table 5).

Exposure to smoking primarily affects the carboxyhaemoglobin level of the smoker himself (Kahn et al., 1974; Landaw, 1973). In some circumstances, such as poorly ventilated enclosed spaces, the tobacco smoke may affect all of the occupants (section 8.1.6).

5.3 Occupational Exposure

Many occupational groups are subject to high carbon monoxide exposure. These include, traffic policemen, garage personnel, workers in the metallurgical, petroleum, gas, and chemical industries, and firefighters.

An average carbon monoxide level of 172 mg/m^3 (149.6 ppm) was recorded in the air of a Paris police garage between 07h30 and 08h00 and 205 mg/m^3 (179 ppm) between 19h30 and 20h00 (Chovin, 1967). Similarly, Trompeo et al. (1964) found an average level of 112 mg/m^3 (97.4 ppm) in 12 underground garages in Rome; a maximum concentration of 570 mg/m^3 (498.5 ppm) was recorded. In similar studies in enclosed garages with capacities of 300–500 vehicles, where the only ventilation was via the entrance, the average concentration of carbon monoxide for a period from 08h00 to 17h00 was 72 mg/m^3 (62.6 ppm) in the summer and 61 mg/m^3 (53 ppm) in the winter (Ramsey, 1967a).

6. METABOLISM

The primary factors that determine the final level of carboxyhaemoglobin are: the amount of inspired carbon monoxide; minute alveolar ventilation at rest and during exercise; endogenous carbon monoxide production; blood volume; barometric pressure; and the relative diffusion capability of the lungs. The rate of diffusion from the alveoli and the binding of carbon monoxide with the blood haemoglobin are the steps limiting the rate of uptake into the blood.

6.1 Endogenous Carbon Monoxide Production

Carbon monoxide can be produced endogenously from the catabolism of pyrrole rings, originating from haemoglobin, myoglobin, cytochromes, and other haem-containing pigments. Haem catabolism is the main source of endogenous carbon monoxide production, but recent *in vitro* investigations suggest additional endogenous sources, e.g., lipid peroxidation (Wolff & Bidlack, 1976).

The endogenous carboxyhaemoglobin level in man is estimated to be about 0.1–1.0%. Increased production of endogenous carbon monoxide has been found in haemolytic anaemias (Coburn et al., 1966), and could be expected in haematomas and after exposure to certain toxic chemicals capable of causing haemolysis. The liver is probably the major source of endogenous carbon monoxide as a consequence of an increase in liver cytochromes induced by certain drugs (Coburn, 1970a), or in porphyria cutanea tarda (acquired or symptomatic porphyria) (White, 1970). Similarly, bone marrow can become a major source of carbon monoxide in haematological diseases, such as sideroblastic anaemia, being characterized by ineffective erythropoiesis (White, 1970). In neonates endogenous carbon monoxide can be markedly elevated, as well as in females during the progesterone phase of the menstrual cycle (Delivoria-Papadopoulos et al., 1970; Longo, 1970), and even more so during pregnancy (see section 8.2.3). Another important cause of carboxyhaemoglobin elevation is exposure to several methane-derived halogenated hydrocarbons (see section 8.1.5).

6.2 Absorption

The classical absorption curves of Forbes et al. (1945) have been re-evaluated for man at rest by Peterson & Stewart (1970) who exposed

volunteers to a variety of different concentrations of carbon monoxide for periods ranging from 0.5 to 24 h. Using a regression approach, they derived the following empirical relationship for blood carboxyhaemoglobin as a function of ambient carbon monoxide concentration and exposure time:

$$\log_{10} y = 0.85753 \log_{10} x + 0.62995 \log_{10} t - 2.29519$$

where y = % carboxyhaemoglobin
x = carbon monoxide concentration in ppm
t = time in minutes

Although these new data come closer to presenting potential uptake in individuals exposed to present-day ambient concentrations of carbon monoxide, they do not apply to the uptake that would occur in active man. Furthermore, they fit only the linear, non-steady-state portion of the absorption curve. Ott & Mage (1974) have objected to the Peterson & Stewart equation as being basically a static model. They indicate that the use of averaging periods as long as 1 h compared with 10–15 min introduces an error into recorded urban concentrations. This error may be serious if many sharp, ambient peaks are present.

The data presented by Forbes et al. (1945) are still the only experimental information available that takes ventilation into account and, even so, this information is inadequate since the full range of inspired, ventilatory volumes possible in exercising man was not considered. Coburn et al. (1965) have developed an equation from which it is possible to calculate blood carboxyhaemoglobin (Peterson & Stewart, 1970) as a function of time, considering appropriate physiological and physical factors. Their basic differential equation is as follows:

$$\frac{d(\mathrm{CO})}{dt} = \dot{V}_{\mathrm{CO}} - \frac{[\mathrm{HbCO}]}{[\mathrm{HbO_2}]} \times \frac{\bar{p}C_{\mathrm{O_2}}}{M} \times \frac{1}{\dfrac{1}{D_{\mathrm{L}}} + \dfrac{pB - 47}{\dot{V}_{\mathrm{A}}}} + \frac{pI_{\mathrm{CO}}}{\dfrac{1}{D_{\mathrm{L}}} + \dfrac{pB - 47}{\dot{V}_{\mathrm{A}}}}$$

where $\dfrac{d(\mathrm{CO})}{dt}$ is the rate of change of CO in the body (ml/min)

[HbCO] is the concentration of CO in the blood (ml CO/ml blood)
$[\mathrm{HbO_2}]$ is the concentration of O_2 in the blood (ml O_2/ml blood)
D_{L} is the diffusion capacity of the lung (ml/min/mmHg)
$\dot{V}_{\mathrm{A}}$ is the alveolar ventilation rate (ml/min)
pB is barometric pressure (mmHg)
pI_{CO} is inspired carbon monoxide pressure (mmHg)
$\bar{p}C_{\mathrm{O_2}}$ is the mean pulmonary capillary oxygen pressure (mmHg)
M is the Haldane constant (220–240 at pH 7.4)
$\dot{V}_{\mathrm{CO}}$ is the rate of endogenous CO production (ml/min)

The same author (Ramsey, 1967b) reported that the carboxyhaemoglobin levels of 14 nonsmoking parking garage employees, exposed to an average concentration of carbon monoxide of 68 mg/m^3 (59 ppm), increased from 1.5 to 7.3%. He also noted that, in smokers exposed to the same environment, initial carboxyhaemoglobin levels of 2.9% rose to 9.3% at the end of the day. Smokers not exposed to this environment had final levels of only 3.9%. Ramsey stated that occupational exposure played a greater role than smoking in increasing carboxyhaemoglobin levels. However, in a study of some 350 Canadian garage and service station personnel, Buchwald (1969) found that cigarette smoking was the more significant contributor to the high levels of carboxyhaemoglobin measured. Of the smokers, 70% had levels in excess of 5%, while a similar level was found in only 30% of the nonsmokers. Breysse & Bovee (1969) used expired air samples to determine exposure to carbon monoxide in stevedores, gasoline-powered lift truck drivers, and winch operators. They made some 700 estimates of carboxyhaemoglobin, almost 6% of which exceeded 10%. Seven percent of the stevedores and 18% of the lift truck operators had carboxyhaemoglobin levels over 10%. Smoking contributed substantially to the attainment of these high levels. Carboxyhaemoglobin levels as high as 10% were also found in dock workers in studies by Petrov (1968). Inspectors at USA–Mexico border crossing stations were found to be exposed to ambient levels of carbon monoxide that fluctuated between 6 and 195 mg/m^3 (5 and 170.5 ppm). During one hour of an evening shift, ambient carbon monoxide averaged 131 mg/m^3 (114 ppm). Carboxyhaemoglobin levels of smokers and nonsmokers which were 4.0 and 1.4% respectively, prior to duty rose to 7.6 and 3.8% (Cohen et al., 1971).

Data obtained by Balabaeva & Kalpazanov (1974) in studies on traffic policemen in 4 large towns in Bulgaria were similar to those Chovin (1967) obtained in his study on the exposure of Paris policemen to carbon monoxide. However, Göthe et al. (1969) found relatively low levels of carboxyhaemoglobin in Swedish traffic policemen. When blood lead levels were studied in 50 London taxi drivers using their carboxyhaemoglobin levels as an index of exposure to exhaust products, carboxyhaemoglobin levels were higher in day drivers than in night drivers and in smokers than in nonsmokers. Concentrations in all groups ranged from 0.4 to 9.7%, and those in nonsmokers (day and night) from 0.4 to 3.0%.

Direct measurement of carboxyhaemoglobin levels in firefighters engaged in prolonged firefighting indicated that 10% had values exceeding 10% (Gordon & Rogers, 1969). However, the high levels of carboxyhaemoglobin found in the control (non-firefighting) groups make these conclusions somewhat uncertain. Goldsmith's study (1970) of longshoremen suggested that the expired alveolar concentrations of carbon monoxide in smokers

were age-related. For example, subjects smoking one packet of 20 cigarettes per day in the 45–54 year age group had an average alveolar value of 31 mg/m^3 (27 ppm), while the 75–84 year age group had an average of only 16 mg/m^3 (14.4 ppm). Nonsmokers did not exhibit this age-related pattern, since even up to 84 years of age, alveolar concentrations remained at the same level 4 mg/m^3 (3.6 ppm).

Exposure to low levels of carbon monoxide may have a significant influence on the health and efficiency of these workers but this awaits further study. Many other instances of occupational exposure are available but most studies are complicated by the unknown or unreported smoking habits of the workers under study (Grut, 1949).

5.4 Carboxyhaemoglobin Levels in the General Population

The most extensive study of blood carboxyhaemoglobin levels in the general population was carried out by Stewart and his associates (1973c and 1974), who took blood samples in 18 urban areas and in some small towns in the States of New Hampshire and Vermont, USA. Similar blood samples were evaluated for carboxyhaemoglobin levels by Kahn et al. (1974), Davis & Gantner (1974), and Wallace et al. (1974) in metropolitan St Louis. A total of 45 649 blood donors provided blood for analysis. Stewart's subjects (29 000 including 1016 from St Louis) were studied in March 1971 and Kahn's (16 649 subjects all from St Louis) from October 1971 to October 1972. Stewart et al. concluded that 45% of all the non-smoking donors exposed to ambient carbon monoxide had a carboxy-haemoglobin saturation greater than 1.5%, while Kahn's group reported a level of less than 1%.

Table 6. Percent carboxyhaemoglobin versus carbon monoxide alveolar pressure

% HbCO	mg/m³	ppm	% in air	Pa	Torr
0.87	5.7	5	0.0005	0.506	0.0038
1.73	11.5	10	0.001	1.013	0.0076
3.45	23.0	20	0.002	2.026	0.0152
5.05	34.5	30	0.003	3.305	0.0248
6.63	46.0	40	0.004	4.052	0.0304
8.16	57.5	50	0.005	5.065	0.0380
9.63	69.0	60	0.006	6.078	0.0456
11.08	80	70	0.007	7.091	0.0532
12.46	92.0	80	0.008	8.104	0.0608
13.80	103.0	90	0.009	9.117	0.0684
15.11	114.5	100	0.010	10.130	0.0760
16.37	126.0	110	0.011	11.143	0.0836
17.60	130.0	120	0.012	12.156	0.0912
18.78	149.0	130	0.013	13.170	0.0988
19.95	160.0	140	0.014	14.183	0.1064
21.05	172.0	150	0.015	15.196	0.1140
22.15	183.0	160	0.016	16.209	0.1216
23.23	195.0	170	0.017	17.209	0.1291
24.26	206.0	180	0.018	18.235	0.1368
25.25	218.0	190	0.019	19.221	0.1442
26.22	229.0	200	0.020	20.261	0.1520

One solution of the equation depends on the assumption that $\bar{p}C_{O_2}$ and HbO_2 are constant and independent of HbCO. However, HbO_2 concentration depends upon HbCO in a complex way and, in general, solution of the equation requires some special computer techniques using a second approximation; these have been attempted and general solutions are available (Coburn et al., 1965). Further development of Coburn's concepts will undoubtedly improve the basis on which theoretical uptakes can be calculated. For immediate, practical purposes, calculations based on the Haldane formula (see section 6.3) can be used.

Table 6 indicates the equilibrium percentage saturation of the haemoglobin with carbon monoxide at various alveolar pressures of carbon monoxide, calculated from the Haldane formula:[a]

$$\frac{\%\ \mathrm{HbCO}}{\%\ \mathrm{HbO_2}} = \frac{230 pA_{CO}}{pA_{O_2}}$$

where pA_{CO} and pA_{O_2} are the alveolar pressures of carbon monoxide and oxygen respectively.

6.3 Reactions with Body Tissues and Fluids

An adequate oxygen supply to maintain tissue metabolism is provided by the integrated functioning of the respiratory and cardiovascular systems to

[a] The alveolar oxygen pressure is assumed to be 13 kPa (98 Torr)

transport oxygen from the ambient air to the various tissues of the body. Nearly all of the oxygen, except that dissolved in plasma, is bound reversibly to the haemoglobin contained within the erythrocytes. The most significant chemical characteristic of carbon monoxide is that it also is reversibly bound by haemoglobin. Therefore, it is a competitor with oxygen for the four binding sites on the haemoglobin molecule.

The equilibrium constant M expresses the relative affinity of haemoglobin for carbon monoxide and oxygen when the concentration of reduced haemoglobin is minimal. This Haldane constant (Douglas et al., 1912) is defined by the following equation:

$$\frac{\mathrm{HbCO}}{\mathrm{HbO_2}} = M \times \frac{p\mathrm{CO}}{p\mathrm{O_2}}$$

where pCO and $p\mathrm{O_2}$ represent the equilibrium partial gas pressures: each pressure being the same in the erythrocytes or haemoglobin solution as in the equilibrated gas phase. [HbCO] and [$\mathrm{HbO_2}$] are the concentrations of carboxyhaemoglobin and oxyhaemoglobin, respectively. The value of M is about 200 in most species, in spite of the fact that carbon monoxide combines with haemoglobin more slowly than oxygen. Carboxyhaemoglobin dissociates very slowly due to the tight binding of carbon monoxide to haemoglobin. Technically, it is not possible to measure the rate of dissociation of carbon monoxide from partly saturated haemoglobin. The dissociation velocity constant has been measured by only a few investigators on sheep and human haemoglobin fully saturated with carbon monoxide. Roughton (1970), however, has presented the most comprehensive analysis of the interaction of carbon monoxide with erythrocyte haemoglobin, showing clearly that, for man, M is higher than commonly thought, i.e., it is more likely to be between 240 and 250; however, the value for M depends on the point of reference on the dissociation curve.

Solution of Haldane's equation would give an approximate level of carboxyhaemoglobin, e.g., exposure to ambient air containing carbon monoxide levels of 28.7, 57.5, or 115 mg/m^3 (25, 50, or 100 ppm) would lead to carboxyhaemoglobin saturations of approximately 4.8, 9.2 and 16.3%, if the arterial oxygen pressure were 10.7 kPa (80 Torr). The carbon monoxide enters the lungs with each breath and diffuses across the alveolar-capillary membrane in a manner similar to oxygen. If air with a constant concentration of carbon monoxide is breathed for several hours, the rate of uptake of carbon monoxide decreases approximately exponentially until an equilibrium state is attained in which the partial pressure of carbon monoxide in the pulmonary capillary blood is the same as that in the alveolar.

Oxygen transport in the blood is best described by the oxyhaemoglobin dissociation curve (Fig. 4). In the presence of carboxyhaemoglobin, this curve is no longer typically sigmoid but is shifted to the left so that a lower oxygen pressure is present for the same oxyhaemoglobin saturation compared with blood without carboxyhaemoglobin (Roughton & Darling, 1944). Fig. 5 illustrates the extent of the Haldane shift to the left more

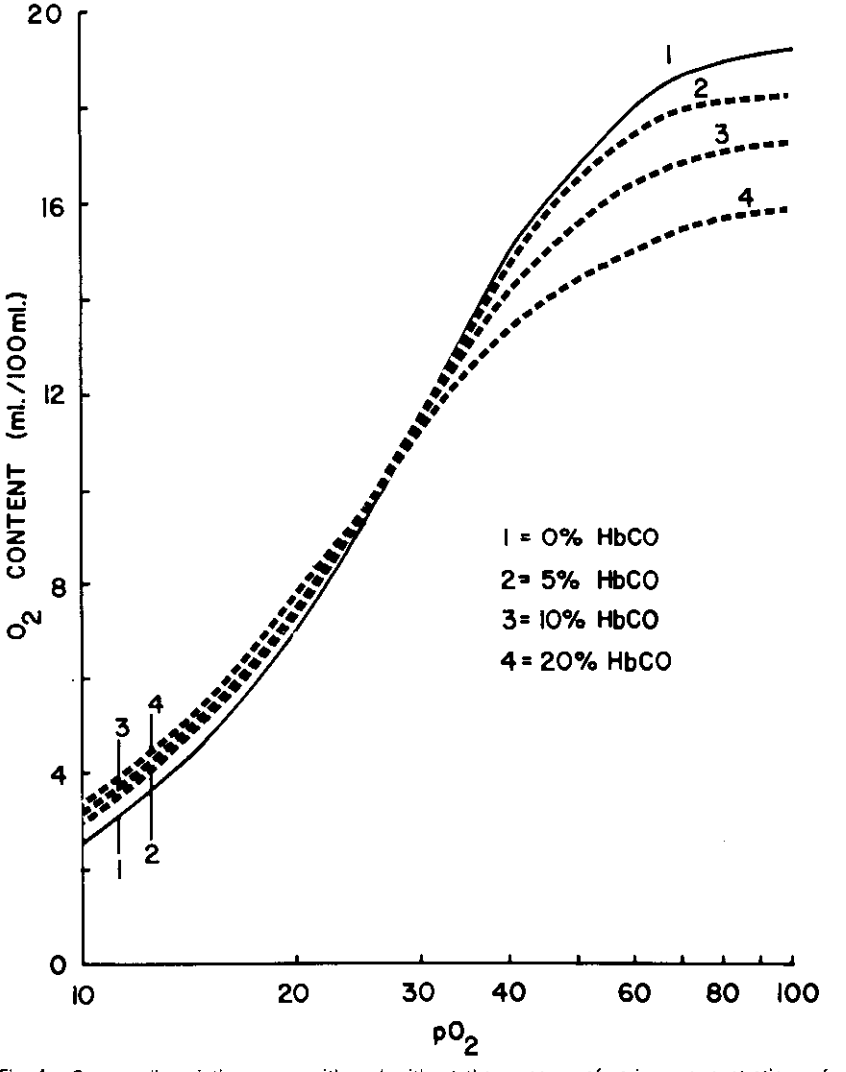

Fig. 4. Oxygen dissociation curve with and without the presence of various concentrations of carbon monoxide.

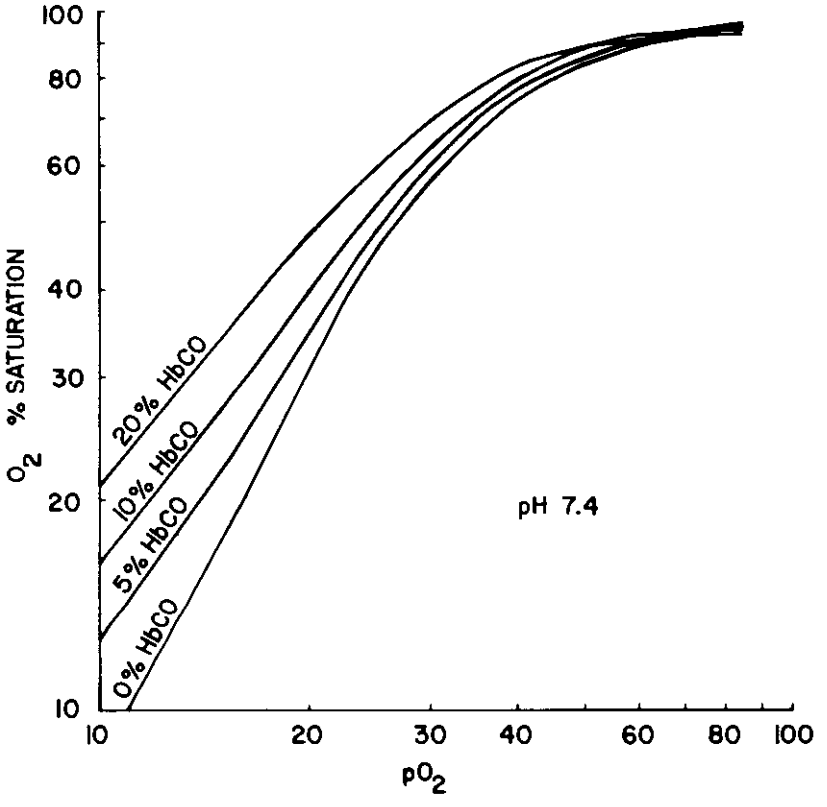

Fig. 5. Blood oxygen dissociation curves at various carboxyhaemoglobin values (From: Dinman, 1968).

clearly than the typical curves of Fig. 4. Mulhausen et al. (1968) illustrated this shift by showing that the half saturation oxygen tension shifted from 3.6 to 3.1 kPa (26.7 to 23.2 Torr) in subjects who were intermittently exposed to a high concentration of ambient carbon monoxide. Carbon monoxide not only diminishes the total amount of oxygen available by direct replacement of oxygen (Fig. 4) but also alters the dissociation of the remaining oxygen so that it is held more tenaciously by haemoglobin and released at lower oxygen tensions. The oxyhaemoglobin curve in the presence of carboxyhaemoglobin progressively resembles the simple oxygen dissociation curve of myoglobin. Myoglobin is a haem compound with only one haem unit per molecule and does not exhibit haem–haem interactions. It is possible that the combination of one or more of the four haem groups in haemoglobin with carbon monoxide decreases the haem–haem interactions of the

remaining haem units and results in a molecule approaching the behaviour of myoglobin.

Any consideration of the toxicity of carbon monoxide must include not only the decrease in the oxygen carrying capacity of haemoglobin but also the interference with oxygen release at the tissue level.

The venous pO_2 values expected to result from various carboxyhaemoglobin levels can be calculated (Forster, 1970; Permutt & Fahri, 1969). If blood flow and metabolic rate remain constant, equilibration with an ambient carbon monoxide concentration of 230 mg/m^3 or 200 ppm (25% carboxyhaemoglobin) will lower venous pO_2 from 5.3 to less than 4 kPa (40 to less than 30 Torr). A similar degree of venous hypoxaemia results from an ascent to an altitude of 3658 metres or a 35% reduction in oxygen capacity in an anaemic patient. It can also be calculated that, at 5% carboxyhaemoglobin, there will be only a slight drop in the mixed venous pO_2. Even more valuable relationships can be obtained by plotting oxygen content against the partial pressure of oxygen (Roughton & Darling, 1944). The difference in oxygen content at various percentages of carboxyhaemoglobin from 0 to 20 reveal the minimal magnitude of the relative unavailability of oxygen due to the Haldane effect (Fig. 4). It was this evaluation that led Roughton & Darling to conclude that carboxyhaemoglobin concentrations of less than 40% produce relatively easily compensated restrictions in the amount of oxygen available for tissue delivery. This can only be applied to subjects with normal respiratory and circulatory systems. The small reductions in oxygen content at 5–10% carboxyhaemoglobin may be quite critical for patients suffering from cardiovascular diseases or chronic obstructive lung disease. Coburn et al. (1965) published a detailed theoretical analysis of the physiology and variables that determine blood carboxyhaemoglobin levels in man. The details of the formulae used in these calculations are presented in section 6.2.

With regard to the intracellular effects of carbon monoxide, consideration must be given to the interactions of all substances within the tissue cells that are involved with oxygen delivery. Since haemoglobin and myoglobin are structurally related, they react with carbon monoxide in a similar manner. The function of myoglobin, *in vivo*, may be to act as a reservoir for oxygen within the muscle fibre. The carbon monoxide and oxygen equilibria of human myoglobin has been studied *in vitro* and a hyperbolic oxygen dissociation curve established (Rossi-Fanelli & Antonini, 1958). This curve, unlike that for haemoglobin, is not affected by the hydrogen ion concentration, the ionic strength, or the concentration of myoglobin. The relative affinity constant, M, is approximately 40 but is still sufficient to induce appreciable formation of carboxymyoglobin. Both Coburn et al. (1970b, 1973) and Luomanmaki (1966) have studied the interrelationships between

carboxyhaemoglobin and carboxymyoglobin. Coburn, using ^{14}CO, showed that identical carbon monoxide exposures can produce different degrees of saturation of haemoglobin, depending upon the partial pressures of oxygen in blood and tissue. Coburn (1970b) determined the ratio of the carbon monoxide content in muscle to the content in blood as a function of arterial pO_2. This ratio, for skeletal muscle, is approximately 1, but in myocardial tissue it was found to be 3. When arterial pO_2 fell below 5.3–4 kPa (40–30 Torr), carbon monoxide disappeared from the blood, presumably entering the muscle. Considerable amounts of extravascular carbon monoxide are stored in muscle. The higher ratio for cardiac tissue may be of considerable significance. In an individual with a blood carboxyhaemoglobin level of 10%, some 30% of cardiac myoglobin may be saturated with carbon monoxide. Coburn and associates (1973) estimated the mean pO_2 of skeletal muscle and myocardium and found that they were 0.8–1.1 and 0.5–0.8 kPa (6–8 and 4–6 Torr), respectively.

Although no final judgement can be made regarding the next lower step involved in oxygen transport, i.e., the role of cytochromes a_3 and P-450, the fact that, experimentally, they react with carbon monoxide in the same way as other haem-containing substances suggests that they may play a role in carbon monoxide poisoning. Available evidence suggests that interactions between carbon monoxide and cytochrome oxidases are of minor significance at the concentrations of carbon monoxide found in community air pollution. All of the data on the cytochromes have been obtained from *in vitro* experiments. Whether similar events occur *in vivo* remains uncertain. The most likely oxidase for *in vivo* inhibition is P-450. Cooper et al. (1965) reported that the ratio of carbon monoxide to oxygen required for 50% inhibition is close to 1, in contrast to a similar ratio of between 2.2 and 28 for cytochrome a_3. Root (1965) believes that at a pCO compatible with life, only nonsignificant blocking of the oxygen consumption system occurs. In terms of the total distribution throughout the body of an inhaled dose of carbon monoxide, the amounts bound to these haemoproteins are small compared with haemoglobin and myoglobin. A diagrammatic representation of the factors influencing body carbon monoxide stores has been presented by Coburn (1970b). The possible significance of the role of these haemoproteins lies in the concept that, under conditions where tissue pO_2 is decreased, the affinity of intracellular haemoproteins for carbon monoxide may increase.

6.4 Excretion

Adequate data are available on the rate of absorption of carbon monoxide but there is considerably less information concerning the rates of

carbon monoxide egress from the lungs. The same factors that determine how much carbon monoxide is taken up by the blood should apply in reverse when clearance of carbon monoxide from blood is considered. The primary factors involved are the amounts of carbon monoxide and oxygen present, the magnitude of ventilation, and the quality of the diffusion barrier. Age influences the quality of the barrier and it appears that with advancing age the barrier becomes "thicker" and there are fewer gas exchange membranes. Sedov et al. (1971) presented data on the elimination of carbon monoxide at various atmospheric pressures and ambient temperatures. Neither lower barometric pressures nor high temperatures appreciably altered the rates of elimination. It has been implied by Pace et al. (1950) that a sex difference in elimination may also exist, a faster rate occurring in females than in males, at least under the experimental conditions of their study. Some sex differences in excretion have been reported by Goldsmith et al. (1963).

Available evidence suggests that there is a biphasic decline in the percentage of carboxyhaemoglobin in the arterial blood (Godin & Shephard, 1972; Wagner et al., 1975). There is a rapid, initial, exponential decline (distribution phase), probably related to the distribution of carbon monoxide from the circulating blood to splenic blood, myoglobin, and cytochrome enzymes. Elimination of carbon monoxide through the lungs also occurs during this phase. The distribution phase, which persists for the first 20–30 min, is followed by a slower linear decline (elimination phase). This phase probably reflects the rates of release of carbon monoxide from haemoglobin and myoglobin, pulmonary diffusion, and ventilation, as well as the fact that pCO decreases with time. Myhre (1974) found that a similar biphasic excretion pattern occurred at an altitude of 1630 metres. However, he noted that the half-time of carboxyhaemoglobin was much longer (5.5 h). After continuous exposure to carbon monoxide for 49 h, 50% was eliminated in 30–180 min and 90% within 180–420 min (Tiunov & Kustov, 1964). Other investigators (Godin & Shephard, 1972; Peterson & Stewart, 1970) reported exponential carboxyhaemoglobin elimination curves over many hours. However, because of inadequate sampling in the early phase of elimination, they were unable to observe the more rapid initial decline. The absolute level of carboxyhaemoglobin, when the elimination studies began, apparently modified the rate of disappearance of carbon monoxide from the blood. Considerable individual variability has been observed and the duration of exposure may also be an important factor. It has been shown that prolonged exposure (more than 3 years) to concentrations of carbon monoxide of 11.5–115 mg/m^3 (10–100 ppm) results in a markedly retarded elimination of carbon monoxide (Kodat, 1971).

In summary, discharge of carbon monoxide occurs rapidly at first

becoming slower with time and the lower the initial level of carboxyhaemoglobin, the slower the rate of elimination. Apparently, no studies have been made to determine elimination rates at the low levels of carboxyhaemoglobin (2–4%) that might be present following exposure to ambient concentrations of carbon monoxide.

Several procedures have been tested that could accelerate the excretion of carbon monoxide from the blood of individuals with high levels of carboxyhaemoglobin (40–70%). Pace et al. (1950) reported that treatment of such individuals in a recompression chamber with an oxygen level equivalent to 2.5 atmospheres (partial pressure of oxygen equal to 253 kPa (1900 Torr) or an alveolar oxygen pressure of 239 kPa (1801 Torr)) would facilitate removal of carbon monoxide. They indicated that 1 h in such a chamber would result in the reduction of the carboxyhaemoglobin level to 10 to 15% of the initial level. In a revival of the old Henderson & Haggard treatment concept, Malorny et al. (1962) evaluated the influence of breathing different gas mixtures on the excretion of carbon monoxide in animals having high carboxyhaemoglobin levels (60–74%). It was determined that 50% of carbon monoxide could be excreted in 19 min if 5% carbon dioxide and 95% oxygen were breathed, compared with a time of 28 min for 100% oxygen, and 41 min for ambient air. Another approach was suggested by Agostini et al. (1974), who employed a total body asanguineous, hypothermic procedure. These approaches to the removal of the body burden of excessive amounts of carbon monoxide remain to be evaluated fully in clinical trials.

7. EFFECTS ON EXPERIMENTAL ANIMALS

Great caution must be used in applying the results[a] obtained from animal experiments to man. Nonetheless, animal studies have provided valuable insight into both the potentially adverse effects of carbon monoxide and the basic mechanisms by which this substance influences physiological processes. However, many studies have used extraordinarily high levels of carbon monoxide, rarely found in air. These studies are not referred to in this document, since the toxic effects of very high levels of carbon monoxide have been well documented for both animals and man.

7.1 Species Differences

The oxygen dissociation curves for different animal species used in carbon monoxide studies are not the same. There are also questions concerning the relative affinities for carbon monoxide of the haemoglobin in various animal species. Fodor & Winneke (1971) reported *in vitro* studies that showed different affinities for different species, the highest being in man followed by rat, mouse, and rabbit, in descending order. Klimisch et al. (1975) found the following sequence of affinities: hamster, rat, pig, rabbit. Apart from different affinities there may well be species differences with respect to susceptibility to carbon monoxide. According to Alexandrov (1973) certain mammals can be classified in order of decreasing carbon monoxide susceptibility as follows: mouse, rat, cat, dog, guineapig, and rabbit. This difference might, in part, be related to different ventilation/body weight-ratios.

Species differences in reaction are ideally illustrated in the studies by De Bias et al. (1972a,b, 1973) on dogs and cynomolgus monkeys (*Macaca fascicularis* = *M. irus*). Chronic exposure (23 h per day) over several months to 115 mg/m^3 (100 ppm) resulted in carboxyhaemoglobin levels of 14 and 12.4% in dogs, and monkeys, respectively. The dogs (De Bias et al., 1972a) remained clinically in good health with no untoward signs that could be interpreted as induced by carbon monoxide. Serum enzymes, haematological variables, and electrocardiograms did not change significantly. Carbon monoxide exposure of normal monkeys resulted in myocardial effects. Experimentally infarcted monkeys had greater P-wave amplitudes and increased incidence of T-wave inversions than normal monkeys similarly

[a] Animal studies have been reported in other sections of this document wherever necessary. Consequently, some data on animals (such as sheep) are not repeated in this section.

exposed. One important fact that may partly explain this difference between dogs and monkeys is, that monkeys, like man, have end-arteries, whereas dogs have a well developed collateral circulation.

7.2 Cardiovascular System and Blood

Increase of coronary blood flow is the normal response of the myocardium to carbon monoxide exposure. Permutt & Farhi (1969) calculated theoretically, that, when carboxyhaemoglobin levels are approximately 5%, an increase in coronary blood flow of about 20% more than the resting level would be necessary to prevent coronary sinus pO_2 from falling below minimum levels. This calculation has been confirmed experimentally by Adams et al. (1973) and Horvath (1973), both of whom demonstrated approximately similar increases in coronary blood flow in spite of using very different methods to increase carboxyhaemoglobin levels.

There is considerable controversy concerning the cardiovascular effects of carbon monoxide in dogs. Long-term exposures of animals to carbon monoxide concentrations sufficiently high to produce carboxyhaemoglobin levels in excess of 20% can induce pathological changes in the heart and brain. As in acute high level intoxication in man, serious sequelae develop. Lindenberg et al. (1961) exposed 8 dogs to carbon monoxide concentrations of 115 mg/m^3 (100 ppm). Four were exposed continuously for 24 h a day, 7 days per week, for 6 weeks and another 4 were exposed intermittently. All dogs had abnormal electrocardiograms and some of the hearts showed histological degeneration of muscle. In another study, Preziosi et al. (1970) exposed dogs continuously to 115 mg/m^3 for 6 weeks and reported abnormal electrocardiograms, right and left heart dilatation, and myocardial thinning. Histological examination showed older scarring in some cases and fatty degeneration of heart muscle in others. Carboxyhaemoglobin levels of 7.7 to 12% were lower than would be predicted from the exposure. When 4 dogs were exposed intermittently to a carbon monoxide concentration of 115 mg/m^3 for 11 weeks, central nervous system and cardiac effects were found (Lewey & Drabkin, 1944).

Ehrich et al. (1944) also exposed 4 dogs to 115 mg/m^3 on an intermittent schedule. They observed that electrocardiographic changes occurred at variable times during the 11 weeks of exposure. The gross appearance of the hearts after exposure were normal but microscopic examination revealed marked degenerative changes in individual fibres. Lindenberg et al. (1961) exposed dogs to a carbon monoxide concentration of 57 mg/m^3 (50 ppm) on the same schedule as for his 115 mg/m^3 exposure studies. Carboxyhaemoglobin levels of 2.6–5.5% were observed. No changes in haemoglobin

levels or haematocrit were noted. Electrocardiographic changes were observed in the third week of exposure similar to, but less severe than, those observed in animals exposed to the higher ambient level of carbon monoxide. Dogs were exposed by Musselman et al. (1959) to a carbon monoxide concentration of 57 mg/m^3 for 24 h per day, 7 days per week, for 3 months. No changes in the electrocardiogram or heart rates were observed. Pathological examination of organs and tissues did not reveal any changes after exposure. Experimental data have been presented by Orellano et al. (1976) who claim that carbon monoxide injected intraperitoneally into dogs is nontoxic. This study, as well as other reports from these investigators, raise some intriguing questions as to the mechanisms involved in carbon monoxide toxicity.

Continuous exposure of cynomolgus monkeys to a carbon monoxide concentration of 115 mg/m^3 resulted in demonstrable electrocardiographic effects in the myocardium of both normal monkeys and monkeys with myocardial infarction (De Bias et al., 1972b, 1973). The same investigators (De Bias et al., 1976) also studied the susceptibility of the ventricles to induced fibrillation. Normal and infarcted monkeys were exposed to a carbon monoxide concentration of 115 mg/m^3 for 6 h. Application of high voltages were required to produce fibrillation in normal monkeys in air but when infarcted animals were exposed to carbon monoxide, the voltage level required was very low. Animals with either infarction alone or carbon monoxide exposure alone also required significantly less voltage to produce fibrillation; when the two were combined, the effects were additive. Intermittent exposure to carbon monoxide (30 min per h, 12 h per day, over a period of 14 months) of cynomolgus monkeys fed either a normal or a semipurified cholesterol diet did not result in myocardial infarctions or electrocardiographic abnormalities (Malinow et al., 1976). In these animals, the blood carboxyhaemoglobin concentration reached 21.6% at the end of the daily period of breathing carbon monoxide at 529 mg/m^3 (460 ppm).

Carbon monoxide exposure did not increase the aortic and coronary atherosclerosis induced in cynomolgus monkeys by cholesterol feeding. Eckardt et al. (1972) exposed cynomolgus monkeys (22 h per day, 7 days per week, for 2 years) to carbon monoxide concentrations of 23 or 75 mg/m^3 (20 or 65 ppm). Carboxyhaemoglobin levels, which showed considerable variation during the experimental period, ranged from 2.0 to 5.5% and 4.8 to 10.2% for low and high carbon monoxide ambient concentrations, respectively. These levels of carboxyhaemoglobin did not lead to compensatory increases in haematocrit, haemoglobin, or erythrocyte counts nor to cardiac fibrosis or pathological effects in the brain. Cholesterol-fed squirrel monkeys were exposed to carbon monoxide at 229–344 mg/m^3 (200–300 ppm) for several hours per day for 7 months (Webster et al.,

1968). No differences were found in plasma cholesterol or in aortic and carotid atherosclerosis which could be ascribed to carbon monoxide. However, the authors did observe an increase in coronary atherosclerosis. Somewhat similar results were later reported in studies on cynomolgus monkeys (Malinow et al., 1976). Jones et al. (1971) exposed rats, guineapigs, dogs, and monkeys to 58, 110, or 229 mg/m^3 (51, 96 or 200 ppm) continuously for 90 days. Haematocrit and haemoglobin levels remained constant at the lowest level of carbon monoxide exposure but were significantly elevated at the two higher levels in all species except the dog. Cynomolgus monkeys (*Macaca irus*) were exposed to a concentration of 286 mg/m^3 (250 ppm) for 2 weeks by Thomsen (1974). In all the exposed animals, the coronary arteries showed widening of the subendothelial spaces in which cells with or without lipid droplets were accumulating. He suggested that monkeys were more sensitive to carbon monoxide than the rabbits studied by Astrup et al. (1967). Experimental studies on rabbits exposed to relatively high concentrations of carbon monoxide at 195–206 mg/m^3 (170–180 ppm) for extended periods indicated the presence of high levels of cholesterol in the arteries or enhanced vascular disease (Astrup et al., 1970). The lesions observed, which included subendothelial oedema, a gap between endothelial cells, and increased infiltration of cells with lipid droplets, might be early precursors of atherosclerotic disease. However, such lesions occurred only in animals concurrently on a high cholesterol or fat diet or on both. Exposure to carbon monoxide alone induced some changes such as endothelial hypertrophy and proliferation.

One experimental study on the effects of carbon monoxide on the natural history of heart disease in the cynomolgus monkey has been reported. De Bias et al. (1973) exposed animals to a carbon monoxide concentration of 137 mg/m^3 (120 ppm) for 24 weeks. The average carboxyhaemoglobin level of 12.4% resulted in a polycythaemia with an increase in haematocrit from 35 to 50%. All animals developed increased P-wave amplitude and T-inversion which suggested nonspecific myocardial stress rather than ischaemia. Animals in which an experimental myocardial infarction was produced prior to exposure to carbon monoxide had more marked electrocardiographic changes than animals breathing room air. In 1976, Ramsey & Casper reported that erythrocytic 2,3-diphosphoglycerate (2,3-DPG) played neither a compensatory nor an aggravating role in the hypoxia induced by the presence of 20 or 30% carboxyhaemoglobin. Stupfel & Bouley (1970) exposed mice and rats for 95 h per week to a carbon monoxide concentration of 57 mg/m^3 (50 ppm) for either 1 to 3 months or for their natural life expectancy of up to 2 years. A large number of measurements were made during exposure followed by pathological examination after death. The authors did not observe any important effects

of carbon monoxide exposure on the animals. In a study by Penney et al. (1974a,b), the influence of hypoxic hypoxia on the development of cardiac hypertrophy in the rat was compared with that of carbon monoxide hypoxia. Exposure to various levels of carbon monoxide resulted in hypertrophy of both the right and left ventricles in contrast with the right ventricle hypertrophy observed in response to the hypoxic hypoxia stress.

Cardiac hypertrophy and a reduction in cytochrome oxidase levels were demonstrated in chick embryos exposed to carbon monoxide for 144 and 168 h (Tumasonis & Baker, 1972). The resistance of young chickens to carbon monoxide decreased with age. Body temperatures decreased during exposure to carbon monoxide with the greatest fall in temperature and the longest survival time occurring in the youngest chickens. Total body asanguineous hypothermic perfusion (total body exsanguination exchange transfusion) has been suggested as a therapeutic measure for carbon monoxide poisoning (Agostini et al., 1974). In an attempt to explain this beneficial effect, Ramirez et al. (1974) compared the survival of normal dogs exposed to high levels of carbon monoxide with that of acutely anaemic dogs transfused with carboxyhaemoglobin blood to normal blood volumes. All normal dogs with carboxyhaemoglobin levels of 54–100% died within 0.25–10 h but the transfused animals, having a final mean carboxyhaemoglobin level of 80% after transfusion, survived. The authors suggested that hypoxic anaemia was not the principal mechanism of carbon monoxide toxicity but rather a blocking out of the energy supply on the cellular level, governed by the cytochrome system.

Most of the investigations using rabbits for carbon monoxide related research originated in Astrup's laboratories, where they first demonstrated that low carboxyhaemoglobin levels enhanced the development of atheromatosis (Astrup et al., 1967). Additional studies (Hellung-Larsen et al., 1968; Thomsen & Kjeldsen, 1975) have shown that lactate dehydrogenase isoenzymes (M subunits) increase and that a higher incidence of focal intimal changes occur in rabbits exposed to carbon monoxide. The myocardial ultrastructure of rabbits exposed to a concentration of 206 mg/m^3 (180 ppm) for at least 4 h showed degenerative changes such as contraction bands, myofibrillar disintegration, myelin body formation, and dehiscence of the intercalated discs (Thomsen & Kjeldsen, 1974). Exposure of rabbits to a similar concentration of carbon monoxide for 2 weeks resulted in more extensive myocardial damage (Kjeldsen et al., 1974).

Astrup et al. (1970) furnished evidence that carbon monoxide increases endothelial membrane permeability. They found that rabbits exposed to carbon monoxide developed arterial lesions resulting in a considerable accumulation of lipids. It has also been shown that human coronary arteries exposed to carbon monoxide *in vitro* have a higher uptake of cholesterol,

although no significant changes in lipid synthesis were observed (Sarma et al., 1975). Myocardial damage and impaired myocardial performance have also been reported in animals and man exposed to carbon monoxide (Ayres et al., 1970). Although there is some evidence which suggests that exposure to carbon monoxide can induce changes in blood vessels and the myocardium, there is also evidence to the contrary (section 8.1).

7.3 Central Nervous System

Because of the brain's high oxygen demand, cerebral function should be influenced at low carboxyhaemoglobin levels. However, data concerning this are contradictory. Sensitivity to carbon monoxide may follow a circadian rhythm (Stupfel, 1975; Stupfel et al., 1973). Maximum sensitivity in rats occurred during the dark period of a 12–12 h light–dark cycle. Dyer & Annau (1976) could find no effect on superior colliculus evoked potentials of rats until the level of ambient carbon monoxide had reached 573 mg/m^3 (500 ppm) in marked contrast to Xintaras et al. (1966), who observed a 20% increase in the amplitude of superior colliculus evoked potentials after only 1 h exposure to 57 mg/m^3 (50 ppm), and a 50% increase after a 2-h period of exposure at this level. This study has, however, been criticized for not taking into account the effects of dark adaptation on the amplitude of visual evoked potentials in rats (Dyer & Annau, 1976).

In view of the conflicting reports it is of some interest to examine the available data on cerebral pO_2 tensions, cerebral blood flow (CBF) and cerebral metabolism. Zorn (1972) studied the effects of carbon monoxide inhalation on brain and liver pO_2 using platinum electrodes. Tissue pO_2 fell in both organs, even at a carboxyhaemoglobin concentration of 2%, and the fall was approximately linear to increases in carboxyhaemoglobin. There was a decrease in pO_2 of 0.027–0.24 kPa (0.2–1.8 Torr) for each 1% fall in oxyhaemoglobin percentage saturation. These data suggest that the carbon monoxide influenced levels other than the intracellular level, since if its effects were limited to this area then tissue pO_2 would have been expected to increase. Similar studies were performed by Weiss & Cohen (1974) on rat brain and muscle. They found a decrease in cerebral cortical pO_2 following inhalation of low levels of carbon monoxide. Unfortunately, they did not measure carboxyhaemoglobin levels in these rats but, in a group of sham-operated animals exposed to similar levels of inhaled carbon monoxide, carboxyhaemoglobin had increased to 3.3%. During progressive administration of carbon monoxide to dogs, CBF did not increase until carboxyhaemoglobin levels reached 20%. Thereafter, CBF increased progressively and was double that in the controls when the carboxyhaemoglobin level

reached 50% (Häggendal et al., 1966). On the other hand, Traystman (1976) did observe a progressive increase in CBF in dogs even at very low carboxyhaemoglobin values. The lowest level studied was 2.5%, which produced a slight but significant CBF increase. Thus, Traystman did not believe in a threshold effect. The effects were produced with both hypoxic hypoxia and carbon monoxide hypoxia. It remains to be seen, how these data relate to cerebral circulation in man.

The respiratory centre or arterial chemoreceptors were not stimulated to increase respiratory minute volume even when carboxyhaemoglobin levels were as high as 40% (Chiodi et al., 1941). Mills & Edwards (1968) measured the frequency of electrical impulses in the afferent nerves from the aortic and carotid chemoreceptors and showed that administration of carbon monoxide did result in chemoreceptor stimulation. The response appeared to have an approximately linear relationship with the carboxyhaemoglobin concentration (at least above 8%). These findings suggest that carbon monoxide might stimulate breathing. Failure to observe an increased minute volume may be explained by the fact that, in the presence of carbon monoxide, the chemoreceptor stimulation was offset by hypoxic depression of brain structures involved in breathing. There is some evidence that this balancing between chemoreceptors and central nervous depression is operative in anaemia (Santiago & Edelman, 1972). Additional investigations are needed to clarify this effect of carbon monoxide inhalation.

7.4 Behavioural Changes and Work Performance

In extensive studies on rabbits, guineapigs, rats, and mice (Gadaskina, 1960; Ljublina, 1960; Rylova, 1960) exposure to a carbon monoxide level of 30 mg/m^3 (26 ppm), although not inducing any morphological blood changes, did result in a number of unfavourable physiological changes. Among these were decreased work capacity, poor adjustment to postural shifts (orthostatic tests), and increased thyroid activity. These changes were more evident during the initial period of the exposure but reverted towards normal later, suggesting some adaptation to carbon monoxide exposure.

7.5 Adaptation

Adaptation apparently can occur in animals exposed to moderate concentrations of carbon monoxide (Gorbatov & Noro, 1948; Tiunov & Kustov, 1969) as shown by their ability to tolerate, with apparent ease, acute exposure to higher concentrations. Both Clark & Otis (1952) and

Tiunov & Kustov (1969) have demonstrated that, after long-term exposure to carbon monoxide, animals developed tolerance to short-term, high altitude exposure, and vice versa, an indication of the development of a common adaptive mechanism. Acclimatization continued despite a subsequent decrease in the initial elevation of the haemoglobin concentration (Gorbatov & Noro, 1948). These investigators noted an acclimatization effect in rats exposed daily to 0.4–0.5% carbon monoxide until loss of consciousness occurred. A progressive improvement in tolerance time to unconsciousness was noted so that by the eighth day of exposure a 3-fold improvement over the time required on the first day had developed. In spite of apparent acclimatization, the general condition of test animals became worse. Unexpectedly, daily exposure to a carbon monoxide concentration of 1.0%, which on the first day necessitated a 5-min exposure prior to unconsciousness, failed to induce any improvement in tolerance. A possible correction of leftward shift of the oxygen dissociation by alterations in the concentration of 2,3-diphosphoglycerate (inducing a shift to the right) has been suggested. However, conflicting results and the necessity to produce high levels of carboxyhaemoglobin negate the possibilities of this beneficial effect (Astrup, 1970; Dinman et al., 1970).

Evidence for adaptation to carbon monoxide is inconclusive. Further studies appear to be warranted with special attention devoted to studies using more realistic current ambient levels of carbon monoxide, and also studies on the possible physiological cost of adaptation, if it occurs.

7.6 Embryonal, Fetal, Neonatal, and Teratogenic Effects

Few studies have been made on the effects of carbon monoxide on mammalian fetal growth and survival. Wells (1933) exposed pregnant rats for 5–8 min to a carbon monoxide concentration of 1718 mg/m^3 (1500 ppm) every other day during pregnancy. Maternal unconsciousness and abortion or absorption of most of the fetuses resulted. Data concerning carboxyhaemoglobin levels and numbers of animals studied were not given. Rats were exposed to 0.34% carbon monoxide for 1 h (carboxyhaemoglobin 60–70%) daily for a period of 3 months (Williams & Smith, 1935). Among 7 pregnant females, the number of young per litter was only half that of the controls and only 2 of the 13 newborns survived to weaning age. Astrup et al. (1972) exposed rabbits during their 30 days of pregnancy to carbon monoxide resulting in carboxyhaemoglobin levels of either 9–19 or 16–18%. Neonatal mortality in the 2 groups increased by 10 and 35%, respectively, compared with a control value of 4.5%. Birth weights decreased by 12 and 17%, respectively.

In their studies on the ewe and fetal lamb, Longo & Hill (1977) indicated that fetal uptake and elimination of carbon monoxide was relatively slow compared with that of the mother. They also reported that, during steady-state conditions, fetal levels of carboxyhaemoglobin were about 25% higher than maternal levels. These results may be related to species differences, since Longo & Hill (1970) found that the *M* values[a] for sheep maternal and fetal blood were 218 and 216 respectively, while Engel et al. (1969) reported that fetal haemoglobin had 20% less preferential binding of carbon monoxide over oxygen than haemoglobin A.

There are very few studies on the teratogenicity of carbon monoxide exposure. When fertilized chicken eggs were continuously exposed to a carbon monoxide concentration of 747 mg/m^3 (650 ppm) for up to 18 days of incubation, the percentage of eggs hatching decreased to 46% and developmental anomalies of the tibia and metatarsal bones were noted (Baker & Tumasonis, 1972).

7.7 Carcinogenicity, and Mutagenicity

No evidence is available on carcinogenicity and mutagenicity in relation to exposure to carbon monoxide.

7.8 Miscellaneous Changes

Kustov et al. (1972) exposed rats to carbon monoxide at 53 mg/m^3 (46 ppm) and noted slower weight gains and an increase in haemoglobin. Some enzyme systems were also found to have increased activity, when rats were exposed to carbon monoxide (Pankow & Ponsold, 1972; Pankow et al., 1974b). A slowing of *in vivo* metabolism of the drugs hexobarbital and zoxazolamine, with prolongation of their pharmacological effects has been reported in rats exposed to carbon monoxide concentrations of 286–3435 mg/m^3 (250–3000 ppm) (Montgomery & Rubin, 1971). With prolonged exposure, these metabolic effects became less pronounced and reverted to normal more quickly following removal from the carbon monoxide environment. Sokal (1975) compared the effect on blood pH and certain carbohydrate metabolic products resulting from either a bolus administration or a fixed level of inspired carbon monoxide, both resulting in equivalent final levels of carboxyhaemoglobin. His data suggest that more intense biochemical effects resulted following a gradual increase in carboxyhaemo-

[a] *M* = Relative affinity of haemoglobin for carbon monoxide compared with oxygen.

globin levels compared with effects seen following rapid elevation of carboxyhaemoglobin from the bolus. Data presented by Marks & Swiecicki (1971) indicated that exposure to high levels of carbon monoxide induced a stresslike response in the form of an elevation in catecholamines. Swiecicki (1973) reported that increased carboxyhaemoglobin levels stimulated the adrenergic system and increased carbohydrate metabolism. He also noted that physical training of the rat neither prevented nor reduced changes in carbohydrate metabolism following carbon monoxide exposure and vibration. Exposure of rats to 57 mg/m^3 (50 ppm) for 5 h per day, 5 days per week, for 12 weeks produced an effect on trace metals at the subcellular level, with a possible reduction in cellular respiration and nucleoprotein synthesis.

Guineapigs exposed to carbon monoxide concentrations of 1.7–30 mg/m^3 (1.5–26 ppm) for 21 days, 8 h per day, did not show any allergenic effects related to carbon monoxide exposure (Vinogradov et al., 1974). Plasma leucine aminopeptidase (EC 5.4.11.1)[a] and glutamic pyruvic transaminase (EC 2.4.1.2) activity, normally increased by exposure to carbon tetrachloride, were further potentiated when blood carboxyhaemoglobin levels were elevated. Pankow et al. (1974a) also observed an additive effect on some enzymes with a combination of alcohol and carbon monoxide giving a carboxyhaemoglobin concentration of 50%.

Rondia (1970) observed a significant reduction of benzopyrene-hydroxylase (EC 1.14.14.2) activity in the liver homogenates of rats exposed to a carbon monoxide concentration of 70–150 mg/m^3 (60–130 ppm) for only a few days. This finding might be interpreted as meaning that carbon monoxide contributes to the induction of lung cancer by lengthening the time of retention of carcinogens in the lung. Additional work is necessary to clarify this important question.

7.9 Interactions

Much of the data reviewed by Pankow & Ponsfold (1974) concerning the combined effects of carbon monoxide and other biologically active agents are based on animal experiments. Because of the extreme exposure conditions used in most of these studies, only a few of them are directly relevant to the environmental exposure of man to carbon monoxide.

The experimental evidence on the aggravation of carbon monoxide-induced atherosclerosis in rabbits by dietary cholesterol has already been

[a] The numbers within parentheses following the names of enzymes are those assigned by the Enzyme Commission of the Joint IUPAC-IUB Commission on Biochemical Nomenclature.

mentioned (see section 7.2). No significant additive effects were noted from ethanol when dogs exposed to a carbon monoxide concentration of 115 mg/m^3 (100 ppm) for 21 weeks, 5 days a week, and 6 h per day were given a daily oral dose of 120 ml of a 15% ethanol solution (Pecora, 1959). However, the excretion of total lipoproteins was higher when carbon monoxide and ethanol treatments were combined than with exposure to carbon monoxide alone. An indication of interaction of sulfur dioxide and carbon monoxide was given by Prohorov & Rogov (1959) in their experiments on rabbits. The depressed activity of succinate dehydrogenase (EC 1.3.99.1) on heart, liver, and kidney due to exposure to sulfur dioxide at 200 mg/m^3 (76 ppm) was exacerbated by exposure to carbon monoxide at a level of 200–400 mg/m^3 (174–348 ppm), for 3 h per day, over a 3-week period. As for the combined effects of carbon monoxide and temperature, Tiunov & Kustov (1969) showed clearly that carbon monoxide toxicity in mice increased at temperatures above or below normal ambient levels.

8. EFFECTS ON MAN

8.1 Healthy Subjects

8.1.1 Behavioural changes

Demonstrable changes in the central nervous system (CNS) function of subjects inadvertently exposed to high levels of ambient carbon monoxide in illuminating gas and in automobile exhaust resulted in a series of studies to determine psychomotor and psychological aberrations in subjects having more modest blood levels of carboxyhaemoglobin than those observed in the potentially moribund patients. Deficiencies in earlier studies have been related to inadequate understanding of the significance of behavioural changes, the inability to distinguish between simple perceptual motor performance and the more complex performance involving sustained and/or selective attention, short-term memory, and decision making among possible alternatives. Furthermore, the physiological mechanisms involved in carbon monoxide intoxication were not appreciated and the available physiological and psychological tools were not adequately exploited. Even today, some physiological and behavioural studies suffer from similar or other inadequacies, e.g., the failure to measure blood carboxyhaemoglobin levels, the inability to distinguish between the physiological effects of a carbon monoxide bolus of high concentration or the slow, insidious increment in carboxyhaemoglobin levels over time with lower inhaled concentrations, the amount of carbon monoxide brought to or removed from the lungs by changes in alveolar ventilatory volumes, and the small number of volunteers examined. Other factors involve failure to provide control measures for bias and effects of the experimental worker (by means of double-blind administration), control periods so that task-learning effects do not mask negative results, homogeneity of the groups labelled "smokers" and "nonsmokers", and control of possible boredom and fatigue effects, all essentially amounting to a failure to adopt a proper experimental design that would produce statistically significant information.

A reduction of logical memory and recognition was demonstrated by Chalupa (1960) in individuals subjected to acute carbon monoxide intoxication. However, these functions returned to normal. Sayers et al. (1929) did not find any significant changes in 6 exposed men despite carboxyhaemoglobin levels of approximately 20–30%; observations included hand–eye coordination and steadiness, tapping speed, arithmetic (continuous addition), location memory, and simple reaction time. Simple sensory-motor times decreased by 10% in subjects with carboxyhaemo-

globin concentrations of approximately 6.2% (5.5–7%) (Tiunov & Kustov, 1969). Simulated driving performance did not deteriorate despite carboxyhaemoglobin levels of 25%, although a small deterioration was observed when the carboxyhaemoglobin levels were above 35% (Forbes et al., 1937). The first demonstrable influences of carbon monoxide on higher CNS functions were noted by McFarland et al. (1944) in conjunction with their altitude studies, when they observed reduction of visual acuity at carboxyhaemoglobin levels as low as 5%. These observations were extended by Halperin et al. (1959) when they reported that visual function was impaired at carboxyhaemoglobin levels as low as 4% and that impairment increased at higher levels. More recently, McFarland et al. (1973) showed that, for glare recovery, the dark adaptation final threshold values increased as carboxyhaemoglobin levels rose from control to 6–17%. Peripheral recognition tasks were not affected until levels reached 17%. They also stated that central and peripheral complex tasks were not influenced by low levels of carboxyhaemoglobin. Schulte (1963) demonstrated that there was a decrease in performance in higher intellectual processes that was observable when the carboxyhaemoglobin level exceeded 5%; further deterioration was noted as the level increased. These results were in direct contradiction to the negative results obtained by Dorcus & Weigand (1929) who used a similar series of tests but with subjects exposed for a shorter period. In studies by Beard & Wertheim (1967), the ability to judge correctly slight differences in successive short time intervals showed significant impairment when carboxyhaemoglobin levels were approximately 2 to 3% above basal levels. These findings, suggesting an altered mental function, represent the lowest levels of carboxyhaemoglobin that produce a significant alteration in behavioural performance. However, attempts to replicate them have been less than satisfactory (O'Donnell et al., 1971a,b; Stewart et al., 1973a) even though the subjects in all these other studies attained higher levels of carboxyhaemoglobin. Some of the discrepancies may be explained on the basis of differences in protocol and in the environmental conditions under which the tests were conducted. Some of the investigators designed their experiments to minimize the factors of boredom and fatigue while others attempted to minimize external influences and conducted their experiments for a relatively long time.

However, the Beard & Wertheim study may actually be more relevant to questions of vigilance and ideally should be discussed in this context. Assessment of vigilance is the determination of an individual's ability to detect small changes in his environment, changes that take place at unpredictable times and so demand continuous attention. In such monotonous tasks, subjects miss signals that they would not have missed when starting the task. Such signals are presented visually or aurally. Fodor

& Winneke (1972) and Groll-Knapp et al. (1972) used auditory signals for their vigilance task. The former investigators used a white noise (frequency range from 20 to 20 000 Hz lasting 0.36 sec and repeated at 2-sec intervals. About 3 out of every 100 of these noises were slightly less intense and were used as the signal to which the subjects responded by pressing a button. Twelve nonsmokers (male and female) were tested at carbon monoxide concentrations of 0 and 57 mg/m^3 (0–50 ppm). They breathed this concentration for 80 min prior to the first of three vigilance tests. Carboxyhaemoglobin levels were estimated to be 2.3 and 3.1% at the beginning and the end of the first vigilance test, respectively. Subjects were likely to miss signals during this initial test. This was not observed during the next two vigilance tests (total exposure to carbon monoxide being 210 min with the carboxyhaemoglobin level estimated to have finally reached 4.3%). These data suggest an initial decrement in performance followed by a compensatory response. Groll-Knapp et al. (1972) exposed 20 subjects for a 2-h period to carbon monoxide concentrations of 0, 57, 115, or 172 mg/m^3 (0, 50, 100, 150 ppm). There is some doubt as to which subjects, if any, were smokers. Carboxyhaemoglobin levels were also estimated by these investigators at the end of the test period to be 0, 3.0, 5.4, and 7.6%. Over the 90 min of the auditory test, some 200 paired tones were given in which a weaker second tone was the signal. The mean number of signals missed during the control test was 26. The number missed increased in the presence of elevated carboxyhaemoglobin levels so that 35, 40, and 44 misses occurred in environments containing carbon monoxide levels of 57, 114, and 172 mg/m^3, respectively. This suggests a significant impairment when a concentration of 57 mg/m^3 is inhaled. Winneke (1974) used a similar test in studies at carbon monoxide concentrations of 0, 57, and 115 mg/m^3. Results with all levels of carbon monoxide exposure were negative, in marked contrast to the previous data, despite an estimated carboxyhaemoglobin level of approximately 9% at the end of the 115 mg/m^3 exposure.

Beard & Grandstaff (1975) examined the effect of carbon monoxide exposure on a visual vigilance task. The signal was a shorter flash of light than the non-signals. Following a 30-min control period, 9 subjects were exposed to carbon monoxide concentrations of 0, 57, 200, or 286 mg/m^3 (0, 50, 175, 250 ppm). Subjects exposed to room air detected 73% of the signals presented to them in three vigils. In environments containing carbon monoxide concentrations of 57 and 200 mg/m^3, respectively, 64% of the signals were detected. These differences were statistically significant at the 5% level. However, exposure to a concentration of 286 mg/m^3 yielded a correct identification rate of about 70% that was not statistically significant. They estimated blood carboxyhaemoglobin levels from alveolar breath samples to be 1.8, 5.2, and 7.5%, respectively. The alveolar samples were

obtained 30 min after the exposures were completed. Krotova & Muzyka (1974) studied subjects working for about 2 years in an environment containing carbon monoxide. Mean carboxyhaemoglobin levels were approximately 3.2% before, and 4% after work. Eleven of 56 workers reported a loss of vigilance. It has been reported by Rummo & Sarlanis (1974) that, during a 2-h vigilance driving simulator task, subjects with carboxyhaemoglobin levels of 6–8% were significantly slower in responding to lead car speed changes. Horvath et al. (1971) also used a visual vigilance test and were the only group of investigators that actually measured blood levels of carboxyhaemoglobin. The vigilance task in these studies was the detection of a light pulse that was slightly brighter than the base level light pulse. A 1-h vigil was preceded by a short alerting pre-test during which a randomly interspersed 10 of 60 light pulses were the brighter signals. After a 1-min rest, the 60-min vigilance task was begun. Only 40 of 1200 light pulses were signals. Ten of these signals appeared randomly out of the 300 presented each 15 min. Three levels of ambient carbon monoxide were used, 0, 30, and 127 mg/m^3 (0, 26, and 111 ppm) with each subject serving as his own control. Exposures were randomized, with 1 week elapsing between each exposure. Fig. 6 illustrates the changes in blood levels of carboxyhaemoglobin with time under all conditions and compares the concentrations with the levels determined from the data obtained by Forbes et al. (1945). The control group breathing filtered air (no carbon monoxide present) had carboxyhaemoglobin levels of 0.9% before and at the completion of the task. Exposure to a carbon monoxide concentration of 30 mg/m^3 led to a level of 1.6% after the first hour (before the vigilance task) and 2.3% at the end. Carbon monoxide exposure at 127 mg/m^3 resulted in carboxyhaemoglobin levels of 4.2% after the first hour and 6.6% at completion of the vigilance test. Performance during the pre-test period gave approximately 88 correct responses in all three conditions, carbon monoxide exposure having no discernible effect. During the vigilance test itself, subjects breathing a concentration of 127 mg/m^3 made significantly fewer correct responses (4.2–6.6% carboxyhaemoglobin) than the same subjects breathing 0 or 27 mg/m^3 (Fig. 7). It appeared that when the carboxyhaemoglobin level was approximately 5%, a significant decrement in performance occurred. It should be noted that the slight improvement at the end of the test period probably represented the usual alerting response observed whenever subjects estimate that the task is completed. Recently, Winneke et al. (1976) attempted to replicate this study without success. Although Horvath's experiments were started with 15 alleged nonsmokers, pre-exposure blood samples from 5 of the subjects showed carboxyhaemoglobin levels of almost 3%. At the completion of all the exposures, these subjects admitted smoking, thus confirming the blood levels. Data on these

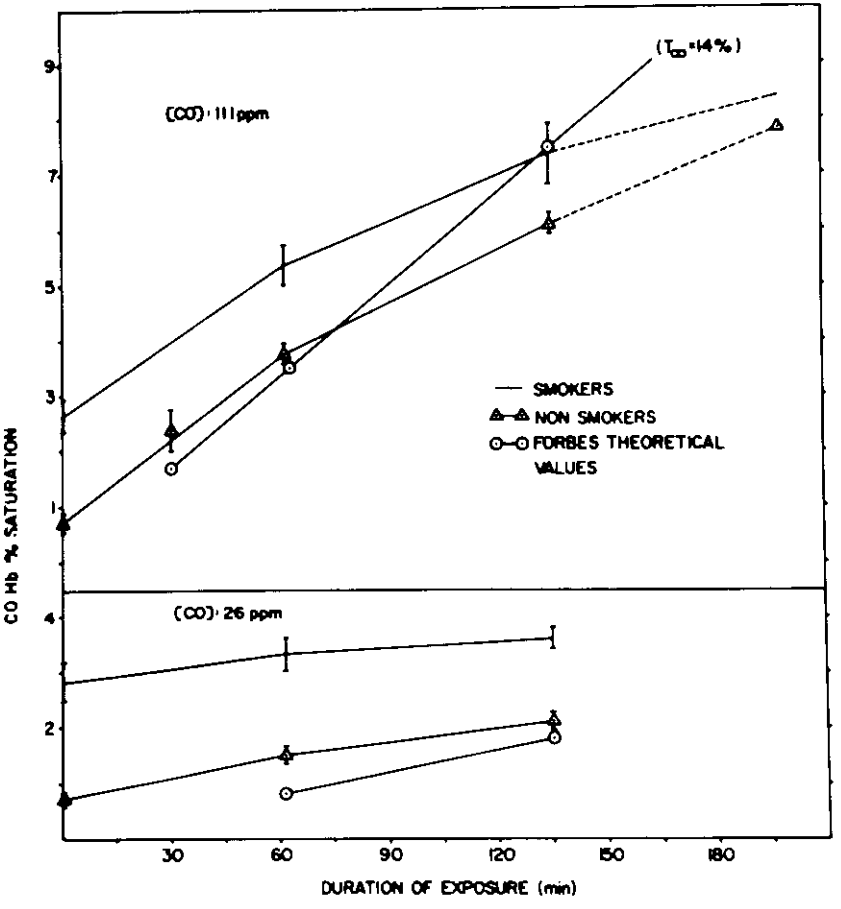

Fig. 6. Percentage of carboxyhaemoglobin in the blood of smokers and nonsmokers (standard error of both indicated) while breathing carbon monoxide at levels of 30 and 127 mg/m^3 (26 and 111 ppm) (reference curve is from Forbes et al., 1945).

subjects were not included in this analysis. When these smokers' data were analysed, performance on the vigilance task showed no deterioration even though, with exposure to a carbon monoxide concentration of 127 mg/m^3, carboxyhaemoglobin levels increased from an initial 2.8% to 5.1% after the first hour and to 6.9% at the completion of the vigilance task (O'Hanlon, 1975). There were too few subjects to permit more than a suggestion that prior, continuous exposure to nonambient carbon monoxide may result in some degree of questionable adaptation. Beard & Wertheim's (1967) earlier indications that some deleterious psychological effects would appear at

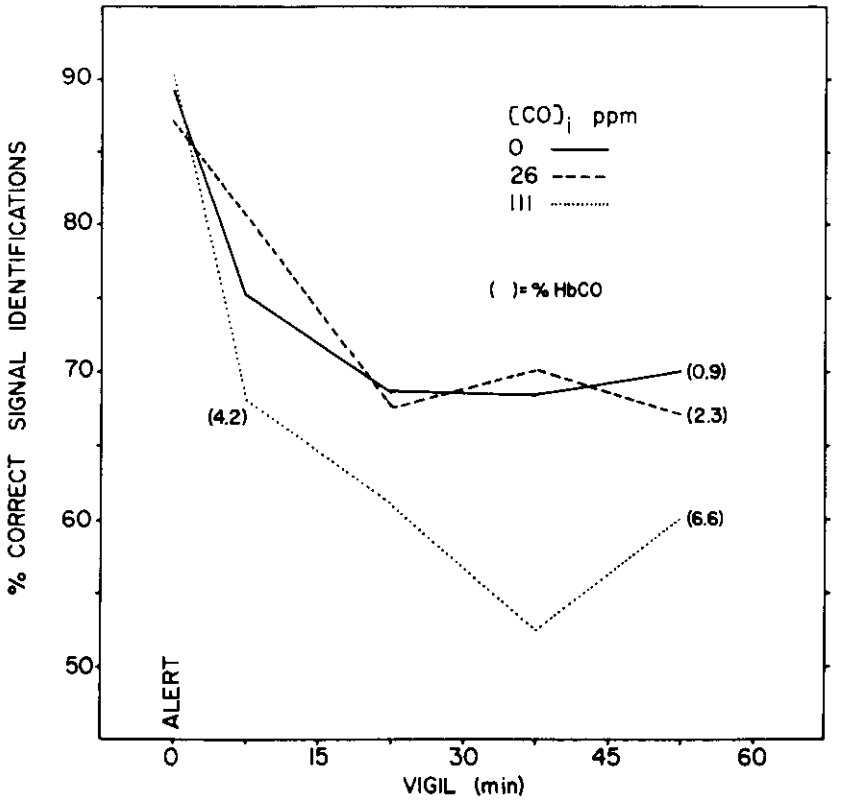

Fig. 7. Percentage of correct signal identifications for the nonsmokers in the alerted test and as a function of time in the vigil for each of the three levels of inspired carbon monoxide 0 [solid line], 30 [dashed line], and 127 [dotted line] mg/m³ (0, 26, and 111 ppm) (From: Horvath et al., 1971).

carboxyhaemoglobin levels of about 2% have not been confirmed or even replicated.

The design and experimental control in the major studies concerned with this subject have been poor with errors of omission, and failure to present finalized data. In the early studies of Forbes et al. (1937), 5 subjects were exposed to a carbon monoxide concentration sufficient to raise carboxyhaemoglobin to a level as high as 30% and their reaction times, coordination, and perceptual skill determined within the context of a test of driving skill. They failed to present adequate control data and did not consider the adaptation that occurs following repetitive tests. McFarland (1973) also studied subjects with relatively high carboxyhaemoglobin levels (17%) in actual driving conditions. The exact effects on driving skills could not be determined from the data presented. Studies by Ray & Rockwell (1970) and

Weir & Rockwell (1973) although first reported in 1970, are still in a preliminary form and despite some interesting indications of effects, the data cannot be really considered of value in determining effects. A "standard driving simulator" was used by Wright et al. (1973) with both smokers and nonsmokers as subjects (final carboxyhaemoglobin levels were 5.6 and 7.0% respectively). They suggested that a 3.4% increase in carboxyhaemoglobin was sufficient to cause unsafe driving. While questions regarding the data raise doubts as to the value of this interpretation, these conclusions should be noted in view of the data reported in the vigilance studies. However, a certain amount of caution must be applied to any extrapolation of specific, behavioural changes and driving performance, since the latter requires integration of many signals in a complex interaction not measured in any of the simpler tasks used in most behavioural testing.

The available information on reaction times and time discrimination is presented in considerable detail in a report from the National Research Council (NAS/NRC, 1977). Despite apparently well-controlled studies on both of these variables, the negative and positive effects reported make it impossible to form any valid conclusions[a]. It would appear that considerable additional effort, using a larger number of subjects, more adequate control of experimental conditions (especially control of boredom and fatigue), direct determinations of carboxyhaemoglobin, and attention to the potential effects of low levels of carboxyhaemoglobin are required before any valid conclusions can be drawn.

Apparently, coordination, dexterity, steadiness, and tracking ability were not influenced by a carbon monoxide concentration which raised carboxyhaemoglobin to levels exceeding 20%. McFarland et al. (1944) and Halperin et al. (1959) reported that carboxyhaemoglobin levels of 4–5% resulted in impaired brightness discrimination. Their findings have been confirmed by Beard & Wertheim (1967). However, Ramsey (1973) was unable to reproduce these deleterious effects on brightness discrimination. The effects of carbon monoxide exposure on complex learned behaviour have been studied by a number of investigators. Exposure of firemen to a concentration of 115 mg/m^3 (100 ppm) for various periods of time (Schulte, 1963) resulted in considerable changes in the performance of a series of complex tasks. In a test where subjects were required to underline all plural nouns in prose passages, decreased performance was noted when the carboxyhaemoglobin level was approximately 8%. The mean time to complete an

[a] The studies by Beard & Wertheim (1967) suggesting a critical carboxyhaemoglobin level of approximately 2% were evaluated under vigilance and are not repeated here. Attempts by other investigators (O'Donnell et al., 1971b; Stewart et al., 1975) to reproduce their results have not been successful.

arithmetic test significantly increased at similar or slightly lower carboxyhaemoglobin levels. This investigator may have underestimated the carboxyhaemoglobin levels since the subjects, although mostly smokers, had initial values close to zero. O'Donnell et al. (1971a) studied the ability of 4 subjects to perform arithmetic problems without pencil and paper. While the subjects required a longer time to complete the answers (89.8 versus 98.6 sec) when carboxyhaemoglobin levels were 5.9% and 12.7%, respectively, some questions as to the experimental design of these studies and the limited number of subjects used preclude full acceptance of the results. A deterioration in the ability to learn meaningless syllables was found by Bender et al. (1972), when the carboxyhaemoglobin levels were about 7%. Other tests failed to show deterioration at these levels of carboxyhaemoglobin.

O'Donnell et al. (1971a) sought to determine how overnight exposure to carbon monoxide concentrations of 86.0 mg/m^3 and 172 mg/m^3 (75 and 150 ppm) (carboxyhaemoglobin levels up to 12.7%) affected sleep and found small but unreliable changes that they interpreted as a possible reduction in central nervous activation. A significant reduction in REM (rapid eye movement) sleep in subjects of botb sexes exposed for 7 h to a carbon monoxide concentration of 115 mg/m^3 (100 ppm) was reported by Groll-Knapp et al. (1976).

Earlier, Helmchen & Künkel (1964) reported changes in the rhythmic after-potential fluctuations following photic excitation of the brain during and following carbon monoxide exposure. However, in contrast, Dinman (1969) analysed the photic responses in subjects with carboxyhaemoglobin levels of 22% and 37% and did not find any changes in latency or voltage following photic stimulation. Šul'ga (1962) did not find any disturbances of the alpha rbythm in 2 subjects exposed to a carbon monoxide concentration of 20 mg/m^3 (17.4 ppm) for 15 min. Carbon monoxide-induced visual invoked responses were reported by Hosko (1970) and Stewart et al. (1973a) but only at carboxyhaemoglobin levels of 20–28%. Stewart et al. (1973b) later reported that neither the spontaneous nor the evoked electrical activity of the brain exhibited significant changes attributable to carbon monoxide exposure (carboxyhaemoglobin levels from 3.2% to 15.2%). Slow-wave brain potentials (correlated to anticipatory responses) were measured by Groll-Knapp et al. (1972) who noted a diminution in the height reached by the anticipation wave and the extent of the drop seen after response stimulus following exposure to a carbon monoxide concentration of 172 mg/m^3 (150 ppm). It appears that another cortical function test, critical flicker fusion frequency (CFFF) is not influenced even by carboxyhaemoglobin levels of between 10% and 12.7% (Guest et al., 1970; O'Donnell et al., 1971a; Ramsey, 1973; Winneke, 1974).

Guest et al. (1970) also used an auditory analogue of CFFF, the auditory flutter fusion threshold. This threshold was not affected by a carboxyhaemoglobin level of 10%. The literature has been reviewed by Grandstaff et al. (1975).

8.1.2 Work performance and exercise

Maximum exercise can increase the oxygen uptake of the whole body by 20 or more times the resting uptake; at this level the oxygen transport system will be maximally stressed. Indeed, Mitchell et al. (1958) have suggested that the maximum sustained energy output is determined by the capability of the cardiovascular system to transport oxygen to the exercising muscle. Assuming this concept to be true, any impairment of oxygen transport, such as can occur when carboxyhaemoglobin is present could limit maximum aerobic capacity ($\dot{V}_{O_2}$ max). In fact, it has been appreciated for some time that individuals, having a large burden of carbon monoxide experience difficulty in performing physical work. Subjects studied by Chiodi et al. (1941) were unable to perform tasks requiring only low levels of physical exertion when their blood levels of carboxyhaemoglobin reached 40–50%. Several collapsed while attempting to perform routine laboratory exercise tests. Roughton & Darling (1944) also suggested, on theoretical grounds, that work capacity would be reduced to zero when carboxyhaemoglobin levels approached 50%. An impaired performance by competitive swimmers was associated with exposure to a carbon monoxide level of 34 mg/m^3 (30 ppm) originating from traffic (MacMillan, 1969)[a]. Douze (1971) presented information on the incidence of carbon monoxide poisoning due to the use of natural gas heaters in Utrecht.

There appears to be complete agreement that performance of light to moderate work (up to 70% $\dot{V}_{O_2}$ max)[b] for a short period of time is not significantly influenced by carboxyhaemoglobin levels as high as 33%. All the submaximal exercise tests were of short duration (5–60 min). Oxygen uptake during work was unchanged despite the presence of carboxyhaemoglobin (Chevalier et al., 1966; Ekblom & Huot, 1972; Gliner et al., 1975;

[a] Quoted by the US National Research Council, Division of Medical Sciences, Committee on Effects of Atmospheric Contaminants on Human Health and Welfare, 1969, p. 55.

[b] This figure may be in error for all levels of carboxyhaemoglobin above 5% since $\dot{V}_{O_2}$ max decreases with increasing level of carboxyhaemoglobin and the initial percentages of $\dot{V}_{O_2}$ max were apparently determined on the basis of a $\dot{V}_{O_2}$ max measured at 0.5% carboxyhaemoglobin for the fixed work loads used in the studies. Thus, the highest percentage of $\dot{V}_{O_2}$ max reported (70%) may have been as high as 91% and would represent hard work. $\dot{V}_{O_2}$ max is identical to the maximum aerobic capacity representing the capability of the organism to take up oxygen.

Mitchell et al., 1958; Nielsen, 1971; Pirnay et al., 1971; Vogel & Gleser, 1972; Vogel et al., 1972). The only clear indication of physiological load appeared to be a slight increase in heart rate. Chevalier and associates (1963, 1966) studying men carrying out light work for a period of 5 min, reported that while the oxygen uptake was unaffected when the carboxyhaemoglobin level was approximately 4% (estimated value), there was a significant increase in oxygen debt when this was related to the total increased oxygen uptake. Five subjects studied by Pirnay et al. (1971) performing work for 15 min had an oxygen uptake of 1.5 litre per min. No changes in oxygen uptake were found even though the carboxyhaemoglobin level reached 15%. In a rather involved study, where carboxyhaemoglobin levels fluctuated between 5% and 17%, Klausen et al. (1968) did not find any differences in energy expenditure in relation to exposure when subjects exercised for 15 min at 50% of their $\dot{V}_{O_2}$ max. It is rather interesting that, despite the considerable variations in such experimental conditions as the duration and magnitude of exercise, the level of carboxyhaemoglobin and the method of administration of carbon monoxide, and also the small numbers and limited age ranges of the exposed subjects—the results from all these studies were essentially similar. Pirnay et al. (1971), Vogel & Gleser (1972), and Vogel et al. (1972) reported consistently higher heart rates for given selected submaximal work loads and increased ventilatory volume exchange per unit of oxygen uptake.

Since populations may be exposed to polluted environments for long periods, Gliner et al. (1975) studied the responses of 2 groups of 10 and 9 men, respectively (mean age 23.0 and 48.4 years) each of which included 5 subjects who smoked. A work load of 35% $\dot{V}_{O_2}$ max was selected (untrained men can work at this level for approximately 8 h with minimum physiological changes), and the men walked for 4 h in an environment containing a carbon monoxide concentration of 57 mg/m^3 (50 ppm). Final carboxyhaemoglobin levels were 5.3 and 6.1% for nonsmokers and smokers, respectively. An additional study was conducted on 4 men exposed to a carbon monoxide concentration of 115 mg/m^3 (100 ppm). Final carboxyhaemoglobin levels for nonsmokers and smokers were 10.3 and 13.2%, respectively. Ambient temperatures were 25° C and 35° C, with a relative humidity of 30%. Cardiovascular and respiratory variables were measured. The only significant change was a higher heart rate in the carbon monoxide environment, irrespective of age of subject (Fig. 8), confirming observations, previously reported. Cardiac index remained constant at approximately 6 litres/min × m^2 in both filtered air and in carbon monoxide concentrations of 57–115 mg/m^3 (50–100 ppm). The full significance of this change in long-term performance in carbon monoxide polluted environments is not apparent, at present.

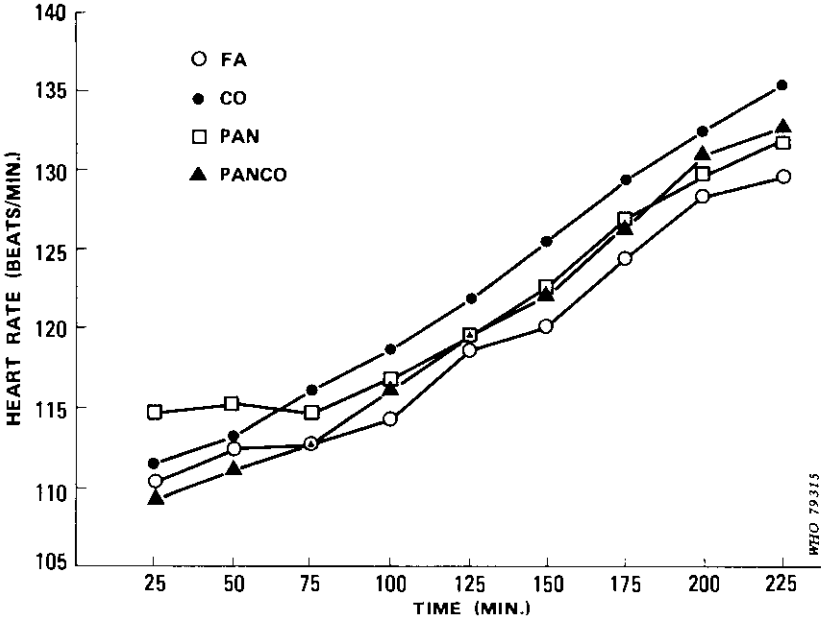

Fig. 8. The mean heart rate of all subjects under different conditions of ambient temperature and pollutant exposure. Filtered air (FA) conditions (○), carbon monoxide conditions (●), peroxyacetylnitrate (PAN) conditions (□), and PAN-CO conditions (▲) averaged across ambient temperature, age, and smoking habits (From: Gliner et al., 1975) (Section 8.1.7).

The oxygen transport capacity of blood is reduced in the presence of carboxyhaemoglobin. In short-term maximum exercise of several minutes duration, where capacity for effort depends mainly on aerobic metabolism, maximum aerobic capacity would be expected to diminish approximately in proportion to the level of carboxyhaemoglobin present in the blood. Such a diminution in $\dot{V}_{O_2}$ max, when the carboxyhaemoglobin level is between 7% and 33% has been observed by a number of investigators (Chiodi et al., 1941; Ekblom & Huot, 1972; Horvath et al., 1975; Nielsen, 1971; Pirnay et al. 1971). In most of these studies, bouts of exercise ranged from 2–6 min and the mode of administration of carbon monoxide involved either breathing relatively high concentrations of the gas or the administration of a bolus with additional carbon monoxide to maintain the desired levels of carboxyhaemoglobin. In some of these studies, the smoking habits of the subjects were not identified.

In all of these studies, the levels of carboxyhaemoglobin were considerably in excess of those anticipated to occur in men exposed to the concentrations of carbon monoxide designated as limiting levels by various governing bodies or even reported to occur in the outdoor air of certain metropolitan areas. The initial studies by Horvath's group (Drinkwater et

al., 1974; Raven et al., 1974a,b) were made on subjects breathing a carbon monoxide concentration of 57 mg/m^3 (50 ppm) at one of 2 thermal environments, i.e., 25° C or 35° C with a relative humidity of 20%. A walking test requiring some 15–24 min to complete was carried out on a treadmill with progressively increasing grade, in order to measure $\dot{V}_{O_2}$ max. The 2 populations consisted of 20 young (24+ years) and 16 middle-aged (48+ years) subjects with equal numbers of smokers and nonsmokers in the young group and 7 smokers and 9 nonsmokers in the older group. The middle-aged subjects demonstrated the anticipated decrease in $\dot{V}_{O_2}$ max associated with advancing age. However, the middle-aged nonsmokers had a $\dot{V}_{O_2}$ max that was about 27% greater than that of smokers of the same age. As the test progressed, the carboxyhaemoglobin levels of nonsmokers increased from 0.7% to approximately 2.8%, while those of smokers rose from 2.6–3.2% to 4.1–4.5%. During control studies conducted on these subjects while breathing filtered air, carboxyhaemoglobin levels decreased in both smokers and nonsmokers. The results of these studies (Drinkwater et al., 1974; Gliner et al., 1975; Raven et al., 1974a,b) failed to demonstrate any reduction in $\dot{V}_{O_2}$ max. The decrement in $\dot{V}_{O_2}$ max that occurred as a consequence of working in a hot environment was greater than the changes observed while breathing carbon monoxide. Other cardiovascular, respiratory, metabolic, and temperature measurements made concurrently with the oxygen uptake studies also failed to show any decrements associated with carbon monoxide exposure. However, a decrease in absolute exercise time consistently observed in nonsmoking subjects but not in smokers was significantly related to carbon monoxide exposure. These observations confirmed those found earlier by Ekblom & Huot (1972), although they reported a surprisingly large (38%) decrease in work time at a carboxyhaemoglobin level of 7%. Aronow & Cassidy (1975) have recently reported a slight decrease in work time during a maximum exercise test on 10 middle-aged (50.7 years) subjects. The only ischaemic S-T segment depression occurred in one female subject. No electrocardiographic changes were observed in the subjects studied by Horvath's group. Nielsen (1971) found that exercising subjects developed higher internal body temperatures in the presence of carbon monoxide than in its absence. Reductions in skin conductance suggested a redistribution of the circulation to the working muscle and away from the skin.

Horvath and co-workers had some doubts about the changes in carboxyhaemoglobin levels in smokers and nonsmokers as well as the lack of change in $\dot{V}_{O_2}$ max under the ambient and exercise conditions employed. For their next series of studies (Dahms et al., 1975), they developed a more precise method to regulate relatively low levels of carboxyhaemoglobin (Fig. 9). It should be noted that a low ambient level of carbon monoxide will reduce the

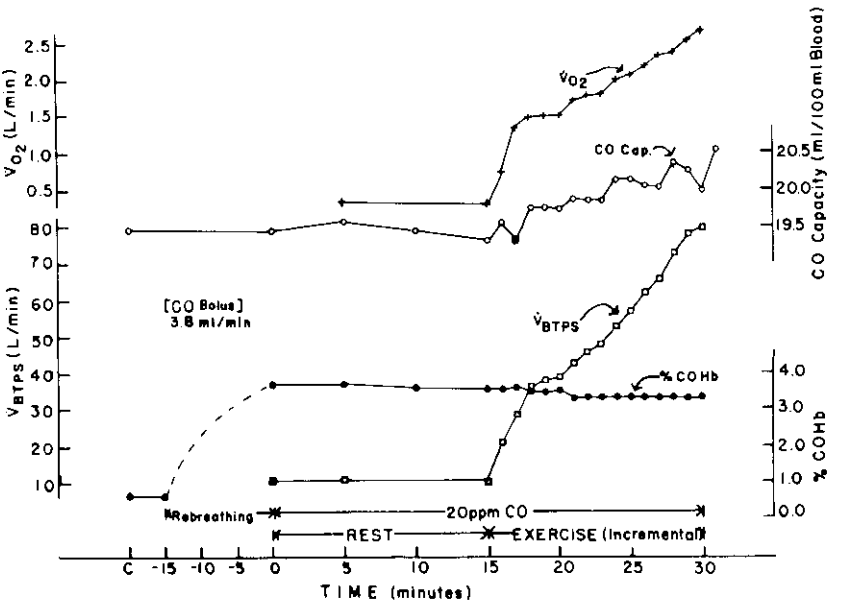

Fig. 9. The maintenance of defined carboxyhaemoglobin level in a subject during rest and at various work levels with a widely ranging ventilatory exchange. Control level of carboxyhaemoglobin was 0.6% prior to the administration of the initial bolus of carbon monoxide to raise carboxyhaemoglobin to desired level (From: Dahms et al., 1975).

rate of pulmonary excretion of carbon monoxide particularly if the carboxyhaemoglobin level is low. In these experiments, a double-blind study was again used in which subjects breathed either filtered air or air containing carbon monoxide which resulted in stable levels of carboxyhaemoglobin. The data suggest that a critical level of carboxyhaemoglobin must be present before significant physiological alterations can be demonstrated. Statistically significant decreases in $\dot{V}_{O_2}$ max were noted when carboxyhaemoglobin levels exceeded 4.3%. Although this was a double-blind, randomized study in which neither the investigators nor the subjects knew the composition of the air breathed, it was subsequently determined that all subjects correctly identified the experiment in which they had been exposed to the highest level of ambient carbon monoxide. In all instances, they noted a heaviness in the lower extremities and greater difficulty in performing the task.

Data obtained by Horvath's group and others are summarized in Fig. 10. There is a linear decline in $\dot{V}_{O_2}$ max when carboxyhaemoglobin levels range from 4 to 33%. This can be expressed as: % decrease in $\dot{V}_{O_2}$ max = 0.91 (% HbCO) + 2.2. It should be noted that this does not apply to smokers in

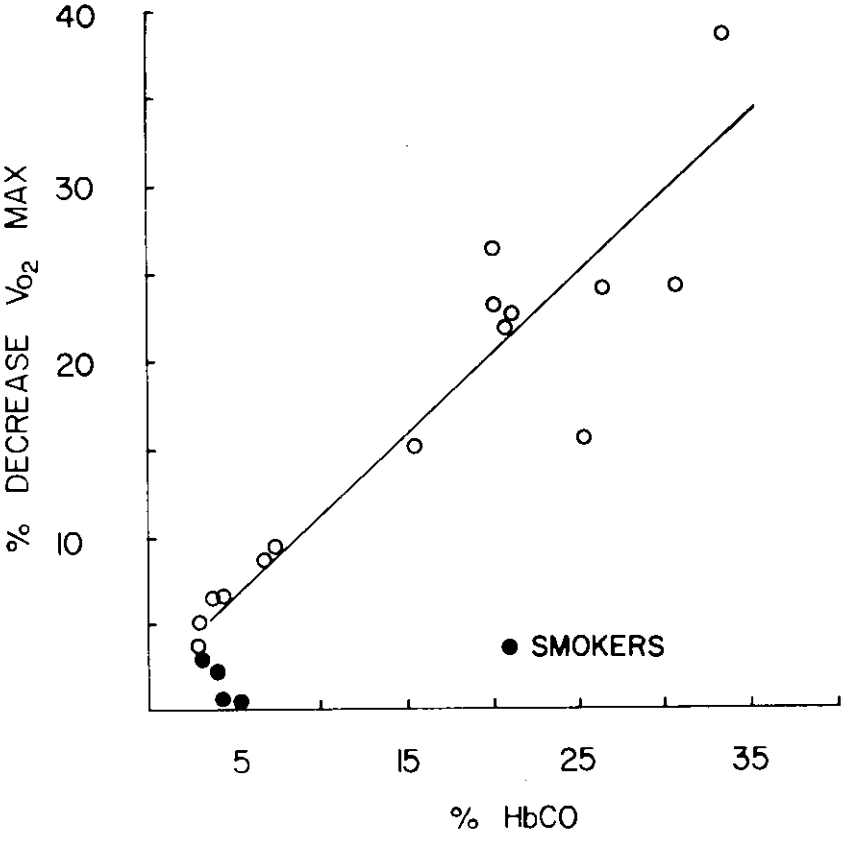

Fig. 10. Relationship between carboxyhaemoglobin and decrease in maximum aerobic capacity.

Horvath's series, who frequently had carboxyhaemoglobin levels considerably in excess of 4–5% with no decrement in their respective $\dot{V}_{O_2}$ max values.

According to data available at present, carbon monoxide can modify physiological responses. The level of blood carboxyhaemoglobin required to induce these effects appears to be approximately 5%. The carboxyhaemoglobin concentration is probably a more accurate assessment of exposure than a statement of the exposure conditions, ambient carbon monoxide concentrations, time, etc. Therefore, physiological effects should be related to a carboxyhaemoglobin level even though in some circumstances the method of exposure, i.e. rapid loading versus slow loading may produce effects not evident from the carboxyhaemoglobin concentration.

8.1.3 Adaptation

The implication that, in the presence of a clinical state of chronic carbon monoxide poisoning, adaptation to carbon monoxide occurs has not been verified. It would appear that such a state could have been identified by studies on long-term heavy smokers or individuals exposed to environmental sources of carbon monoxide. Early concern with carbon monoxide intoxication in England and Scandinavia resulted in studies suggesting the possibility of such a condition (Grut, 1949; Killick, 1940). However, doubts regarding the use of high levels of inspired carbon monoxide (several hundred parts per million) and inadequate experimental methods give rise to some scepticism about the conclusions presented. Killick (1940), using herself as a subject, reported that she developed acclimatization in the form of diminished symptoms, slower heart rate, and the attainment of a lower carboxyhaemoglobin equilibrium level following exposure to a given inspired concentration of carbon monoxide. A similar finding concerning the attainment of a different carboxyhaemoglobin equilibrium following exposure to a fixed level of carbon monoxide in the ambient air had been reported earlier by Haldane & Priestley (1935). Additional information on other possible adaptation effects in the pre-1940 literature can be found in Killick's review.

The changes indicated above, which have been reported as evidence of adaptation, are probably related to compensatory haematological changes. Some polycythaemia occurs as a response to chronic or repeated exposure corresponding roughly to the ambient levels of carbon monoxide. Brieger (1944) reported an increase in red cell mass following exposure to 115 mg/m^3 (100 ppm) and industrial workers exposed to rather ill-defined levels of carbon monoxide have been reported to be polycythaemic (Jenkins, 1932). Wilks et al. (1959) believed that acclimatization was purely a function of increased red cell mass.

The possibility that adaptation to carbon monoxide following extensive exposure (as occurs in the case of adaptation to high altitudes) could alter the position of the oxygen dissociation curve appears to have been answered. Mulhausen et al. (1968) did not find any change in the degree of left shift in the blood of individuals exposed to carbon monoxide for a period of 8 days. Unfortunately, the average carboxyhaemoglobin level of 13% was based on considerable individual variations in carboxyhaemoglobin levels and periodic exposure to relatively high concentrations of inhaled carbon monoxide. Several investigators have sought evidence of a potential shift of the curve back to the right. Red cell levels of 2,3-diphosphoglycerate compounds are higher in individuals with anaemia and also during residence at high altitudes (2,3-diphosphoglycerate is a phosphorylated by-

product of glycolysis). In the erythrocytes of man and most other mammals, the molar concentration of this compound is roughly equal to that of haemoglobin. Both it and some other organic phosphates are bound rather strongly to deoxyhaemoglobin but have little affinity for oxyhaemoglobin. Increases in 2,3-diphosphoglycerate shift the effective oxygen affinity, i.e., there is a shift of the oxyhaemoglobin dissociation to the right. Astrup (1970) found a small decrease in erythrocyte 2,3-diphosphoglycerate in human subjects with carboxyhaemoglobin levels maintained at 2 % for 24 h. Conversely, Dinman et al. (1970) found a small increase in 2,3-diphosphoglycerate in human subjects after 3 h at an approximate carboxyhaemoglobin level of 20% and in rats exposed to higher but variable concentrations of carbon monoxide. A shift in the dissociation curve does not appear to be an important adaptation mechanism when carbon monoxide exposure lasts less than a few days.

8.1.4 Effects on the cardiovascular system and other effects

Functional heart disturbances (lability of blood pressure and heart acceleration, extrasystoles, exacerbations of angina pectoris), as well as temporary heart dilatation and cardiac asthma have been reported in cases of acute carbon monoxide poisoning (Lazarev, 1965). According to the same author, various changes were also seen in the peripheral vascular system (vasodilation, stasis, vasopermeability etc.). Lazarev (1965) also noted severe cardiovascular disturbances such as heart acceleration, extrasystoles, pulse and blood pressure lability (more often hypotension than hypertension) in groups of workers exposed to carbon monoxide for long periods. Disturbances of atrioventricular and interventricular conductance were observed after 1 to 1.5 years of exposure and even after cessation of contact with carbon monoxide.

The first evidence of left ventricular abnormality was presented by Corya et al. (1976) in 5 cases of nonfatal poisoning (carboxyhaemoglobin level of 20%). Abnormal left ventricular wall motion was shown by echocardiograph in 3 of the 5 cases. A similar number showed mitral valve prolapse. A ballistocardiogram was used by Gorski (1962) to demonstrate hypoxaemia of the myocardium in similar cases. Byczkowska & Milan (1971) described functional kidney disturbances in a patient poisoned with carbon monoxide. Clinical and physiological haemodynamic studies on 2 groups (individuals in constant contact with carbon monoxide and individuals having no evidence of chronic carbon monoxide intoxication) were conducted by Zenkevič (1973). He noted considerable cardiovascular abnormalities in the carbon monoxide-exposed group. A study on cast-iron workers by Ejam-Berdjev (1973) also suggested a larger frequency of cardiovascular, as well

as central nervous system disturbances in these workers, related to their increased blood levels of carboxyhaemoglobin.

Evidence of a myocardosis was found in 18% of Japanese farmers chronically exposed to a mean carbon monoxide concentration of 80 mg/m^3 (70 ppm), (Komatsu, 1959). The exposure occurred as a result of spending the winter months preparing hemp in enclosed dwellings heated by charcoal fires. Following exposure, the farmers exhibited symptoms of dizziness, palpitation, and congestive heart failure. The diagnosis of a myocardosis was supported by clinical evidence of congestive heart failure and ECG changes such as prolonged QT interval, ST segment depression, and T-wave flattening.

Aleksieva & Dimitrova (1971) studied a large group of workers exposed to a carbon monoxide concentration of 60 mg/m^3 (52 ppm) and reported changes in peripheral vessels suggesting impaired vascular tone.

An additional hazard to patients, especially those undergoing cardiovascular surgery, may develop during anaesthesia. Markedly elevated carboxyhaemoglobin levels have been reported in patients under cardiac bypass surgery (Middleton et al., 1965). This increase could be related in part to the carbon monoxide present in transfused blood and to the closed-circuit method of anaesthesia that precludes the loss of endogenously produced carbon monoxide. This is also important for infants undergoing transfusions (see sections 5.4 and 8.2.3).

8.1.5 Carboxyhaemoglobin levels resulting from exposure to methane-derived halogenated hydrocarbons

The belated discovery that at least one chemical substance used in industry and commerce is "degraded" within the body to carbon monoxide has potentially significant epidemiological and clinical implications. Methane-derived halogenated hydrocarbons have been widely used as organic solvents, replacing carbon tetrachloride. A chance observation (Stewart et al., 1972b) indicated that the inhalation of dichloromethane (methylene chloride, CH_2Cl_2) was followed by a sustained elevation in carboxyhaemoglobin concentrations. Inhalation of methylene chloride at a concentration of 1740–3480 mg/m^3 (500–1000 ppm) (industrial TLVs for USA and USSR = 1740 mg/m^3 (500 ppm) and 50 mg/m^3 (14 ppm), respectively) for 1–2 h resulted in carboxyhaemoglobin levels of more than 14% (Stewart et al., 1972a). This elevation in carboxyhaemoglobin levels continued beyond the time of exposure and gradually returned to normal during the next 24 h. Nunes & Schoenborn (1973) demonstrated that the binding affinity of carbon monoxide for haemoglobin increased in the presence of methylene chloride. A number of studies have confirmed that

methylene chloride was metabolized to carbon monoxide (Divicenzo & Hamilton, 1975; Kubic et al., 1974; Ratney et al., 1974; Roth et al., 1975). Roth et al. (1975) noted that rabbits rarely succumbed to methylene chloride at a concentration of 40 g/m^3 (11 520 ppm) possibly because of saturation of the pathways of methylene chloride metabolism and the rate of carbon monoxide excretion. The mechanism by which methylene chloride is metabolized to carbon monoxide has still to be elucidated. *In vitro* studies (Ahmed et al., 1977; Hogan et al., 1976) suggest that the mixed function oxygenase system of microsomes is responsible for the metabolic conversion of methylene chloride to carbon monoxide.

Several investigators have studied the influence of methylene chloride on physiological functions. Astrand et al. (1975) examined the effects on work performance of exposure to concentrations of 870 and 1740 mg/m^3 for four, 30-min periods but did not find any impairment, apparently because carboxyhaemoglobin levels were low (4%). Central nervous system depression was observed in some subjects exposed to concentrations of 1740–3480 mg/m^3 (500–1000 ppm) (Stewart et al., 1972a).

In studies by Winneke (1974), the effects of exposure to ambient levels of carbon monoxide of up to 115 mg/m^3 (100 ppm) on vigilance and CFFF were less marked than those resulting from exposure to methylene chloride at 1044–2784 mg/m^3 (300–800 ppm).

According to Stewart & Hake (1976) a potentially more dangerous complication of exposure to methylene chloride is the sustained carboxyhaemoglobin level that results from the metabolic production of carbon monoxide from lipid stores of methylene chloride and continues for many hours following exposure. The potential hazard of chemical compounds that may be metabolized to carbon monoxide deserves further investigation.

8.1.6 Levels and effects of carboxyhaemoglobin resulting from smoking

It would be extremely presumptive in a review of the effects of ambient carbon monoxide to discuss all the possibilities arising from the incomplete combustion of tobacco and paper. Many of the products inhaled may produce subtle physiological and biochemical effects on the smoker. Individuals breathing either pre-inhaled materials or the smokers' exhaled products are affected to a much lesser degree than the smoker (Russell et al., 1973; Srch, 1967). It is suggested that those interested in the problems related to smoking tobacco, carcinogenesis, and cardiovascular and pulmonary disease, refer to the documents specifically concerned with these matters (Fletcher & Horn, 1970; Hammond, 1962; US Department of Health, Education and Welfare, 1973; WHO, 1975). Prospective and retrospective epidemiological studies have identified cigarette smoking as

one of the major factors in the development of coronary heart disease. The risk of developing coronary heart disease for pipe and cigar smokers is apparently much less than it is for cigarette smokers but more than for nonsmokers. Furthermore, experimental studies suggest that tobacco smoking may contribute to the development and aggravation of coronary heart disease through the action of several independent or complementary mechanisms, one of these being the formation of significant levels of carboxyhaemoglobin. The role of carboxyhaemoglobin in cancer development appears to be negligible and unproven. The possible interaction of carbon monoxide and other constituents of smoke that may occur in the lungs and other tissues and so induce pathological changes remains to be elucidated since the basic chemistry has not been adequately defined.

Kuller et al. (1975) in their epidemiological study in Baltimore, USA, stated that, if there is an association between carbon monoxide exposure and heart attacks, the significant exposures are probably related to micro-environmental factors and cigarette smoking rather than to community air pollution. They noted that relatively few heart attacks occurred while an individual was smoking a cigarette. In Los Angeles, USA (Cohen et al., 1969; Goldsmith & Landaw, 1968; Hexter & Goldsmith, 1971), the case fatality rate for hospitalized myocardial infarction (M.I.) patients was higher in areas with high ambient levels of carbon monoxide (9–16 mg/m^3 or 8–14 ppm) and was positively correlated with ambient carbon monoxide levels. However, there was no association between ambient carbon monoxide levels and the admission rates per day. Wallace et al. (1974) concluded that "from the human health hazard point of view, restriction or elimination of cigarette smoke makes the most sense in terms of protecting the atherosclerotic population and preventing a possible future incidence of coronary heart disease due to chronic carbon monoxide exposure". It has also been suggested by Astrup (1972) that the risk of developing arterial diseases from intermittent exposure to carbon monoxide may be much higher for smokers than for nonsmokers. Wald et al. (1973) and Ball & Turner (1974) came to similar conclusions. In a study by Rissanen et al. (1972), cigarette smokers had more advanced atherosclerosis than nonsmokers. An extensive review and some experimental evidence for this viewpoint has been presented by Kjeldsen (1969).

Smoking cigarettes resulted in higher carboxyhaemoglobin levels than exposure to carbon monoxide levels present in street air (Castleden & Cole, 1975; Göthe et al., 1969). Manual workers had lower carboxyhaemoglobin levels than sedentary workers (both groups being tobacco smokers), probably because of the increased ventilation required by the occupations of the manual workers (Castleden & Cole, 1975; Sammons & Coleman, 1974). Unless extreme experimental conditions are considered (Russell et al.,

Table 7. Carbon monoxide (volume percent) in main stream smoke[a]

Cigarette		Cigar		
(nonfilter)	(filter)	A (85 mm)	B (85 mm)	C (95 mm)
4.6	4.5	5.3	11.1	7.1

[a] From: Hoffman & Wynder (1972).

1973; Srch, 1967), carbon monoxide produced by passive smoking does not seem to present a health risk (Hinds & First, 1975; Antweiler, 1975; Harke, 1975). Rylander (1974) also concluded that carbon monoxide exposure through passive smoking was negligible and that adverse effects upon health would not be expected. The quantity of carbon monoxide actually entering the lung depends upon the form in which the tobacco is smoked, the pattern of smoking, and depth of inhalation. Very little carbon monoxide is absorbed in the mouth and larynx (approximately 5%) so that most of the carbon monoxide available for transfer to haemoglobin must reach the alveoli in order to raise the level of carboxyhaemoglobin present in the blood stream. Cigarette smokers inhale to a greater extent than cigar smokers who, in turn, inhale more than pipe smokers, but there are quite marked individual differences in this pattern. Heavy cigarette smokers may have carboxyhaemoglobin levels as high as 15–17%. The carbon monoxide concentration in the mainstream smoke of cigarettes (Table 7) is approximately 4% (V/V) (Fletcher & Horn, 1970; Hoffman & Wynder, 1972; Wald & Howard, 1975). It has been estimated that the cigarette smoker may be exposed to a carbon monoxide concentration of 460–575 mg/m^3 (400–500 ppm) for the approximately 6 min needed to smoke a cigarette. Landaw (1973) noted that the half-time of carbon monoxide elimination in smokers was approximately 291 min. Fig. 11 illustrates the pattern of change in carboxyhaemoglobin in a typical heavy cigarette smoker (Horvath, personal communication). An indwelling venous catheter permitted the frequent sampling of this smoker's blood. The subject smoked only during his working hours. It should be noted that, by the time he began to smoke the next day, he still had a body burden of 1.7%. Cigarette smokers generally excrete carbon monoxide into the air rather than inhale it from the ambient environment.

Dalhamn et al. (1968) determined the retention of cigarette smoke components in the human lung. They found a 54% retention of carbon monoxide and an 86–97% retention of all other compounds. Carbon monoxide yields from cigarettes increased with puff volume and tobacco moisture decreased with increased paper porosity, but remained constant with puff duration (Robinson & Forbes, 1975). In studies by Haebisch

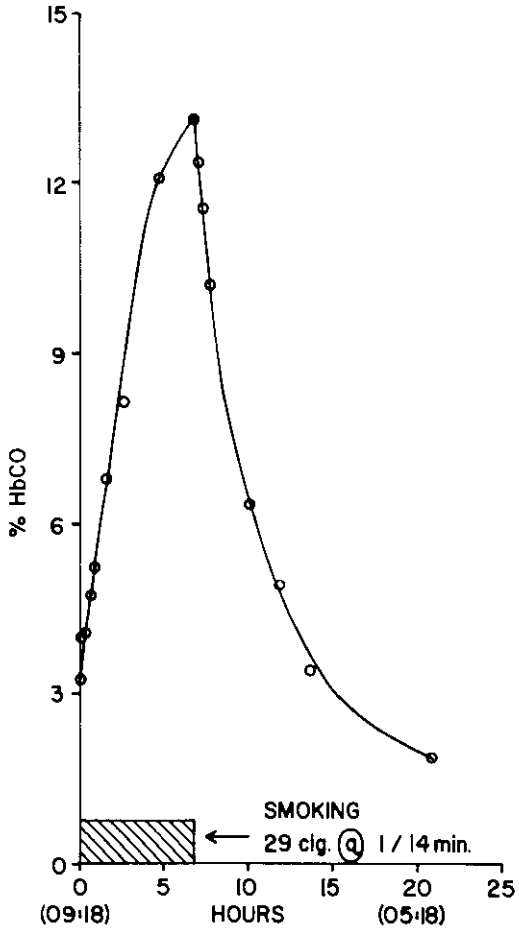

Fig. 11. Pattern of change in carboxyhaemoglobin in a typical cigarette smoker (From: Horvath, personal communication).

(1970), the carbon monoxide content of smoke increased as a greater portion of the cigarette was consumed. Although Cohen et al. (1971b) reported that different cigarette preparations did not result in significant variations in the smoker's levels of carboxyhaemoglobin. more recent studies (Gori, 1976; Turner et al., 1974) suggested that so-called "low toxicity" cigarettes produced significantly smaller amounts of carbon monoxide. However, the smoking pattern of the individual smoker markedly altered the absolute amount of carbon monoxide inhaled. Frankenhaeuser et al. (1971) reported another response to cigarette smoking that may have important consequences for the smoker. They observed a progressive

increase in adrenaline excretion with the number of cigarettes smoked. They also found that, in moderate smokers, certain psychophysical performance measures did not deteriorate when the subjects smoked, in contrast to the decrement observed in nonsmoking conditions (Myrsten et al., 1972). Aronow et al. (1971a) carried out cardiovascular measurements on 8 volunteer anginal patients who, after abstaining for 12 h, smoked 3 cigarettes. One week later the same subjects were given carbon monoxide to breathe so that the final carboxyhaemoglobin levels were almost equivalent (3.90 and 3.86, respectively). As the patients were smokers, their initial carboxyhaemoglobin levels were above 2%. Catheterization of both the left and right ventricles permitted an evaluation of the functions of the myocardium. The major differences observed under the two conditions were as follows: cardiac output decreased with carbon monoxide inhalation but did not change with smoking; heart rate did not change with carbon monoxide inhalation but increased with smoking; systolic and diastolic arterial pressures did not change with carbon monoxide inhalation but increased with smoking; left ventricular stroke work (dp/dt) decreased with inhalation but did not change with smoking; left ventricle end-diastolic pressure increased in both situations; and, finally, the partial pressure of oxygen in arterial, mixed venous, and coronary sinus blood decreased in patients inhaling carbon monoxide. These divergent effects need to be further evaluated. The authors believed that the increased systemic pressure and heart rates following cigarette smoking were related to the nicotine in the cigarette.

A critical problem arises in attempts to separate the effects of carbon monoxide in cigarette smoking from those of other substances present in the inhaled cigarette smoke. In further studies by Aronow et al. (1971b), 10 male angina patients smoked lettuce leaf, non-nicotine cigarettes, resulting in blood carboxyhaemoglobin levels of 7.8%. Heart rate and blood pressure were unaffected by smoking this type of cigarette but again angina occurred earlier on effort. The investigators suggested that the presence of carboxyhaemoglobin following the smoking of cigarettes is the major factor in decreasing exercise tolerance in subjects with angina pectoris.

It has been suggested by Ball & Turner (1974) that carbon monoxide and nicotine from cigarette smoke may, by different mechanisms, accelerate thrombus formation and the development of atherosclerosis. Carbon monoxide reduces the amount of oxygen available to the myocardium at the time when the work of the heart has been increased by the absorption of nicotine. Kjeldsen (1969) reported that in a group of 1000 Danish individuals a clear relationship between high carboxyhaemoglobin concentrations after smoking and the occurrence of atherosclerotic disease was observed. On the other hand, selective evidence would suggest that carbon

monoxide exposure might not be related to the underlying atherosclerosis. Heavy cigarette smokers in Japan, where diets are low in fat and cholesterol, do not appear to be at high risk as regards heart attacks.

As Wald & Howard (1975) stated in their overall review on smoking, carbon monoxide exposure, and arterial disease: "There is at present only indirect evidence that carbon monoxide may be a cause of atheroma in man" and "For the present, however, it is necessary to reserve judgement on whether carbon monoxide is a cause of arterial disease, while at the same time suspecting that it may be the principal agent in tobacco smoke". Aronow and co-workers, as well as Anderson et al. (1973) have shown that, in patients with ischaemic heart disease, exercise-induced angina occurs earlier when the patients are exposed to low levels of carbon monoxide (section 8.2.1). Carbon monoxide exposure also exacerbates the pain of intermittent claudication and the duration of effects in patients with this disease. The potential deleterious influences of cigarette smoking and/or carbon monoxide exposure on the pregnant woman, fetus, and neonate will be considered in section 8.2.3. The only direct evidence that carbon monoxide adversely influences fetal development was derived from studies conducted on rabbits (Astrup et al., 1972).

A number of studies have suggested that cigarette smoking reduces working capacity (Goldbarg et al., 1971; Krone et al., 1972; US Department of Health, Education & Welfare, 1973) and, as presented in section 8.1.2, this reduction has been directly related to the level of carboxyhaemoglobin present in the exercising subject. In young smokers, 21–30 years of age, no differences in maximal aerobic capacity were observed in spite of reductions in vital capacity and maximum breathing capacities (Raven et al., 1974a). Older smokers (40–57 years of age) had significantly lower (27%), aerobic capacity than nonsmokers of a similar age (Raven et al., 1974b). Younger smokers had only a 6% lower aerobic capacity than nonsmokers of the same age. There still remain some questions as to the possible role played by materials other than carbon monoxide in cigarette smoke in the reduction of aerobic capacity.

8.1.7 Interactions

There is only a small amount of data available on the combined effects in man of carbon monoxide and other chemical or physical agents. Experimental work, carried out by Horvath and his collaborators (Drinkwater et al., 1974; Gliner et al., 1975; Raven et al., 1974b), dealt with the combined effects of a concentration of carbon monoxide of 57 mg/m^3 (50 ppm) and peroxyacetylnitrate 1.4 mg/m^3 (0.27 ppm) on the work capacity of healthy men. Combined exposure to both pollutants did not produce greater effects

than exposure to carbon monoxide alone. Hackney et al. (1975) did not find any consistent changes (synergistic or additive) in pulmonary functions in a 2-h exposure of young male subjects to a combination of pollutants namely ozone at 0.5 mg/m^3 (0.25 ppm), nitrogen dioxide at 0.56 mg/m^3 (0.30 ppm) and carbon monoxide at 34.5 mg/m^3 (30 ppm). As for the combined effects of carbon monoxide and physical agents, there are occupational data suggesting additive effects of carbon monoxide and heat (Vyskocil, 1957), and of carbon monoxide (carboxyhaemoglobin levels up to 35%) and noise in workers exposed to this stress combination for more than 10 years (Wagemann, 1960; Zorn, 1968).

There is a complete lack of information on the combined effects of carbon monoxide and drugs or alcohol in man. Furthermore, it is quite apparent that the question of interactions on the organism of carbon monoxide and other air contaminants needs clarification.

8.2 High-Risk Groups

The limited clinical research on populations other than healthy, normal subjects makes it difficult to identify with certainty the groups that are at increased risk from exposure to carbon monoxide. However, as will be discussed later in this section, one of these groups includes individuals with known coronary heart disease. In view of the susceptibility of this group to the hypoxic stress of carbon monoxide exposure, it is implicit that other groups are also potentially subject to increased risk including individuals with cerebrovascular and peripheral vascular diseases, anaemias, and lung diseases. In addition, hospitalized individuals suffering from tissue hypoxia (e.g. shock) or those undergoing operations may be at increased risk. Individuals with undetected or undiagnosed coronary artery disease as well as the fetus *in utero*, the newborn, or, even pregnant women may be assumed to be at increased risk because of the anticipated reduced capacity to accommodate hypoxic stress or some inherent sensitivity to hypoxia. Furthermore, other populations such as those living at high altitudes, young children, or older adults may also be at increased risk.

8.2.1 Individuals with cardiovascular and chronic obstructive lung disease

This section will not be concerned with the potential pathological effects of cigarette smoking on the development of cardiovascular disease, chronic pulmonary obstructive disease, and cancer (section 8.1.6). No adequate evidence has been presented, as yet, that carbon monoxide *per se* is directly involved in the pathogenesis of these disorders. Only the potential influence of ambient carbon monoxide on individuals at risk will be considered.

Epidemiological studies in Los Angeles County (Cohen et al., 1969;

Goldsmith & Landaw, 1968; Hexter & Goldsmith, 1971), have suggested the possibility of increased mortality from myocardial infarction, associated with high (9–16 mg/m^3 or 8–14 ppm) atmospheric levels of carbon monoxide. There have been some differences of opinion concerning the interpretation of these data. A somewhat similar study, at least in design, was completed in Baltimore by Kuller et al. (1975). The Baltimore data did not indicate any apparent relationship between either the incidence of myocardial infarction or sudden death due to atherosclerotic heart disease and average 24-h ambient carbon monoxide concentrations. Neither group of investigators was able to detect a relationship between post mortem carboxyhaemoglobin levels and causes of sudden death. In the latter study the diagnoses of disease state were more precise and the population involved more clearly defined. The ambient levels of carbon monoxide in Baltimore appeared to be considerably lower than those reported for Los Angeles. Thus, the possibility of an association between ambient carbon monoxide and the incidence of myocardial infarction or sudden deaths remains questionable. It is apparent that more comprehensive and extensive epidemiological studies need to be conducted in order to clarify this issue.

There are no adequate studies in man describing the relationship between exposure to carbon monoxide and the rate of development of atherosclerotic heart disease. Goldsmith & Aronow (1975) have reviewed the available evidence.

The heart has a specialized circulatory system in which the primary response to increased metabolic demands can only be secured by an increased coronary blood flow. Even under no-stress conditions (rest) there is an almost complete extraction, roughly 75–80%, of the available oxygen supply. Adams et al. (1973) monitored conscious dogs breathing a carbon monoxide concentration of 1718 mg/m^3 (1500 ppm) for a period of 30 min and were able to show a linear relationship between carboxyhaemoglobin concentration and coronary blood flow. A 13% increase in coronary blood flow occurred at a carboxyhaemoglobin level of 4% and, at a concentration of 20%, flow rate increased by 54%. Since measurements were not reported for the lower carboxyhaemoglobin levels, the existence of a threshold could not be determined. The observations of Mehmel et al. (1973) suggest that increases in coronary blood flow are stimulated by shifts in the oxyhaemoglobin dissociation curve. They demonstrated that increasing pH from 7.4 to 7.6 decreased the p_{50} (pO_2 at half saturation of haemoglobin) from 4 to 3.2 kPa (30 to 24 Torr) and increased coronary blood flow by more than 20%. Earlier studies by Ayres et al. (1969, 1970) also indicated increased blood flow in response to the presence of increased levels of carboxyhaemoglobin.

Ayres' studies of the haemodynamic and respiratory responses of man

during diagnostic coronary catheterization suggested that carbon monoxide would have a significant effect on arterial pO_2 in patients with lung disease as well as in patients with certain cardiovascular disorders.

Studies by Anderson et al. (1973) Aronow et al. (1972) and Aronow & Isbell (1973) on patients with angina pectoris are listed in Table 8. Aronow et al. (1972) studied the influence of riding in an open car on a major Los Angeles freeway. Two trips were made, in one of which the patients breathed compressed carbon monoxide-free air. Carboxyhaemoglobin levels after this ride averaged 0.65%, in contrast to the 5.08% observed in the trip in the open car. The trips were of 90 min duration and ambient carbon monoxide levels in the car averaged 61 mg/m^3 (53 ppm). Exercise time, on a bicycle ergometer, to the onset of angina, was determined prior to, and after the completion of the exposure. Although no changes in the length of time of work to onset of anginal pain were noted in the ride while breathing compressed air, a significant reduction from a mean time of 247 to 174 sec was found when the carboxyhaemoglobin concentration was elevated. Anginal pain also appeared to persist for a longer time under these conditions. In a study by Anderson et al. (1973), patients with stable angina walked on a treadmill. They then breathed air containing 57 or 115 mg/m^3 (50 or 100 ppm) intermittently while resting for a period of 4 h, raising their carboxyhaemoglobin levels to 2.9% and 4.5% respectively. The repeat exercise tests clearly demonstrated a reduction in walking time to onset of angina. No differences in time were observed at the 2 carboxyhaemoglobin levels although the duration of the pain was longer at the higher level. There appeared to be some additional depression of the ST segment but the degree was not of a significant order. Other measures of cardiac function–systolic time intervals, left ventricular ejection time, pre-ejection period index, and pre-ejection peak to ejection time ratio remained within normal limits.

Another study by Aronow & Isbell (1973) was somewhat similar to that of Anderson et al. (1973). Aronow and his co-workers exposed patients (nonsmokers at the time of the test) to a carbon monoxide concentration of

Table 8. Exercise-induced angina and carbon monoxide (10 subjects per study)

Carboxyhaemoglobin (%)		Ambient CO mg/m^3(ppm)	Time to angina response	Reference
Initial	Final			
1.12	5.08	61[a] (53)	Shortened	Aronow et al (1972)
1.07	2.68	57[b] (50)	Shortened	Aronow & Isbell (1973)
1.40	2.90	57[c] (50)	Shortened	Anderson et al. (1973)

[a] Freeway trip.
[b] Continuous exposure for 2 h in laboratory.
[c] Intermittent exposure for 4 h in laboratory.

57 mg/m^3, resulting in a carboxyhaemoglobin concentration of 2.68%. This study was also conducted as a double-blind random trial with one day of breathing carbon monoxide and another day breathing compressed carbon monoxide-free air. The angina pectoris of all patients was documented by history and coronary angiography. A 23% reduction in exercise time (bicycle) resulted following the carbon monoxide exposure. No electrocardiographic changes were seen in these patients during any exercise period. Plotting of Aronow's data suggests that there was a linear relationship between carboxyhaemoglobin levels and the decrease in time to angina.

This evidence suggests that a deleterious effect could occur at carboxyhaemoglobin levels as low as 2.5% in certain subjects with coronary heart diseases. The USA National Health Survey Examination (US Environmental Protection Agency, 1975) reported that in the USA there were 3 215 000 adults, aged 18–79 years, with definite coronary heart disease and another 2 410 000 with suspected disease. Many of these individuals, as well as others in the general population, have carboxyhaemoglobin levels equal to, or above 2.5%. It would be rash to even suggest that the above-mentioned studies implicate carbon monoxide as a factor in determining the natural history of heart disease in a community. It is even more dangerous to imply that exposure to carbon monoxide increases the frequency or severity of chest pain, or shortens life expectancy among patients with angina pectoris or other clinical manifestations of heart disease. The necessary epidemiological evidence for an association between the frequency of episodes of angina pectoris and community ambient levels of carbon monoxide is inadequate and additional information from more and varied sources is required.

Patients with chronic obstructive pulmonary disease are probably at high risk, although few studies on them have been reported. Any increase in hypoxia could result in respiratory failure. However, these individuals may absorb less carbon monoxide because of their disease as the hypoxia may be compensated for by increased erythropoiesis and a shift of the oxygen dissociation curve to the right. An interesting approach to the evaluation of individuals at risk from carbon monoxide and other pollutants can be found in a publication of the US Environmental Protection Agency (US Environmental Protection Agency, 1975). Ogawa et al. (1974) have presented evidence on the development of pulmonary oedema and discussed possible mechanisms of the role of carbon monoxide in the disorder.

8.2.2 Anaemic individuals

The information available on the effects of carbon monoxide on anaemic patients is still inadequate.

The oxygen dissociation curve of blood obtained from patients with anaemia is shaped like the normal curve but is vertically compressed. However, when curves from individuals with a 50% reduction in haemoglobin content are compared with dissociation curves determined in the presence of 50% carboxyhaemoglobin, there are striking differences. Consequently, the tendency to make such comparisons is likely to lead to erroneous deductions concerning effects occurring at the tissue level. Brody & Coburn (1970) discussed these differences in relation to arterial and venous pCO and pO_2. Because the capacity of the oxygen transport system is reduced in anaemic persons, it can be assumed *a priori* that they could be more at risk from carbon monoxide exposure than normal persons. Brody & Coburn (1970) indicated that, if the oxygen content of the mixed venous blood is abnormally low, as in anaemia or carbon monoxide poisoning, the effect of the shunted blood in lowering arterial pO_2 will be greater than normal, and a small increase in the alveolar-arterial pressure difference ($AaDO_2$) will result. The change in the shape of the oxyhaemoglobin curve due to the presence of carbon monoxide will also increase the $AaDO_2$. Furthermore, Brody & Coburn (1970) showed that mild increases in carboxyhaemoglobin concentrations would have little or no influence on the $AaDO_2$ in normal subjects. However, in patients with large intracardiac right-to-left shunts or with chronic lung disease and regional variation in the ventilation perfusion ratio ($\dot{V}_A/\dot{Q}_A$), the presence of carbon monoxide in the blood will increase the $AaDO_2$.

Tissue oxygenation may be involved initially because of the anaemic state, since mixed venous pO_2 is decreased (Cropp, 1970) and the reduction in venous pO_2 from a particular carboxyhaemoglobin value is somewhat greater in anaemic than in normal subjects. In patients with haemolytic anaemia and sickle cell disease (Engel et al., 1971), the rate of endogenous carbon monoxide production from haemoglobin catabolism is increased. Normal subjects produce approximately 18 μmoles of carbon monoxide per hour, resulting in carboxyhaemoglobin levels of 0.5 to 0.8%. Carbon monoxide production in anaemic patients (Coburn et al., 1966; Logue et al., 1971) has been reported to vary from 31 to 158 μmoles per hour, producing carboxyhaemoglobin levels of 1.3–5.2%.

Anaemic subjects approach equilibrium levels of carboxyhaemoglobin more rapidly than those with normal haemoglobin levels at any given exposure to carbon monoxide. Exposure to a concentration of 22.9 mg/m^3 (20 ppm) for approximately 4 h in an individual with a haemoglobin level of 7 g/100 ml could result in a carboxyhaemoglobin concentration of 4–5% compared with an anticipated level of 2.5% for normal individuals. Exogenous carbon monoxide exposure of anaemic individuals could result,

in conjunction with higher endogenous production, in their attaining critical levels of carboxyhaemoglobin more rapidly than normal individuals.

8.2.3 Embryo, fetus, neonate, and infants

Pregnant mothers and their fetuses may be exposed acutely or chronically to carbon monoxide either by maternal smoking or by environmental pollution. The biological effects of carbon monoxide exposure on fetal tissues during intrauterine development or during the newborn period are far from clear.

Several studies (Astrup et al., 1972; MacMahon et al., 1966) have demonstrated that babies delivered by mothers who smoke cigarettes weigh less than those delivered by nonsmoking mothers. Relative maternal, fetal, or placental hypoxia may be responsible, as suggested by the observation that infants born at high altitudes also weigh less than those born at sea level (Grahn & Kratchman, 1963). The New Mexico State Department of Public Health (1975) provided additional confirmation of the relationship between altitude and birth weights.

Mothers who smoked were reported to have carboxyhaemoglobin concentrations ranging from 2 to 14%, while concentrations in the fetuses ranged from 2.4 to 9.8%. These values may not represent conditions present during pregnancy, since these data were obtained just prior to birth. Another factor that may produce differential effects on the fetus is related to the endogenous production of carbon monoxide by pregnant women. Delivoria-Papadopoulos et al. (1969) indicated that nonsmoking pregnant women produced 0.9 ml of carbon monoxide per hour in contrast to the nonpregnant female's production of 0.4 ml reported by Longo (1970). Fetal production of endogenous carbon monoxide accounted for 3% of the total carboxyhaemoglobin present in the blood of a nonsmoking normal pregnant woman. The source of the remainder is not well known but may be related to progesterone levels (Delivoria-Papadopoulos et al., 1969). Even though hyperventilation of pregnancy may partially compensate for the increased carbon monoxide production in the absence of exogenous exposure, the maternal carboxyhaemoglobin still remains about 13% above that in nonpregnant women (Longo, 1970). It should be noted that the post partum (24 h) female may be producing 3 times as much carbon monoxide as a near term nonsmoking pregnant woman.

Behrman et al. (1971) measured carboxyhaemoglobin concentrations in 25 relatively normal newborn infants in a downtown Chicago nursery and found the mean value to be 6.98%. These investigators indicated that absolute carboxyhaemoglobin levels were related to ambient levels of carbon monoxide. Some doubts about this conclusion exist, since the

monitoring reference site was 2.4 km from the nursery; the investigators did not report any untoward clinical effects from exposure to these levels, and no consideration was given to the possibility of increased endogenous carbon monoxide production in these infants.

Of the several mechanisms that may account for the influence of carbon monoxide on developing tissue, the most important is the interference with tissue oxygenation. Carbon monoxide decreases the capacity of haemoglobin to transport oxygen and shifts the oxygen saturation curve to the left. The normal arterial pO_2 supplying fetal tissue is approximately 3.7 kPa (28 Torr). The shift to the left will tend to further decrease the oxygen gradient from maternal to fetal blood across the tissue. The decreased pO_2 and the diminished oxygen transport due to the presence of carboxyhaemoglobin may also produce undesired influences on the fetus. One of the possible mechanisms by which carbon monoxide or other components of tobacco smoke may adversely influence fetal development is through interference with the metabolic function of placental cells. These cells have a role in metabolizing hormones as well as in the transport of vitamins, carbohydrates, amino acids, and other substances through their energy dependent processes. Tanaka (1965) reported that the oxygen uptake of placental slices from mothers who smoked varied inversely with maternal levels of carboxyhaemoglobin, being markedly reduced when this level was higher than 7.0%. The preponderance of evidence concerning maternal carboxyhaemoglobin levels, along with fetal and perinatal exposure, tends to warrant the reduction of exposure to exogenous carbon monoxide sources that might cause this group to be at risk, to a minimum.

The potential toxicity of carbon monoxide present in transfused blood has received little attention. Kandall et al. (1973) measured carboxyhaemoglobin concentrations in donor blood and in relatively healthy infants receiving exchange blood transfusions. The mean pre-transfusion carboxyhaemoglobin concentration in 6 cases was 1.34%. Donor blood contained a carboxyhaemoglobin concentration of 5.17%, resulting in a mean value of 4.92% in the transfused infant. In one infant transfused with blood containing a carboxyhaemoglobin concentration of 8.87%, the resultant carboxyhaemoglobin value in the infant was 7.43%. Although it was stated that the infants did not appear to be adversely affected by the levels of carboxyhaemoglobin reached during exchange transfusion, it should be noted that adverse effects have been observed in adults at these levels. Furthermore, in individuals whose oxygen transport system or cardiovascular reserve is already compromised, the presence of additional carboxyhaemoglobin, from transfused blood, may result in a further and more potentially dangerous decrement in arterial, mixed venous, and coronary sinus oxygen tensions. It should be recalled that some blood

samples collected from blood donors had carboxyhaemoglobin values that exceeded 18%.

8.2.4 Individuals living at high altitudes

The effects of carbon monoxide and of hypoxia induced by high altitude are similar. Carbon monoxide produces effects that aggravate the oxygen deficiency present at high altitudes. When high altitude and carbon monoxide exposures are combined (Table 9) the effects are apparently additive. It should be noted, however, that decreased pO_2 in the air and increased carboxyhaemoglobin, produce different physiological responses. They have different effects on blood pO_2, on the affinity of oxygen for haemoglobin, on the extent of oxyhaemoglobin saturation (carbon monoxide hypoxaemia shifts the oxyhaemoglobin dissociation curve to the left, and a decrease in $p_{A_{O_2}}$ shifts it to the right), and on ventilatory drive. These effects have been discussed earlier.

The actual influence of a combination of increased carboxyhaemoglobin and decreased oxyhaemoglobin has not been adequately documented by experimental data. The few available studies refer only to acute exposures to lower pO_2 and raised pCO. The most supportive information on the additive nature of this combination originates from psychophysiological studies and even this information is not very convincing. When Blackmore (1974) analysed the cause of aircraft accidents in Britain, he found that carboxyhaemoglobin levels provided valuable information in relation to altitude and sources of carbon monoxide. The high levels of carbon monoxide found (up to 74%) could be attributed to equipment failure, smoking, and fires. No data are available on the effects of carbon monoxide on the native inhabitants at high altitudes or on the reactions of these natives when they are suddenly removed to sea level and possible high ambient carbon monoxide concentrations.

Table 9. Approximate physiologically equivalent altitudes at equilibrium with ambient carbon monoxide levels[a]

Ambient CO concentration		Actual altitude (metres)		
mg/m³	ppm	0 (sea level)	1524	3048
		Physiologically equivalent altitudes with carboxyhaemoglobin		
0	0	0 (sea level)	1524	3048
28.6	25	1829	2530	3962
57.3	50	3048	3658	4572
114.5	100	3749	4663	5486

[a] From: NAS/NRC (1977).

In their studies on altitude exposures of young males, McFarland et al. (1944) showed that changes in visual threshold occurred at carboxyhaemoglobin levels as low as 5% or at a simulated altitude of 2425 m. These observations were confirmed by Halperin et al. (1959), who also noted that recovery from the detrimental effects on visual function lagged behind the elimination of carbon monoxide. However, the data given were sparse and the variability among the four subjects was not given. Vollmer et al. (1946) studied the effects of carbon monoxide at simulated altitudes of 3070 and 4555 m and reported that there were no additive effects of carbon monoxide and altitude. They suggested that the effects of carbon monoxide were masked by some compensatory mechanisms. The data presented were not convincing. However, Lilienthal & Fugitt (1946) indicated that a combination of altitude (1540 m) and a carboxyhaemoglobin level of 5–9% induced a decrease in flicker fusion frequency, although either one alone did not have any effect. They also reported that the presence of 8–10% carboxyhaemoglobin was effective in reducing altitude tolerance by 1215 m. During light activity at an altitude of 4875 m, carbon monoxide uptake increased, probably owing to the hyperventilation at altitude caused by the respiratory stimulus of decreased pO_2 (Forbes et al., 1945). Evidence that carbon monoxide elimination was similar at sea level and at altitudes up to 10 000 m was obtained by several investigators (Gorodinsky et al., 1970; Sedov et al., 1971). However, increased ambient temperatures up to 35° C and hard physical work increased the rate of elimination (Vollmer et al., 1946). Pitts & Pace (1947) stated that every 1% increase in carboxyhaemoglobin (up to 13%) was equivalent to a 109 m rise in altitude if the subjects were at altitudes of 2100–3070 m. These observations were based on changes in the heart rate response to work. A number of unanswered questions arise from all these studies, which in general were obscured by such factors as poor control and no identification of subjects who may have been smokers.

Two groups of investigators have presented data comparing the physiological responses of subjects to altitude and carbon monoxide exposure where the hypoxaemia due to altitude and the presence of carboxyhaemoglobin were approximately equal. In one study (Astrup & Pauli, 1968), the carboxyhaemoglobin concentration was about 12% (although the mode of exposure to carbon monoxide was such that carboxyhaemoglobin ranged from 5% to 20% and the altitude study was conducted at 3977 m). The second study (Sedov et al., 1971) compared responses at an altitude of 4000 m and a carboxyhaemoglobin content of 20%. In both studies, carboxyhaemoglobin content was much in excess of that anticipated for typical ambient pollution. However, they both suggested that the effects attributable to carbon monoxide and to altitude were equal.

8.3 Summary Table

Table 10 is a summary of controlled human studies that provide useful information for evaluating the relationship between exposure to carbon monoxide and its health effects.

Table 10. Summary of exposure-effect relationships

Exposure (HbCO %)	Reported effects	Reference
(a) Behavioural changes		
20	Essentially no impairment in time discrimination (using Beard–Wertheim task)	Stewart et al. (1973b)
11.3	No vigilance decrement (using Horvath task)	Winneke et al. (1976)
9[a]	No vigilance decrement (using Fodor–Winneke task); no change in reaction time	Winneke (1974)
8.4	No vigilance decrement (using their own vigilance task (1972))	Groll-Knapp et al. (1976)
7.6	Longer reaction times	Ramsey (1973)
7.3	Disturbance in certain perceptual and cognitive processes	Bender et al. (1972)
5	Vigilance decrement	Horvath et al. (1971)
4.5	Longer reaction times	Ramsey (1972)
3.1[b]	Initial vigilance decrement with subsequent normalization; no change in response latency	Fodor & Winneke (1972)
3[b]	Vigilance decrement	Groll-Knapp et al. (1972)
2[b]	Impaired performance in time-discrimination	Beard & Wertheim (1967)
(b) Changes in work performance		
6.3	Decrease in maximal work time	Ekblom & Huot (1972)
4.3 (1.7[c])	Decrease in a maximal oxygen uptake ($\dot{V}_{O_2}$)	Horvath et al. (1975)
4.0 (0.6[c])	Decrease in mean exercise time until exhaustion	Aronow & Cassidy (1975)
2.5	Decrease in absolute exercise time in non-smokers	Drinkwater et al. (1974)
(c) Aggravation of symptoms in patients with cardiovascular disease		
5.1 (1.1[c])	Shortened time to angina response immediately after exposure	Aronow et al. (1972)
2.9 (1.1[c])	Shortened time to angina response 2 h after exposure	Aronow et al. (1972)
2.9 (1.1[c])	Shortened time to angina response	Anderson et al. (1973)
2.8 (1.0[c])	Decrease in mean exercise time until onset of intermittent claudications	Aronow et al. (1974)
2.7	Shortened time to angina response	Aronow & Isbell (1973)

[a] Estimated values using the formula by Coburn et al. (1965).
[b] Estimated values using the formula by Peterson & Stewart (1970).
[c] HbCO % before exposure to CO.

9. EVALUATION OF HEALTH RISKS

9.1 Introduction

The acute toxicity of carbon monoxide has long been recognized and is well documented. Much has been learned of the main sources of the gas, its absorption, the kinetics of its reactions with blood, and the biochemical and pathological consequences of poisoning by excessive absorption. More recently, a great deal of attention has been paid to the effects, demonstrable or suspected, of exposure to concentrations much lower than those that cause definite poisoning. Such concentrations are those commonly found in urban air (caused almost wholly by traffic pollution) and indoors (caused by faulty ventilation of heating or cooking appliances), but there has been much concern with the effects of the gas on smokers, who inhale considerable quantities of carbon monoxide with tobacco smoke. Since the main source of carbon monoxide as an urban pollutant is the petrol engine, the problems posed by the inhalation of relatively low concentrations of the gas are likely to grow rather than diminish, as traffic becomes denser and more widespread. The recognition of the importance of pollution of the domestic environment is relatively recent and deserves more study; the problems posed by smoking tobacco are common and are, unfortunately, increasing. There is much published evidence, some of which is of debatable value, that suggests that the comparatively low concentrations of carboxyhaemoglobin produced by exposure to pollution of the ambient air and the higher concentrations usually associated with smoking, might cause demonstrable impairment of vigilance, discrimination, and of the performance of fine tasks and physical work in healthy subjects, and the exacerbation of symptoms such as angina pectoris on effort in patients with cardiovascular diseases. Likewise there is evidence, derived from experimentation on animals, that chronic exposure to carbon monoxide leading to the levels of carboxyhaemoglobin commonly found in smokers may, in association with high cholesterol intakes, play a part in the genesis of atherosclerosis. Moreover, there are reasons to suspect that exposure to carbon monoxide may enhance the effects of other pollutants, commonly administered therapeutic agents, socially acceptable amounts of beverages such as alcohol, and other environmental stresses. This section is intended as a brief assessment of these topics in the hope that sound advice may be given on the need to control levels of carbon monoxide in the ambient air.

9.2 Exposure

9.2.1 Assessment of exposure

Concentrations of carbon monoxide in air may be measured with comparative ease by such methods as non-dispersive spectroscopy, gas chromatography etc. But human body burdens of carboxyhaemoglobin depend on many factors other than the partial pressure of carbon monoxide in the inhaled air; among these factors are time of exposure, pulmonary ventilation (which mainly depends on work done), and blood volume. Since these quantities, especially ambient concentrations of carbon monoxide, may vary widely, it is obviously difficult, if not impossible at times, to calculate the likely body burden of carboxyhaemoglobin in an exposed individual. There is, therefore, much to be gained by sampling blood to obtain an integrated estimate of carboxyhaemoglobin derived from all sources under various conditions of exposure. It must be emphasized that the measurements of carbon monoxide in air and in blood give complementary results and are not merely alternative forms of monitoring. Methods of analysis are discussed in sections 2.2 and 2.3.

There is a tendency to forget that the reaction between haemoglobin and carbon monoxide is reversible and that, in a given environment, a subject may acquire carbon monoxide, excrete it, or remain in equilibrium with the ambient air depending on the carbon monoxide concentration and the initial level of carboxyhaemoglobin in the individual. The time taken to achieve equilibrium between blood and ambient air depends on the initial carboxyhaemoglobin concentrations as well as on the factors mentioned above. The rate of excretion of carbon monoxide will depend not only on ambient air levels, the initial carboxyhaemoglobin and on factors such as pulmonary ventilation, but also on the partial pressure of oxygen in inspired air, which might be introduced therapeutically to increase elimination. Fig. 12 shows estimates of equilibrium times for various ambient concentrations and levels of activity. The half-life for excretion, at rest, is approximately $4\frac{1}{2}$ h.

9.2.2 Endogenous production

The normal breakdown in the body of blood pigments produces carbon monoxide to give endogenous carboxyhaemoglobin values of 0.1–1.0% and normal blood is in equilibrium with carbon monoxide levels in air of roughly 5 mg/m^3 (4.3 ppm). These data could be used as a basis for establishing air quality criteria for carbon monoxide. Various causes of increased endogenous production of carbon monoxide are discussed in section 6.1.

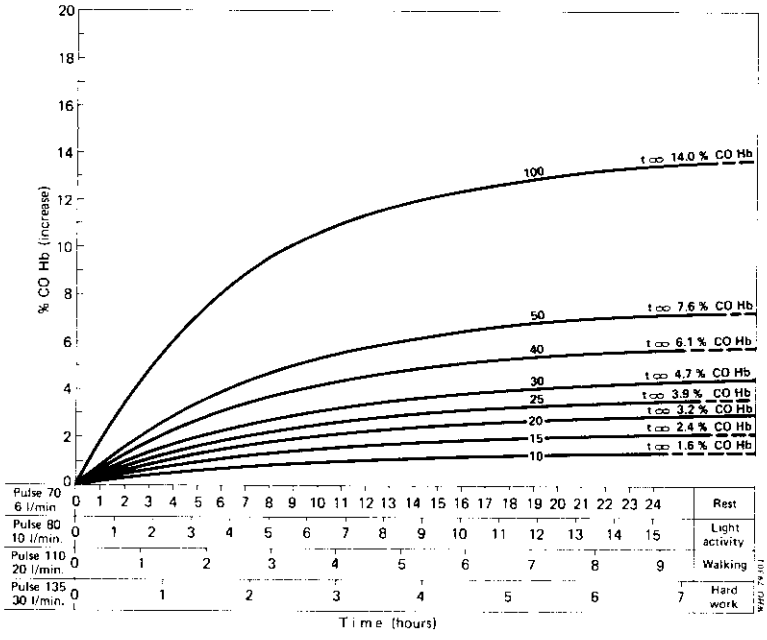

Fig. 12. Uptake of carbon monoxide by blood. This is a typical dose–response curve derived empirically from observations of Forbes et al. (1945). The actual carboxyhaemoglobin level in any individual may differ considerably from the predicted figure, depending on the conditions prevailing at the time of exposure. (By courtesy of the Clinical Section, Medical Research Council Toxicology Unit, London, UK.)

9.2.3 Outdoor environmental exposure

Natural sources of carbon monoxide (section 3.1) are of considerable magnitude but are diffuse, and ambient air concentrations at locations removed from man-made sources range from 0.01 to 0.9 mg/m^3 (0.01 and 0.8 ppm) which is negligible in the context of this report. By far the most important sources of carbon monoxide at breathing level are petrol engine vehicle exhausts (section 3.2). The diesel engine (compression ignition), when properly adjusted, emits little carbon monoxide. The density, distribution, and mode of operation of vehicles vary greatly and these and other factors, the most important of which is the weather, produce great variations in the concentrations of pollutants produced by traffic. Concentrations fall steeply with distance from the street. However, distinct patterns are often discernible (section 5.1). Concentrations for 8-h averaging times are frequently used and quoted and usually vary from <10 mg/m^3 (8.7 ppm) to over 60 mg/m^3 (52.2 ppm) but are mostly <20 mg/m^3 (17.6 ppm) in city streets. Away from heavy traffic, even in towns, annual average concentra-

tions are usually well under 10 mg/m^3 (8.7 ppm). Obviously, in especially stagnant weather, very heavy traffic may produce much higher levels. There is little information about concentrations of carbon monoxide near large stationary sources.

9.2.4 Indoor exposure

Carbon monoxide diffuses readily and, being relatively chemically inert and not absorbed on surfaces, concentrations indoors are usually similar to those found immediately outside. Not infrequently, however, high concentrations may be found in kitchens and living rooms in which there are coal, gas, or oil-fired cooking or heating appliances that are maladjusted and inadequately vented to outside air; in some countries, cases of acute and even fatal poisoning due to these causes are not uncommon. The possible contribution of the domestic environment must be noted in surveys. The smoking of tobacco indoors can obviously increase the carbon monoxide concentration of the air but recent work has shown that, before carbon monoxide reaches significant levels, the irritation from the other constituents of tobacco smoke becomes unacceptable if not actually intolerable.

9.2.5 Exposures related to traffic

In garages and tunnels, being in effect closed streets, pollution by carbon monoxide can reach high levels. However, since transit time in tunnels is relatively short, higher concentrations than those found in streets are tolerable. Usually, there are monitoring instruments that control ventilation and sound alarms if concentrations exceed agreed values, which may vary from 115 to 570 mg/m^3 (100–500 ppm) depending on the use and length of the tunnel. High (sometimes lethal) concentrations of carbon monoxide may accumulate inside motor vehicles because of fractures in exhaust systems or other mechanical defects.

9.2.6 Occupational exposure

Traffic policemen, garage attendants, and drivers of taxis and trucks are exposed to pollution from traffic and many studies have shown a consequent increase in carboxyhaemoglobin levels (up to about 3% in nonsmokers), but there is much evidence that this increase may be relatively undramatic, when compared with the manifest effects of cigarette smoking. Exposure in certain industries, especially in iron and steel works and in the manufacture of various gases, may be relatively massive (in excess of 115 mg/m^3 or 100 ppm), and high carboxyhaemoglobin levels (>15% in

nonsmokers) have been reported in workers. Firemen may be exposed to very high concentrations of carbon monoxide in fighting certain fires, but this exposure is obviously episodic. These matters are discussed in section 5.3.

9.2.7 Tobacco smoking

The smoking of tobacco, especially in the form of cigarettes, has been shown in many studies to be the major cause of raised carboxyhaemoglobin levels in adult populations. Table 7 displays some of this evidence and the topic is discussed in detail in section 8.1.6. Whereas carboxyhaemoglobin concentrations of 3% are rarely found in nonsmokers exposed to town air, concentrations of 5–15% are often found in smokers. It is important to remember that the effects of smoking and exposure to town air are not simply additive and that the resulting carboxyhaemoglobin levels will depend on other factors already discussed.

9.2.8 Multiple exposures

Enough has been said to leave no doubt that carbon monoxide, produced exogenously or endogenously, is a widespread pollutant emanating from many sources to which people may be exposed in various ways. This variety of exposure must be taken into account in the interpretation of epidemiological surveys, the design of experiments, and, above all, in giving advice about the fixing of air quality criteria.

9.3 Effects

The main areas of concern that have arisen from acute or chronic exposure to low levels of carbon monoxide in experimental and epidemiological research in animals and man are: (*a*) its role in the genesis of arteriosclerotic vascular diseases; (*b*) its role in the aggravation of symptoms of cardiovascular diseases; (*c*) its contribution to performance deficits in certain psychomotor tasks; and (*d*) its role in limiting the working capacity of exercising man.

9.3.1 Cardiovascular system

9.3.1.1 *Development of atherosclerotic cardiovascular disease*

Extensive experimental work has been carried out over many years on animals, mainly rabbits, showing that prolonged exposure to moderate levels of carbon monoxide can produce atherosclerotic changes, especially

in the presence of high cholesterol levels (1–2%) in the diet. The relevance of this work for man has not been established. However, other animal work, and some epidemiological studies of prolonged human exposures to elevated carbon monoxide levels through smoking, occupation, or both, such as those carried out in Denmark, Finland, and Japan, indicate the need for further investigation of the possible role of carbon monoxide in the genesis of atherosclerotic vascular changes in animals and man. The degree of intermittency of exposure at various levels should be taken into account as well as the possible contribution of other agents such as nicotine and high-fat diets. There is some evidence of adaptation, but such changes may not be entirely beneficial. None of the information, currently available, is useful for the purpose of setting standards.

9.3.1.2 *Acute effects on existing heart illness*

The few existing epidemiological studies on the possible effects of carbon monoxide on the severity or fatality of coronary occlusion are insufficient to allow any conclusions. It is hoped that additional work of this type will clarify matters.

Two carefully conducted human studies of the effects of low carbon monoxide exposure and exercise on pain in volunteer patients with angina pectoris offer valuable quantitative information. Although limited in the number of patients studied, the findings are consistent in the 2 investigations showing effects at carboxyhaemoglobin concentrations of 2.5–3.0%. A third single-blind study revealed the same detrimental effects in patients with angina pectoris when exposure to traffic exhausts caused carboxyhaemoglobin levels to rise to 5.1%. A no-adverse-effect level has not been established in these observations, nor is it possible to determine whether there is a graded response in this type of experiment. More work of a similar nature would be useful to explore these questions.

9.3.1.3 *Acute effects on existing vascular disease*

One study, similar to those done on patients with angina, has been carried out on patients with intermittent claudication from peripheral vascular disease. Effects on pain with exercise were observed in the same exposure range as with angina i.e., at carboxyhaemoglobin concentrations of 2.5–3.1%, with a mean of 2.8%. Here, too, more data of a similar kind are needed, preferably designed to provide dose–response relationships.

9.3.2 Nervous system

As for the role of carbon monoxide in affecting psychomotor functions, no definite conclusions can be drawn from the existing data. The behavioural

functions tested in such studies include vigilance and psychomotor performance, visual acuity and sensitivity, the ability to estimate time intervals, complex motor coordination as tested by driving simulators, and different perceptual and mental operations[a]. Some workers observed detrimental effects at carboxyhaemoglobin levels as low as 2%, whereas others were unable to detect significant impairment even at levels from above 5% to about 20%. In evaluating these discrepancies, it should be mentioned, that these behavioural functions are easily influenced by a number of other factors besides carbon monoxide-induced hypoxia, e.g., degree of sensory deprivation, compensatory abilities, drugs, temperature, time of day, competition, etc.

9.3.3 Work capacity

That elevated carboxyhaemoglobin levels affect work capacity has long been known. Levels of 40–50% will usually prevent working entirely. Recent studies in the laboratory, on man, using maximum work capacity or maximum aerobic capacity as indicators of performance, have been carried out in relation to carboxyhaemoglobin levels. Here, dose–response data are available for maximum effort. The limitation appears at a carboxyhaemoglobin concentration of about 4% and increases at higher levels. Lower exposure levels have been studied and do not produce this effect. It should be noted that while levels of carboxyhaemoglobin of 2.5–4%, did not reduce maximum work capacity, they did reduce the length of time for which such effort could be carried out. It is not known what specific levels of carboxyhaemoglobin will reduce the capacity of individuals to perform at ordinary work levels, such as 30–50% of their maximum capacity, for prolonged periods of time.

9.4 Recommended Exposure Limits

It has already been stated that the major contributor to carboxyhaemoglobin concentrations in the body is the smoking of tobacco; however, in many of the experiments currently quoted to justify the formulation of exposure limits, the smoking habits of the subjects were not taken into account. Results of recent work suggest that smokers and ex-smokers might

[a] The possible importance of performance deficiencies resulting from carbon monoxide is considerable, particularly in relation to accidents at work, and while driving or flying. Further studies, particularly of the vigilance type are urgently needed for a better understanding of this problem.

be less sensitive to carbon monoxide exposure than nonsmokers. In view of this suggestion, and because of the deficiencies in the experiments mentioned, recommendations for exposure limits should be confined to the protection of nonsmokers. There is an urgent need for more work on possible adaptation following exposure to carbon monoxide from smoking or from other sources. It is also important to note that carboxyhaemoglobin levels have been the measurement of exposure in most experimental work. Thus, it is desirable to recommend the primary exposure limits in terms of carboxyhaemoglobin, and follow this by comments on the derivation of an appropriate air concentration equivalent.

9.4.1 General population exposure

Data used in arriving at a recommendation for an exposure limit for the general population were mainly those obtained from the exposure of subjects with cardiovascular illness to carbon monoxide in conjunction with exercise. Agreement was not reached on a single level. Thus, a range of carboxyhaemoglobin concentrations of 2.5–3.0% is recommended for the protection of the general population including those who have impaired health. The recommendation must be regarded as tentative, since ideal dose–response or concentration–response information is not yet available. However, it must also be recognized that complete protection of all persons, at all times, cannot reasonably be sought by environmental control alone. Persons who are ill should be educated by their physicians concerning their own responsibility to avoid stressful exposures.

9.4.2 Working population exposure

Better quality data are available for recommending an exposure limit for the working population. In this case, the Task Group unanimously agreed on maintaining carboxyhaemoglobin levels below 5%, on the basis of present knowledge, since working populations comprise individuals who are assumed to be healthy, physiologically resilient, and under regular supervision.

9.4.3 Derived limits for carbon monoxide concentrations in air

It is important, wherever possible, to have both biological and environmental assessments of human exposure to pollutants. While the biological measurements may be more relevant in relation to effects, 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

variables, including exposure time and it is not easy to estimate. However, such estimates may be sufficiently accurate for many practical purposes (for reviews see Committee on the Challenges of Modern Society, 1972; Commission of the European Communities, 1974; NAS/NRC, 1977; Winneke, 1977; Ott & Mage, 1978). It should be emphasized yet again that analyses of carbon monoxide in air and of carboxyhaemoglobin in blood are complementary, and should in no way be 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.

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Annex 1

THE RELATIONSHIP BETWEEN CARBON MONOXIDE CONCENTRATION IN AIR AND CARBOXYHAEMOGLOBIN[a]

(*1*) Several empirical equations have been proposed for estimating carboxyhaemoglobin levels from environmental exposure conditions. These equations were based on controlled exposures of human volunteers. Most of them referred to subjects at rest, or performing sedentary activities or light work. The simplest empirical equations described carboxyhaemoglobin levels as a linear function of carbon monoxide concentration in the inspired air [CO], and of exposure time (t) (Forbes et al., 1945; Pace et al., 1946). They were applicable only within a limited range of exposure conditions. Hanks & Farquhar (1969) and Peterson & Stewart (1970) compiled empirical equations involving more complex functional relationships that had a wider application.

(*2*) In addition, models have been proposed that relate carboxyhaemoglobin levels to both environmental exposure conditions and a number of physiological variables such as blood volume, V_B, endogenous carbon monoxide production, $\dot{V}_{CO}$, diffusion capacity of the lung, D_L, and alveolar ventilation rate, $\dot{V}_A$. The best known model, developed by Coburn et al. (1965), has been briefly discussed in section 6.2. A more recent model, that took into account the dynamic condition of urban carbon monoxide concentrations, was suggested by Ott & Mage (1978) (p. 118).

(*3*) A simple linear relationship, proposed by Forbes et al. (1945), linked the increase in the carboxyhaemoglobin level with the carbon monoxide concentration in air, [CO](ppm) and exposure time, t(min):

$$[HbCO](\%) = k \times [CO] \times t \qquad (1)$$

where k was a constant equal to 0.0003 for "an individual at rest" ($\dot{V}_A = 6$ litre/min, pulse rate 70), 0.0005 for "light activity" ($\dot{V}_A = 9.5$ litre/min, pulse rate 80), 0.0008 for "light work" (50 watts, $\dot{V}_A = 18$ litre/min, pulse

[a] This annex has been prepared by the Secretariat and has not been reviewed by the Task Group, with the exception of Table 3. Equations are presented in the form given in the original studies and no attempt has been made to change to SI units. The Secretariat wishes to express its appreciation to Dr H. Buchwald (Canada), Chairman of the Task Group, for providing information contained in Tables 3 and 4 and to Dr R. Horton, Dr D. J. McKee, USEPA, and Dr V. Armstrong, Health and Welfare, Canada for reviewing the annexes.

rate 110), and 0.0011 for "heavy work"[a] (about 100 watts, $\dot{V}_A = 30$ litre/min, pulse rate 135).

This equation was based on sets of controlled exposure observations on human volunteers. Exposure concentrations ranged from 100 to 20 000 ppm (0.01 to 2.0%), and exposure times up to 6 h. At a [CO] of 100 ppm, the equation holds only up to Δ[HbCO] of about 7%. At 1000 ppm, the equation is applicable up to 30% [HbCO].

The equation of Forbes et al. was used by the California State Department of Health for estimating [HbCO] after shorter periods of exposure to carbon monoxide concentrations higher than 100 ppm in individuals at rest or engaged in light work (Goldsmith & Landow, 1978).

(*4*) The empirical equation suggested by Pace et al. (1945) was derived from controlled carbon monoxide exposures of 32 volunteers, aged 18–40 years. The concentrations of carbon monoxide in the inspired air varied from 90 to 21 800 ppm, and the subjects were either sitting quietly or walking on a level treadmill (about 4.3 km/h, $\dot{V}_A$ about 19.2 litre/min). The exposure times ranged from 20 to 300 min. The equation was also linear, but it took into account the alveolar ventilation rate, $\dot{V}_A$, and the blood volume, V_B:

$$\Delta[\mathrm{HbCO}](\%) = \frac{[\mathrm{CO}](\mathrm{ppm}) \times \dot{V}_A\,(\mathrm{litre/min}) \times t(\mathrm{min})}{4650 \times V_B(\mathrm{litre})} \qquad (2)$$

If it is assumed that the blood volume equals 5.5 l and $\dot{V}_A = 6$ litre/min (rest or light sedentary activity) or 18 litre/min (light physical work), the equation takes the same form as that of Forbes et al., but k values are somewhat lower (0.00023 and 0.00070, respectively).

(*5*) Hanks & Farquhar (1969) also conducted carefully controlled exposure studies on sedentary volunteers, and expressed their results by the equation:

$$[\mathrm{HbCO}](\%) = 0.147[\mathrm{CO}](1 - e^{-0.00289t}) \qquad (3)$$

where [CO] is in ppm and t in min. The equation was valid for subjects having a ventilation rate of about 6 litre/min.

According to Chovin (1974), the "coefficient of (pulmonary) ventilation" K could be introduced into equation (3), which then became applicable to subjects performing various degrees of activity. Chovin's modified equation read:

$$[\mathrm{HbCO}](\%) = 0.147[\mathrm{CO}](1 - e^{-\frac{K}{0.147}t}) \qquad (4)$$

[a] $\dot{V}_A$ for heavy physical work may be as high as 60 litre/min.

where t was in hours. For subjects at rest, K = 0.025, and for those performing heavy physical work, K = 0.065. For intermediate degrees of activity, Chovin proposed K values of 0.035, 0.045, and 0.055.

(6) Another empirical equation, referred to on p. 36, was suggested by Peterson & Stewart (1970). It could also be written in the following form:

$$[\mathrm{HbCO}](\%) = 0.0051[\mathrm{CO}]^{0.858} \times t^{0.63} \quad (5)$$

where [CO] is in ppm, and t in min. The equation was based on controlled human exposure data. The volunteers (18 healthy graduate students) were exposed to carbon monoxide concentrations of <1, 25, 50, 100, 200, 500, and 1000 ppm for periods ranging from 30 min to 24 h, while performing strictly sedentary activities. Like linear equations, this equation needed to be used with caution, since it did not yield a finite [HbCO] value for an infinite exposure time. It was used in developing US national ambient air quality standards, and is strictly valid for constant [CO] and for shorter periods of exposure (Ott & Mage, 1978).

(7) A model proposed by Coburn et al. (1965) has been discussed on pp. 36 and 37. It is valid for male subjects only.[a] A solution of their differential equation has been provided in the original paper; it assumes that the mean pulmonary capillary oxygen pressure ($\bar{p}C_{O_2}$) and the concentration of oxyhaemoglobin [HbO_2] are constant and independent of carboxyhaemoglobin levels [HbCO]. However, the oxyhaemoglobin level depends on carboxyhaemoglobin concentrations in a complex way. Solutions of the differential equation taking this into account are available, and their application is illustrated in the NAS/NRC (1977) document. Nevertheless, for most practical purposes, the solution given in the original paper appears to be adequate. It has been used, for example, by Peterson & Stewart (1970) and in the criteria document of the National Institute of Occupational Safety and Health (US Department of Health, Education and Welfare, 1972). A useful form of this solution is given in the document of the Committee on the Challenges of Modern Society (1972):

$$[\mathrm{HbCO}]_t = \frac{\mathrm{I}}{\mathrm{A}} \{e^{-kt}(\mathrm{A}[\mathrm{HbCO}]_0 - \dot{V}_{CO} - [\mathrm{CO}]) + \dot{V}_{CO}\,\mathrm{B} + [\mathrm{CO}]\} \quad (6)$$

where $[\mathrm{HbCO}]_t$ and $[\mathrm{HbCO}]_0$ are the carboxyhaemoglobin levels at times t and $t = 0$, $[\mathrm{CO}] = pI_{CO}$, $\mathrm{A} = \dfrac{\bar{p}C_{O_2}}{\mathrm{M}[\mathrm{HbO_2}]}$, and $\mathrm{B} = \left(\dfrac{1}{D_L} - \dfrac{(pB - 47)}{\dot{V}_A}\right)$;

[a] Endogenous CO production may be different for females due to menstruation, pregnancy, and other metabolic factors.

the symbols used to define [CO], A, and B are explained on p. 36. The relationships between [CO] in ppm and pI_{CO}, and between [HbCO]% and [HbCO] in ml CO/ml blood are:

$$[CO](\text{ppm}) = \frac{pI_{CO} \times 10^6}{pB},$$

and

$$[HbCO](\%) = 497.5\,[HbCO](\text{ml CO/ml blood})$$

(*8*) Ott & Mage (1978) designed a model that took into consideration the dynamic characteristics of urban carbon monoxide concentrations. The differential equation describing it reads:

$$\tau \frac{d[HbCO]}{dt} + [HbCO] - \beta = \alpha[CO] \qquad (7)$$
$$O \leq [CO] \leq 100 \text{ ppm}$$

where β was the endogenous level of blood carboxyhaemoglobin and was assumed to be 0.5%, α was assumed to be 0.15, and $\tau = 2.49$h.

The main conclusion of the authors was that [CO] in ambient air should be reported for averaging periods of 10–15 min, if the monitoring stations were located near heavy traffic or on congested streets. In such cases, sharp carbon monoxide peaks of short duration might occur fairly often, and concentrations reported with longer averaging periods, e.g., 1 h or more, might introduce an error of up to 21% in the estimated [HbCO].

(*9*) Several empirical equations are compared with Coburn's model in Table 1, for persons at rest ($\dot{V}_A = 6$ litre/min) or performing light physical work

Table 1. [HbCO](%) predicted by different empirical equations and by the model of Coburn et al. (1965). Exposure to a carbon monoxide concentration of 115 mg/m³ (100 ppm)

Time (min)	Subjects at rest					Subjects performing light work			
	F	P	H	PS	C	F	P	H	C
15	1.0	0.8	1.1	2.0	1.2	1.7	1.6	1.9	2.0
30	1.4	1.0	1.7	2.8	1.8	2.9	2.6	3.2	3.3
45	1.9	1.5	2.3	3.4	2.4	4.1	3.6	4.4	4.6
60	2.3	1.9	2.8	4.0	3.0	5.3	4.7	5.4	5.7
120	4.1	3.3	4.7	5.9	5.0	10.1	8.9	8.7	9.2
180	5.9	4.5	6.4	7.5	6.8	14.9	13.1	10.9	11.6
240	7.7	6.0	7.8	8.9	8.3	19.7	17.3	12.3	13.2
300	9.0	7.4	9.0	10.1	9.6	24.5	21.5	13.3	14.1
360	10.8	8.8	10.0	11.3	10.7	29.3	25.7	13.9	15.1
420	12.6	10.2	10.8	12.4	11.6	34.1	29.9	14.3	15.6
480	14.4	11.5	11.5	13.5	12.4	38.9	34.1	14.6	15.9

F = Forbes et al. (1945), P = Pace et al. (1946), H = Hanks & Farquhar (1969), PS = Peterson & Stewart (1970), C = Coburn et al. (1965).

($\dot{V}_A$ = 18 litre/min), at a carbon monoxide exposure concentration of 100 ppm. For subjects performing light work, Hanks & Farquhar's equation has been used in Chovin's modification with K = 0.060. The following assumptions have been made in calculating $[HbCO]_t$ values from Coburn's equation (6): [HbCO] = 0.5% or 0.001 ml CO/ml blood, $\dot{V}_{CO}$ = 0.007 ml/min, V_B = 5500 ml, pC_{O_2} = 100 mmHg, $[HbO_2]$ = 0.2 ml O_2/ml blood, M = 218, pB − 47 = 713 mmHg; sedentary subjects: D_L = 30 ml/min/mmHg, $\dot{V}_A$ = 6000 ml/min; light work: D_L = 40 ml/min/mmHg, $\dot{V}_A$ = 18 000 ml/min. For all empirical equations, $[HbCO]_0$ = 0.5% has been added to the calculated values of [HbCO].

Table 1 shows clearly that Hanks & Farquhar's equation agrees best with Coburn's model. Peterson & Stewart's equation gives values that are higher than the other equations up to 6 h of exposure; then it gives lower results than Forbes' equation. At a carbon monoxide concentration of 100 ppm, Pace's equation gives lower [HbCO] values for subjects at rest than the other equations, up to 7 h of exposure; for subjects performing light work, it

Table 2. [HbCO] values predicted from Coburn et al. (1965) model

Time	200 ppm			100 ppm			75 ppm			50 ppm		
	S	L	H	S	L	H	S	L	H	S	L	H
15 min	1.8	3.5	5.2	1.2	2.0	2.8	1.0	1.6	2.2	0.82	1.2	1.6
30 min	3.1	6.2	9.2	1.8	3.3	4.8	1.5	2.6	3.7	1.1	1.9	2.6
45 min	4.3	8.7	12.6	2.4	4.6	6.5	1.9	3.5	4.9	1.4	2.5	3.4
60 min	5.5	11.0	15.5	3.0	5.7	7.9	2.3	4.3	6.0	1.7	3.0	4.1
90 min	7.7	14.9	20.2	4.0	7.6	10.2	3.1	5.8	7.7	2.2	4.0	5.2
2 h	9.7	18.1	23.7	5.0	9.2	11.9	3.9	7.0	9.0	2.7	4.7	6.1
4 h	16.3	26.2	30.4	8.3	13.2	15.3	6.3	10.0	11.5	4.4	6.9	7.7
6 h	21.1	30.0	32.4	10.7	15.1	16.2	8.1	11.3	12.2	5.5	7.6	8.2
8 h	24.5	31.7	32.9	12.4	15.9	16.5	9.4	12.0	12.4	6.4	8.0	8.3
24 h	32.7	33.2	33.2	16.5	16.7	16.6	12.4	12.5	12.5	8.4	8.4	8.3
∞	33.4	33.2	33.2	16.8	16.7	16.6	12.7	12.5	12.5	8.5	8.4	8.3

Time	35 ppm			25 ppm			10 ppm			5 ppm		
	S	L	H	S	L	H	S	L	H	S	L	H
15 min	0.72	1.0	1.3	0.66	0.84	1.0	0.55	0.61	0.67	0.52	0.54	0.56
30 min	0.93	1.4	1.9	0.80	1.2	1.5	0.61	0.72	0.82	0.54	0.57	0.60
45 min	1.1	1.9	2.5	0.95	1.4	1.9	0.66	0.81	0.95	0.56	0.61	0.64
60 min	1.3	2.2	3.0	1.1	1.7	2.2	0.71	0.90	1.1	0.58	0.63	0.68
90 min	1.7	2.9	3.7	1.3	2.1	2.7	0.80	1.1	1.2	0.62	0.69	0.74
2 h	2.0	3.4	4.3	1.6	2.5	3.1	0.89	1.2	1.4	0.66	0.73	0.78
4 h	3.2	4.7	5.4	2.4	3.4	3.9	1.2	1.5	1.6	0.77	0.84	0.86
6 h	4.0	5.4	5.7	2.9	3.9	4.1	1.4	1.6	1.7	0.85	0.88	0.88
8 h	4.5	5.7	5.8	3.3	4.1	4.2	1.5	1.7	1.7	0.91	0.91	0.89
24 h	5.9	5.9	5.9	4.3	4.2	4.2	1.9	1.8	1.7	1.05	0.93	0.89
∞	6.0	5.9	5.9	4.4	4.2	4.2	1.9	1.8	1.7	1.06	0.93	0.89

S = sedentary subjects, L = light physical work, H = heavy physical work, all as defined in sections 9 and 10.

is applicable up to 2 h of exposure. For subjects at rest, Forbe's equation is applicable up to 6 h, and for persons performing light work, up to 2 h.

(*10*) Table 2 shows [HbCO] values predicted by Coburn's model.[a] The assumptions are the same as those specified in paragraph 9. For heavy work, it has been assumed that D_L = 60 ml/min/mmHg and that $\dot{V}_A$ = 30 000 ml/min.

(*11*) Guidelines on exposure conditions that would prevent carboxyhaemoglobin levels exceeding 2.5–3% in general nonsmoking populations are given in Table 3.

Table 3. Guidelines for exposure conditions to prevent carboxyhaemoglobin levels exceeding 2.5–3% in nonsmoking populations

(*a*)	A ceiling or maximum permitted exposure of 115 mg/m³ (100 ppm) for periods of exposure not exceeding 15 min (No exposure over 115 mg/m³ (100 ppm) permitted, even for very short time periods).
(*b*)	A time-weighted average exposure of 55 mg/m³ (50 ppm) for periods of exposure not exceeding 30 min.
(*c*)	A time-weighted average exposure of 29 mg/m³ (25 ppm) for periods of exposure not exceeding one h.
(*d*)	A time-weighted average exposure of 15 mg/m³ (13 ppm) for periods of exposure of more than one h.
(*e*)	A time-weighted average exposure of 11.5 mg/m³ (10 ppm) for periods of exposure of 8–24 h.[a]

[a] Suggested by the Secretariat.

These guidelines were reviewed by the Task Group. Comparison with Tables 1 and 2 indicates the degree of protection provided, if these guidelines are applied, both for sedentary individuals and for persons performing light work. The exposure guidelines for 8–24 h have been added by the Secretariat, after the Task Group meeting, to facilitate comparison with national air quality standards.

(*12*) Guidelines on exposure conditions, which would prevent carboxyhaemoglobin levels exceeding 5% in nonsmoking occupational groups, are shown in Table 4. They were prepared, after the meeting, by Dr Buchwald, at the request of the Secretariat, and have not been reviewed by the Task Group. Guidelines for heavy work have been suggested by the Secretariat, also after the meeting. Heavy work has been defined by $D_L = 60$ ml/min/mmHg and $\dot{V}_A = 30\,000$ ml/min. The degree of protection provided by these guidelines is indicated in columns 3 and 4 of Table 4. Column 3 shows carbon monoxide concentrations that would produce 5% HbCO

[a] The Secretariat wishes to thank Dr M. A. Vouk, University Computing Centre, Zagreb, Yugoslavia, for programming Coburn's equations and providing computer printouts.

Table 4. Guidelines for exposure conditions that would prevent carboxyhaemoglobin levels exceeding 5% in nonsmoking occupational groups performing light and heavy physical work.

Concentration		Exposure time not to be exceeded		Concentrations that would produce 5% HbCO[c]		Safety factor	
ppm	mg/m³	Light work[a]	Heavy work[b]	Light work	Heavy work	Light work	Heavy work
200[d]	230	15 min	—	298	—	1.5	—
100[e,f]	115	30 min	15 min	157	193	1.6	1.9
75[f]	86	60 min	30 min	87	105	1.2	1.4
50[f]	55	90 min	60 min	64	62	1.3	1.2
35[f]	40	4 h	2 h	37	41	1.1	1.2
25[f]	29	8 h	8 h	31	30	1.2	1.2

[a] Limits suggested by Dr Buchwald.
[b] Limits suggested by the Secretariat.
[c] Calculated from Coburn's equation (6).
[d] Short-term limit or maximum permissible concentration for light work.
[e] Short-term limit or maximum permissible concentration for heavy work.
[f] Time weighted average.

within exposure times given in column 2, for light and heavy work, respectively. Column 4 provides "safety factors" obtained by dividing the concentrations in column 3 by concentrations in column 1. Unless otherwise indicated, the guidelines given in Table 4 should be considered as desirable conditions rather than maximum acceptable limits.

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All other references are included in the list of references for the main body of the document (pp. 98–114).

Annex 2

SELECTED NATIONAL AMBIENT AIR QUALITY STANDARDS AND OCCUPATIONAL EXPOSURE STANDARDS FOR CARBON MONOXIDE[a]

1. NATIONAL AMBIENT AIR QUALITY STANDARDS

1.1 Canada (1974)

National air quality objectives

Desirable concentrations:

(*a*) 0–6 mg/m^3 (0–5 ppm)[b] average concentration over an 8-h period.

(*b*) 0–15 mg/m^3 (0–13 ppm) average concentration over a one-h period.

Acceptable concentrations:

(*a*) 6–15 mg/m^3 (5–13 ppm) average concentration over an 8-h period.

(*b*) 15–35 mg/m^3 (13–31 ppm) average concentration over a one-h period.

Method of measurement:

Nondispersive infrared spectrometry, Report No. EPS 1-AP-73-1.

Source: Velma Ouellet (1978) *The Clean Air Act—Compilation of Regulations and Guidelines*, Ottawa, Environment Canada (Report EPS 1-AP-78-2).

In addition to the desirable and acceptable concentrations listed, a tolerable range of 15–20 mg/m^3 average concentration over a continuous 8-h period was prescribed in 1978.

Source: Canada Gazette (1978) Part 2, Volume 112, No. 3 (February 8).

1.2 Federal Republic of Germany (1974)

In the Federal Republic of Germany, immissions[c] (Immissionen) are legally defined as "air pollutants, noise, vibrations, light, heat, radiations,

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[a] Prepared by the Secretariat.

[b] Concentrations in alternative units have been added by the Secretariat to facilitate comparison of national quality standards.

[c] Immission A German term for which there is no simple English equivalent. Immis[illegible] are to be distinguished from emissions (Emissionen), which are defined as air pol[illegible] noise, vibrations, light, heat, radiations, and analogous phenomena originating [illegible] installation (Federal Republic of Germany Law on Protection against Emis[illegible] March 1974).

and analogous environmental factors affecting human beings, animals, plants, or other objects". "As a rule, air pollutants occurring at a height of 1.5 metres above ground or at the upper limit of vegetation or at a distance of 1.5 metres from the surface of a building shall be considered active air pollutants."

"Immission standards are the values for long-term exposure (IW 1) and short-term exposure (IW 2)."

The following immission standards have been established for carbon monoxide:

Long-term exposure (IW 1): 10.0 mg/m³ (9 ppm).

Short-term exposure (IW 2): 30.0 mg/m³ (26 ppm).

Method of measurement: VDI 2455, Sheet 1 (August 1970) and 2455, Sheet 2 guidelines (October 1970).

"Characteristic value I 1 for comparison with IW 1 shall be the arithmetic mean of all individual data for a measurement area. Characteristic value I 2 for comparison with IW 2 shall be the 95% value for the cumulative frequency distribution of all individual values for a measurement area; this may be also calculated with the formula $I\ 2 = \bar{x} + ts$ where $\bar{x}$ is the arithmetic mean of individual data for a measurement area,

$$s = +\sqrt{\frac{2\sum (x - x_i)^2}{2z - 1}},$$

x_i = individual data which are greater than $\bar{x}$, z = number of individual data, which are greater than $\bar{x}$, and $t = 1.64$ for the 95% confidence level."

Source: Federal Minister of the Interior (1974) *Technical Instructions for Maintaining Air Purity, 28 August 1974*, Bonn.

1.3 Japan (1973)

Ambient air quality standards are defined as follows:

(*a*) Average of hourly values in 8 consecutive hours shall not exceed 20 ppm (23 mg/m³).

(*b*) Daily average of hourly values shall not exceed 10 ppm (11 mg/m³).

These standards do not apply to industrial zones, roadways, and other areas or places where people do not usually live.

Source: Environment Agency (1978) *Environmental Laws and Regulations in Japan (II) Air*. Tokyo.

1.4 Union of Soviet Socialist Republics (1971)

Maximum permissible (single exposure) concentration for carbon monoxide is 3 mg/m^3 (2.6 ppm). This concentration should not provoke reflex (i.e., subsensory) reactions in human organisms.

Maximum permissible (24-hour average) concentration for carbon monoxide is 1.0 mg/m^3 (0.9 ppm). This concentration should not have either a direct or indirect harmful effect on man, for unlimited in time, continuous exposure, 24 hours a day.

Method not specified.

Source: Krotov, Ju. A. (1975) *Maximum permissible concentrations of harmful substances in air and water*, Himija, Moscow.

1.5 United States of America (1971)

"The national primary and secondary ambient air quality standards for carbon monoxide, measured by the reference method described in Appendix C to this part, or by an equivalent method, are:

(*a*) 10 milligrams per cubic meter (9 ppm)—maximum 8-hour concentration not to be exceeded more than once per year.

(*b*) 40 milligrams per cubic meter (35 ppm)—maximum 1-hour concentration not to be exceeded more than once per year."

Reference method for the continuous measurement of carbon monoxide in the atmosphere is nondispersive infrared spectrometry.

Source: *Federal Register*, **36** (228), Thursday, November 25, 1971, Washington DC, pp. 22385 and 22391–22392.

1.6 Other Member States

For further information on national ambient air quality standards for carbon monoxide, the reader is referred to W. Martin & A. C. Stern (1974) *The world's air quality management standards*, Washington, DC, US Environmental Protection Agency (EPA-650/a-75-001-a).

2. OCCUPATIONAL EXPOSURE LIMITS

An occupational exposure limit for carbon monoxide of 50 ppm or 55 mg/m^3 has been set in the following Member States: Australia, Belgium, Finland, Federal Republic of Germany, Italy, Japan, Netherlands, Switzerland, the USA, and Yugoslavia.

Bulgaria and the USSR have established a limit of 20 mg/m^3 (17 ppm), Hungary and Poland, 30 mg/m^3 (26 ppm) and Sweden, 40 mg/m^3 (35 ppm). Czechoslovakia's standard includes average and maximum values of 30 mg/m^3 (26 ppm) and 150 mg/m^3 (130 ppm), respectively. Other standards that include both average and maximum values are those of the German Democratic Republic, (35 and 110 mg/m^3) (30 and 96 ppm) and Romania, (30 and 50 mg/m^3) (26 and 44 ppm).

These values should be interpreted in terms of definitions of occupational exposure limits, which may be different in different countries. The reader is referred to the International Labour Office publication: *Occupational Exposure Limits for Airborne Toxic Substances*, Occupational Safety and Health Series 37, ILO, Geneva, 1977. The values given in paragraphs 1 and 2 have been extracted from this publication.

The US National Institute of Occupational Safety and Health (NIOSH, 1972) has recommended environmental exposure limits of 35 ppm (40 mg/m^3) (time weighted average) and 200 ppm (229 mg/m^3) (ceiling) (Summary of NIOSH Recommendations for Occupational Health Standards, July, 1978).