THE EFFECT OF CARBON MONOXIDE ON HUMANS

❖6627

Richard D. Stewart
Department of Environmental Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin 53226

INTRODUCTION

This review critiques the scientific literature reporting the effects of carbon monoxide (CO) upon humans, examining those exposure situations that result in blood saturation of carboxyhemoglobin (COHb) below 18%, saturations which generally do not result in signs or symptoms of overt intoxication. A reappraisal of the CO literature is desirable for several reasons:

1. A recently reported national survey disclosed that 45% of the nonsmoking blood donors in 18 sections of the country, each one of which included metropolitan and rural areas, had COHb saturations greater than 1.5%, which indicated that exposure to CO in excess of that permitted by the quality standards of the Clean Air Act of 1971 was widespread and occurring regularly (1–3). If the air quality standard for CO is judged to be scientifically sound, the decision not to enforce it but to relax the standard because of the national energy crisis could place the health of some citizenry in jeopardy.
2. A series of air quality standards for CO for various civilian populations, industrial operations, and special military groups has been promulgated (Appendix A). In several instances these have been based upon scientific observations currently held to be of questionable validity.
3. The administration of certain drugs has been observed to accelerate the catabolism of hepatic heme, doubling the endogenous CO production (4–6). In certain individuals with compromised cardiovascular systems, such an increase could pose a significant toxic stress.
4. Diseases manifesting increased hemolysis feature elevated COHb saturations that could be toxic to individuals with already compromised cardiovascular systems (7).

This literature review itemizes the expected and unexpected sources of CO, summarizes the basic pathophysiology of the gas, and then scrutinizes the effects of CO on human cognitive performance and cardiovascular system.

EXPECTED AND UNEXPECTED SOURCES OF CARBON MONOXIDE

Humans have always been exposed continuously to small quantities of CO endogenously produced from the normal catabolism of hemoglobin with a minor fraction contributed by the breakdown of nonhemoglobin heme (8, 9). In healthy male subjects at rest, the average rate of endogenous CO production is approximately 0.4 ml/h (10–12 μmol/24 hr/mmole heme). During the progesterone phase of the menstrual cycle, endogenous CO production is approximately double that of the estrogen phase (10, 11). The presence of these small quantities of CO in the blood results in a COHb saturation of 0.4–0.7% and has been considered neither beneficial nor harmful. In patients with hemolytic anemia, COHb saturation may rise to 4–6%.

Most of the exogenous CO is produced from the incomplete oxidation of carbonaceous material. Because complete combustion is seldom attained, varying concentrations of CO can be expected to be produced

Tobacco smokers are the most heavily exposed nonindustrial segment of the population (1–3, 12, 13). The majority of cigarette smokers consuming one pack per day have a COHb of 5–6% saturation during their waking hours. Two- to three-pack-a-day smokers average 7–9% saturation, while heavy cigar consumers may reach peak saturations of 20% (1). The COHb saturation resulting from tobacco smoking is additive to that resulting from other exogenous CO sources in the environment (1, 3). For example, a one-pack-a-day cigarette consumer in Milwaukee would have a COHb saturation of 5.5% when nonsmokers in the same area had 1.2%, compared with a COHb of 6.5% in Chicago when nonsmokers in that city had 2.2% (1, 3).

The major source of CO in the environment is the exhaust of motor vehicles, which accounts for approximately 60% of the total CO emission per year. Exhaust tailpipe CO concentrations range from 0.5–7%, depending upon the year the automobile was manufactured and the state of engine tuning. A lethal CO concentration can be reached in a closed one-car garage in ten minutes. Concentrations of 25 ppm are commonly encountered on expressways in major metropolitan areas during peak traffic periods, and during weather inversions CO concentrations may exceed 100 ppm.

Fuel combustion in stationary sources, industrial processes, and solid waste disposal account for another 20% of the total CO emission. In the home environment improperly vented hot water heaters, furnaces, space heaters, and fireplaces are the usual sources of excessive CO exposure.

One of the most unexpected sources of excessive CO exposure occurs following the use of a paint stripper, whose basic ingredient is methylene chloride (14). Methylene chloride is metabolized to CO (15), and a 3-hr exposure to paint stripper vapors in a well-ventilated room can result in COHb saturations of 8–16% (R. D. Stewart and co-workers, unpublished data).

Drug therapy can increase COHb saturation. Coburn (6) has demonstrated that phenobarbital and diphenylhydantoin induce hepatic heme, and after "induction,"

catabolism of hepatic heme contributes over 50% of the total endogenous carbon monoxide production.

SUMMARY OF PATHOPHYSIOLOGY

Mechanism of Toxic Action

Carbon monoxide is classified as a chemical asphyxiant gas whose toxic action is a direct result of the anoxia produced by a given exposure. The gas rapidly diffuses across the alveolar membrane and is reversibly bound to one of the heme proteins, hemoglobin, in the red blood cells. Since the affinity of hemoglobin for CO is approximately 200–250 times its affinity for oxygen, exposure to a low concentration of CO can result in a clinically significant reduction in the oxygen-carrying capacity of the blood. Furthermore, the presence of COHb shifts the oxyhemoglobin dissociation curve to the left so that tissue oxygen tensions must fall to much lower levels before the remaining oxyhemoglobin can give up its oxygen. Following CO exposure the resultant decrease in the oxygen-carrying capacity of the blood together with the impaired release of oxygen to the tissues results in a greater tissue oxygen deficiency than would be produced by an equivalent reduction in ambient pO_2, or an equivalent reduction in hemoglobin secondary to anemia.

Myoglobin, cytochrome oxidase, cytochrome P-450, and hydroperoxidases are other heme proteins capable of reversibly binding CO, although collectively they account for only 10–15% of the total CO in normal humans.

Absorption and Elimination

Carbon monoxide is rapidly absorbed through the lungs. While many mathematical models that describe the rate of COHb formation have been derived, clinically the most precise is that of Coburn et al, which was developed to describe the endogenous formation of COHb (16). Coburn's equation is graphically displayed in Figure 1. It takes into account such important variables as exposure duration, alveolar ventilation, partial pressure of CO in the inhaled air, blood volume, barometric pressure, diffusivity of the lung for CO, rate of endogenous CO production, average partial pressure of oxygen in lung capillaries, and the exact ratio of the affinity of blood for CO. Superimposed on the theoretical equation are the experimentally obtained data of Stewart et al, which attests to the accuracy of the Coburn-Forster-Kane equation (17).

Of these variables CO concentration and duration of exposure are the most influencial in determining COHb saturation. Figure 2 shows the increase in COHb per liter of air breathed for concentrations of CO up to 35,600 ppm (18). Thus, a brief exposure to a high CO concentration can result in a significantly elevated COHb saturation.

Alveolar ventilation is a major variable in the rate of COHb formation. Forbes has reported that the absorption of CO varies almost in proportion to the rate of ventilation up to minute volumes of 20 liters (19). Above 20 liters the uptake is 10–15% lower than expected from true proportionality.

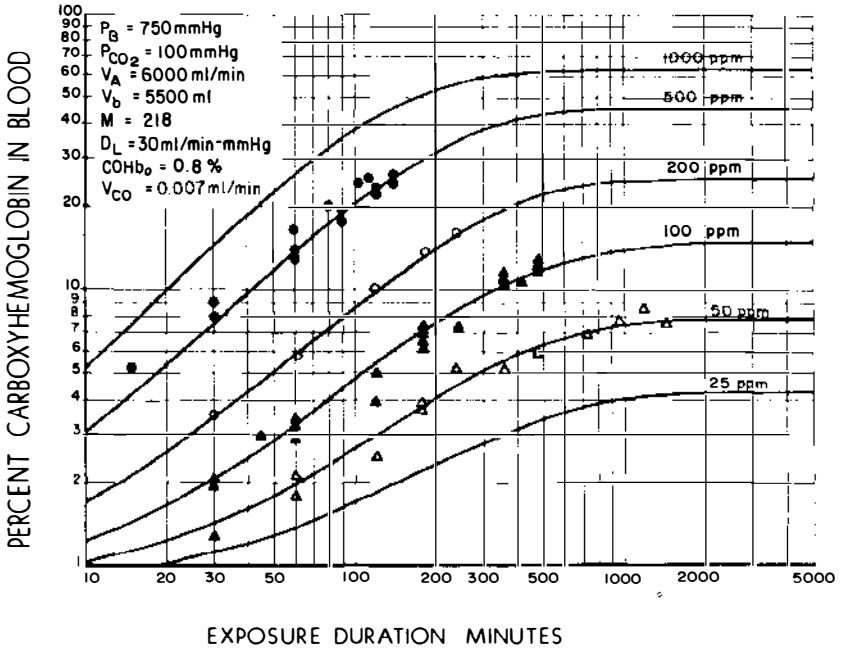

Figure 1 The absorption of carbon monoxide can be predicted using the Coburn-Forster-Kane equation (16). Carboxyhemoglobin saturations obtained during experimental human exposure to CO are superimposed on the theoretical absorption curves. Modified from *Arch. Environ. Health* 21:168, 1970, with permission of the publisher.

The partial pressure of oxygen in the lung capillaries is also a major determinant of COHb saturation. In atmospheres featuring reduced oxygen tensions, higher COHb saturations result.

Table 1 lists the maximum carboxyhemoglobin saturations that can be attained as a result of exposure to a given concentration of CO at sea level with different oxygen tensions.

Most of the CO is eliminated unchanged by the lungs with less than 1% of the gas being oxidized within the body to carbon dioxide. The biological half-life of the gas in healthy sedentary adults at sea level is 4–5 hr. One hundred percent oxygen administered by plastic face mask reduces the biological half-life to approximately 80 min. In the hyperbaric setting the administration of 100% oxygen (20, 21) at 3 atmospheres of pressure (ATA) reduces the biological half-life of the gas to 23.5 min.

Acute Toxicity

The classical signs and symptoms of acute CO poisoning as related to COHb saturation are presented in Table 2. It must be emphasized that these are the anticipated signs and symptoms of intoxication and that exposure to CO concentra-

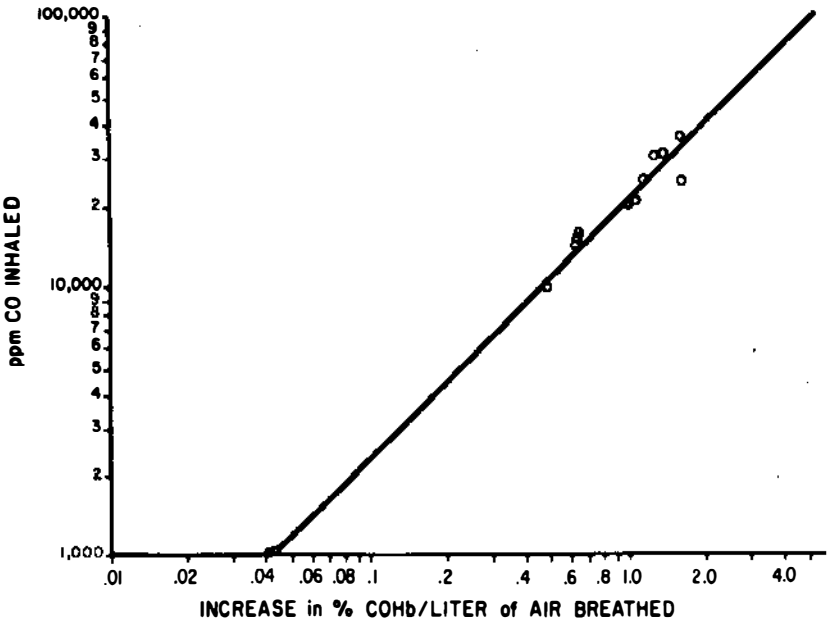

Figure 2 Relationship between CO exposure and increase in peak venous %COHb saturation. The following equation was derived, with use of the "least squares" method: log (Δ%COHb/liter) = 1.036 log (ppm CO inhaled) -4.4793. Reproduced from *Arch. Environ. Health* 26:6, 1973, with permission of the publisher.

tions in excess of 1% (10,000 ppm) can culminate in a loss of consciousness without the classical symptoms of headache, nausea, and vomiting. The following groups of individuals have far greater susceptibility to the toxic effects of the gas: infants, and patients with cardiovascular disease, anemia, lung disease, and increased metabolic rate.

Exposures to concentrations of CO ranging from 200 to 1200 ppm, if sufficiently prolonged, will result in a progression of all of the symptoms listed in Table 2. At COHb saturations of 35%, manual dexterity is imparied. At 40% saturation, mental confusion added to increasing incoordination precludes driving an automobile safely. Carboxyhemoglobin saturation of 67% generally results in death if untreated.

Following recovery from coma, complete recovery without permanent sequelae is the rule providing tissue anoxia has not been too severe. With profound anoxia, CNS residuals, such a impairment of memory, vision, hearing, and speech have been reported (22, 23).

Chronic Toxicity

Controversy exists regarding the potential of repeated exposures to low concentrations of CO to induce disease. It is generally agreed that CO causes anoxemia and therefore produces the same pathology as simple oxygen deprivation. Repeated

Table 1 Carboxyhemoglobin equilibrium at a barometric pressure of 1 atm

ppm CO inhaled	COHb saturation (%) 15% O_2	18% O_2	21% O_2
1	0.62	0.46	0.38
3	1.12	0.83	0.69
5	1.61	1.19	0.99
7	2.09	1.55	1.30
8.7	2.50	1.85	1.55
10	2.81	2.08	1.75
25	6.25	4.68	3.94
30	7.34	5.51	4.65
35	8.41	6.33	5.34
50	11.47	8.71	7.38
70	15.24	11.69	9.96
90	18.71	14.49	12.40
100	20.34	15.83	13.57
300	43.14	35.84	31.81
500	55.80	48.17	43.69
700	63.85	56.53	52.05
900	69.43	62.58	58.25
1000	71.62	65.01	60.78
3000	88.36	84.82	82.30
5000	92.69	90.33	88.58
7000	94.69	92.91	91.58
9000	95.83	94.42	93.33
10,000[a]	96.24	94.96	93.96
30,000	98.76	98.32	97.94
50,000	99.28	99.02	98.78
70,000	99.50	99.32	99.15
90,000	99.63	99.49	99.35

[a] 10,000 ppm = 1%.

acute exposures of sufficient severity to produce permanent tissue damage as a result of anoxia would be additive in their pathological impact upon the exposed individual. Repeated acute exposures to carbon monoxide, none of which resulted in anoxia sufficient to produce permanent injury at the time, would not be anticipated to culminate in a chronic disease state. While neurological and cardiac lesions have been attributed to chronic CO exposure, the majority of the investigators have not reported observing pathological changes at similar or even higher CO concentrations. The only effect of long-term CO exposure agreed upon by the various researchers is the observation that experimental animals exposed for more than 2–3 weeks to CO concentrations at or above 100 ppm show a compensatory increase in red blood cell mass. Cigarette smokers show this compensatory increase and, not too surprisingly, so do nonsmokers in those metropolitan areas with the greatest air pollution (3).

Table 2 Human response to various concentrations of carboxyhemoglobin

Blood saturation COHb (%)	Response of healthy adult[a]	Response of patient ill with severe heart disease
0.3–0.7	Normal range due to endogenous CO production; no known detrimental effect	
1–5	Selective increase in blood flow to certain vital organs to compensate for reduction in oxygen-carrying capacity of the blood	Patient with advanced cardiovascular disease may lack sufficient cardiac reserve to compensate
5–9	Visual light threshold increased	Less exertion required to induce chest pain in patients with angina pectoris
16–20	Headache; visual-evoked response abnormal	May be lethal for patients with severely compromised cardiac function
20–30	Throbbing headache; nausea; fine manual dexterity abnormal	
30–40	Severe headache; nausea and vomiting; syncope	
50–60	Coma; convulsions	
67–70	Lethal if not treated	

[a] Exposure to CO in concentrations in excess of 50,000 ppm can result in a fatal cardiac arrhythmia and death before the carboxyhemoglobin saturation is significantly elevated.

EFFECT OF CO ON COGNITIVE FUNCTION

The question of significant changes in mental function produced by COHb saturation between 2–5% is somewhat controversial at the time of this writing. Complete resolution of the conflicting reports will not be possible until independent research groups using double-blind procedures are able to determine the precise effects of CO upon the human brain.

The most sensitive untoward effect produced by CO is reported to be a gross impairment in the ability to distinguish between short intervals of time and to estimate 30-sec intervals (24, 25). Alarmingly, these decrements in time perception are reported to have been produced by exposures to CO at concentrations as low as 50 ppm for 90 min, exposures commonly encountered by urban populations, and much lower than those experienced by the average adult who smokes one pack of cigarettes per day. The implications of these CO-induced decrements were judged to be of such critical importance that two independent research groups using double-blind procedures investigated time perception in an attempt to corroborate the observations of the original investigators. Neither research group was able to do so (17, 26–29). The issue became more confused when the original investigators announced that they were unable to reproduce their original findings when using a double-blind procedure (30).

Important methodologic differences must be considered when comparing the time perception data reported by the preceding three groups of investigators. Each group performed its investigations in a different manner. The latest studies by Stewart and co-workers (14) most closely simulate the original Beard-Wertheim experiments (24, 25) but very basic procedural differences are still obvious (Table 3) and possibly are responsible for the differences in time perception reported.

The effect of low COHb saturations on other psychomotor and cognitive tasks including arithmetic problem solving, vigilance testing, and driving performance is also controversial (Table 4). Several investigators have reported decrements at low COHb saturations (33–37, 39, 43), while equally competent investigators have failed to corroborate the observations (17, 26–28, 38, 40–42, 44). It does appear that an abrupt elevation of COHb saturation to 5% will transiently alter the visual light threshold (31, 32) while the ability to perform complex tasks requiring both judgment and motor coordination is not affected adversely by COHb saturations below 10% (17, 26–28, 38, 40–42, 44).

Since the human brain has a highly efficient mechanism to compensate quickly for any decrease in oxygen-carrying capacity caused by carbon monoxide (45) it is illogical to postulate that COHb saturations below 5% have the potential to effect psychomotor and cognitive functions solely on the basis of anoxia. Therefore, it is the opinion of the author that the reported decrements in cognitive task performance

Table 3 Comparison of technical procedures used by two laboratories performing time discrimination tests[a]

Procedure experimental protocol	Beard-Wertheim single-blind	Stewart et al double-blind
Chamber carbon monoxide monitoring system	Single, infrared instrument; calibration standards not run from within chamber; CO concentration mean and standard deviation not reported	Three independent monitoring systems; calibration standards run every hour from within the chamber; CO concentration mean and standard deviation reported
Carboxyhemoglobin determinations	Blood obtained, results not reported; COHb estimated from breath samples in one of two studies	Hourly COHb determinations made by two independent methods
Test populations	Stanford University students	Marquette University graduate students and medical school faculty
Test setting	Audiometric booth	Three settings; audiometric booth, subject isolated in large room, subjects tested in small groups

[a]Reproduced with permission of the publisher from *Arch. Environ. Health* 27:159, 1973.

Table 4 Effects of experimental carbon monoxide exposure on humans

CO Conc. (ppm)	Duration	Effects	Comments	Investigators Year (Ref.)
		Time Perception and Psychomotor		
0, 50, 100, 175, 250	4 hr	At estimated COHb 2.5% sound duration discrimination decrement noted. No subjective effects	Single blind. 18 subjects; each isolated in audiometric booth during test. First effect noted after 90 min exposure to 50 ppm; proportionately shorter times required for higher CO concentrations. COHb *not* measured	Beard & Wertheim 1967 (24)
[redacted], 100, 250	4 hr	At estimated COHb 2.5% significant overestimation of 30 sec time interval *and* sound duration discrimination decrement	Single blind. 7 subjects. Same conditions and conclusions as above. COHb *not* measured	Beard & Wertheim 1969 (25)
0, 50, 125, 200, 250	3 hr	*No decrement* in estimating 10 sec interval or in psychomotor battery	Double blind for concentrations < 200 ppm. 10 subjects; each isolated in Thomas Dome during test. COHb measured	Mikulka et al 1970 (26)
< 1, 25, 50, 100, 200, 500, 1000	30 min to 24 hr	*No decrement* in estimating 1, 3, or 5 sec sound or light stimuli. Normal psychomotor battery	Double blind for concentrations < 500 ppm. 18 subjects; Tested in *group* setting in 20′ × 20′ × 8′ environmental chamber. COHb measured	Stewart et al 1970 (17)
0, 50, 125	3 hr	*No decrement* in estimating 10 sec interval. Normal psychomotor battery	Double blind. 9 subjects; each isolated in Thomas Dome during test. COHb measured	O'Donnell et al 1971 (27)

Table 4 Continued

CO Conc. (ppm)	Duration	Effects	Comments	Investigators Year (Ref.)
0, 75, 150	9 hr	*No decrement* in estimating 10 sec or 30 sec time interval or performing Beard-Wertheim time discrimination test. Normal psychomotor battery	Double blind. 4 subjects; each isolated in Thomas Dome during test. COHb measured.	O'Donnell et al 1971 (28)
< 2, 50, 100, 200, 500	2.5–5 hr	*No decrement* in estimating 10 sec or 30 sec time interval or performing Beard-Wertheim time discrimination test	Double blind. 27 subjects; tested in audiometric booth, isolated in large environmental chamber, and in group setting. COHb measured	Stewart et al 1973 (29)
		Visual Threshold		
Not stated	Not stated	Visual threshold decrement at 5% COHb	COHb saturations of 5–20%	McFarland et al 1944 (31)
1×10^6 (100–300 ml)	10–15 min	Visual disturbance at 4.5% COHb (statistical validity in doubt)	COHb saturations up to 20%	Halperin et al 1959 (32)
		Miscellaneous Cognitive Tests		
0, 100	Varied	*Decrement* in arithmetic performance and in multiple cognitive tasks at 5% COHb	Single blind. 49 subjects. Reported COHb saturations up to 20%, hence analytical method suspect	Schulte 1963 (33)
0, 100	8 hr	*Decrement* in performance of an extensive battery of psychological tests while COHb at 7%	42 subjects of both sexes	Bender et al 1971 (34)
0, 50, 100, 150	110 min	Decrement in auditory vigilance test at 50 ppm	20 subjects of both sexes	Groll-Knapp et al 1972 (35)

Table 4 Continued

CO Conc. (ppm)	Duration	Effects	Comments	Investigators Year (Ref.)
0, 50	5 hr	*Decrement* in auditory vigilance test after 89 min of exposure. Normal ability to perform test regained after 35 min of testing. Normal psychomotor test performance immediately following exposure	12 subjects of both sexes	Fodor & Winneke (36)
0, 26, 111	135–140 min	*Decrement* in vigilance test at 6.6% COHb. Normal vigilance performance at 2.3% COHb	Single blind. 10 subjects	Horvath 1971 (37)
0, 100	4 hr	Normal performance on critical tracking task and visual pursuit task	Studied untrained subjects	Hanks 1970 (38)
< 100	8 hr Occupational	Increased headache and general debility observed in exposed group. EEGs showed flat, low voltage with scanty alpha rhythm	Mean COHb in exposed group was 7%. Mean COHb in control group was 3%	Grudzinska 1963 (39)
< 1, 25, 50, 100, 200, 500, 1000	30 min to 24 hr	Changes in visual evoked response at COHb > 20%. No gross alteration in spontaneous EEG at COHb saturations up to 33%	Part of Stewart et al study	Hosko 1970 (40)
		Driving		
960-1,060	58–76 min	Normal driving performance with COHb 25.1–30.4%		Forbes 1937 (41)
1,1	45–65 min	Marked *decrement* in performance at COHb > 30%		Forbes 1937 (41)

Table 4 Continued

CO Conc. (ppm)	Duration	Effects	Comments	Investigators Year (Ref.)
Not stated	Not stated	*Decrement* in driving performance with COHb > 10%	Effect of COHb saturations of 0, 10, and 20% evaluated	Ray & Rockwell 1970 (42)
1×10^6 (80 ml)	Not stated	*Decrement* in driving skills at 3.4% COHb	50 subjects	Wright et al 1973 (43)
0, 700	Up to 1 hr to achieve desired COHb	*Decrement* in ability to drive at COHb saturations of 11 and 17%. Normal driving performance at 6% COHb	Well-controlled experiment	McFarland 1973 (44)

observed in subjects with COHb saturations of less than 5% must be considered suspect until verified by an independent investigator using a proper experimental method.

EFFECTS OF CO ON CARDIOVASCULAR FUNCTION

Each molecule of CO entering the body through the lungs combines with hemoglobin, reducing the oxygen-carrying capacity of the blood and exerting a finite stress on the organism. Thus, the situation exists where there is no dose of CO that is not without an effect on the body. The body compensates for this anoxic stress by increasing cardiac output or by increasing blood flow to a specific organ, such as the brain. When this ability to compensate is overpowered or is limited by disease, tissue anoxia results.

The effects of CO on myocardial function in healthy adults, patients with coronary artery heart disease, and patients with noncoronary heart disease have been examined by Ayers, who reported that rapidly increasing COHb saturation of 9% over 30–120 sec in patients with no evidence of coronary heart disease resulted in increased coronary blood flow, increased oxygen extraction ratio by the myocardium, and an insignificant decrease in coronary sinus oxygen tension (46). In patients with coronary heart disease the rapid increase in COHb did not result in a significant increase in coronary blood flow. While the oxygen extraction ratio by the myocardium was increased, the coronary sinus tension decreased significantly and significant decreases in the lactate extraction ratio and the pyruvate extraction ratio were observed. Ayers concluded that a potentially serious state could result from the inhalation of CO by a patient with coronary heart disease incapable of responding to the anoxic stress by increasing coronary blood flow.

Two other groups of investigators have proved Ayers prediction to be correct (46–49). These investigators have convincingly demonstrated that patients with advanced coronary artery disease and angina pectoris have their exercise tolerance significantly decreased following exposure to low concentrations of CO sufficient to increase their COHb saturation to 5%.

This author would carry the interpretation of these data one step farther than did the investigators by suggesting that there is *no* concentration of CO that does not exert a significant and measurable untoward effect upon a diseased cardiovascular system. Those individuals with significant coronary heart disease will be stressed by any exposure to this ubiquitous gas, which could adversely affect the natural course of their disease. (50).

In summary, it is apparent that the primary effect of CO on humans results from the anoxic stress secondary to the reduction in the oxygen-carrying capacity of blood. Healthy humans are exquisitely sensitive to any anoxic stress, immediately compensating by increasing cardiac output and flow to critical organs. Humans with significant cardiovascular disease may not be able to compensate adequately and are rendered more vulnerable to the toxic effect of CO.

Appendix A Carbon monoxide air standards

Standard	Source	Comments
	Nonindustrial populations	
8.7 ppm, 8 hr	Ambient air (1)	Not to be exceeded more than once per year
35 ppm, 1 hr	Ambient air (1)	Not to be exceeded more than once per year
30 ppm, 8 hr	Ambient air (2)	"Warning" level for ambient air
40 ppm, 8 hr	Ambient air (2)	"Emergency" level for ambient air
125 ppm, 1 hr 75 ppm, 4 hr 50 ppm, 8 hr	Ambient air (2)	"Significant" harm to health levels for ambient air
	Occupational populations	
50 ppm, 8 hr	OSHA (3)	8 hr time weighted average
50 ppm, 8 hr	Threshold limit value (4)	Allowable limit in workroom air. Based on an air concentration that should not result in blood CO levels above 10%
1000 ppm, 10 min	Pennsylvania short-term limits (5)	Maximum allowable levels in workroom. Assumes no CO in blood at beginning of exposure and a maximum allowable COHb of 14%. Excursions should not exceed two per work shift
90 ppm, 10 min 35 ppm, 30 min 25 ppm, 60 min 15 ppm, 4–5 hr/day 3–4 days/mo.	Short-term public limits (6)	Exposures occurring at predictable times and arising from single or occasionally repeated events
275 ppm, 10 min 100 ppm, 30 min 60 ppm, 60 min	Public emergency limits (6)	Exposures occurring at unpredictable times and places as the result of fire or accident. Temporary illness may occur.

References

1. Environmental Protection Agency. National primary and secondary ambient air quality standards. April 30, 1971. *Federal Register* 36(84):8186–8201
2. Environmental Protection Agency. Title 42, Chapter IV, miscellaneous amendments. October 23, 1971. *Federal Register* 36(206):20513
3. Department of Labor. Occupational Safety and Health Standards, miscellaneous amendments. August 13, 1971. *Federal Register* 36(157):15102
4. *Documentation of the Threshold Limit Values for Substances in Workroom Air.* 1971. Cincinnati, Ohio: Am. Conf. Govern. Ind. Hygienists. 3rd ed.
5. *Short-Term Limits for Exposure to Airborne Contaminants: A Documentation.* 1972. Pennsylvania Dept. Health, Harrisburg, Pa.
6. *Guides for Short-Term Exposures of the Public to Air Pollutants VI. Guide for Carbon Monoxide.* 1972. Washington DC: Committee on Toxicology, National Academy of Sciences, National Research Council

Literature Cited

1. Stewart, R. D. et al 1973. National Clearinghouse for Federal and Technical Information NTIS Report No. PB 22503, Springfield, Va.
2. Stewart, R. D. et al 1973. *Science* 182:1362–64
3. Stewart, R. D. et al 1974. *J. Am. Med. Assoc.* 229:1187–95
4. Schmid, R., Marver, H. S., Hammaker, L. 1966. *Biochem. Biophys. Res. Commun.* 24:319–28
5. Coburn, R. F. 1967. *J. Clin. Invest.* 46:1046
6. Coburn, R. F. 1970. *N. Engl. J. Med.* 283:512–15
7. Coburn, R. F., Williams, W. J., Forster, R. E. 1964. *J. Clin. Invest.* 43:1098–1103
8. Sjostrand, T. 1949. *Acta Physiol. Scand.* 16:211–31
9. Coburn, R. F., Blakemore, W. S., Forster, R. E. 1963. *J. Clin. Invest.* 42:1172–78
10. Delivoria-Papadopoulos, M., Coburn, R. F., Forster, R. E. 1970. *Physiologist* 13:178
11. Lynch, S. R., Moede, A. L. 1972. *J. Lab. Clin. Med.* 79:85–95
12. Cohen, S. I. et al 1971. *Arch. Environ. Health* 22:55–60
13. Public Health Service. 1968. *The Health Consequences of Smoking: A Public Health Service Review, 1967.* Washington DC: US PHS
14. Stewart, R. D. et al 1972. *Arch. Environ. Health* 25:342–48
15. Kubic, M. W. 1974. *Drug Metab. Disposition* 2:53–57
16. Coburn, R. F., Forster, R. E., Kane, P. B. 1965. *J. Clin. Invest.* 44:1899–1910
17. Stewart, R. D. et al 1970. *Arch. Environ. Health* 21:154–64
18. Stewart, R. D. et al 1973. *Arch. Environ. Health* 26:1–7
19. Forbes, W. H., Sargent, F., Roughton, F. J. W. 1945. *Am. J. Physiol.* 143:594–608
20. Pace, N., Strajman, E., Walker, E. L. 1950. *Science* 111:652–54
21. Peterson, J. E., Stewart, R. D. 1970. *Arch. Environ. Health* 21:165–71
22. Dutra, F. R. 1952. *Am. J. Clin. Pathol.* 22:925–35
23. Plum, F., Posner, J. B., Hain, R. F. 1962. *Arch. Intern. Med.* 10:56–63
24. Beard, R. R., Wertheim, G. A. 1967. *Am. J. Pub. Health* 57:2012–22
25. Beard, R. R., Wertheim, G. A. 1969. *Behavioral Manifestations of Carbon Monoxide Absorption.* Presented at 16th Int. Congr. Occupational Health, Tokyo
26. Mikulka, P. J. et al 1970. *Ann. NY Acad. Sci.* 174:409–20
27. O'Donnell, R. D. et al 1971. *Toxicol. Appl. Pharmacol.* 18:593–602
28. O'Donnell, R. D., Chirkos, P., Theodore, J. 1971. *J. Appl. Physiol.* 31: 513–18
29. Stewart, R. D. et al 1973. *Arch. Environ. Health* 27:155–60
30. Beard, R. R. First Annual Conference on Environmental Toxicology, September 9–11, 1970. Statement made during the discussion of his paper
31. McFarland, R. A. 1944. *J. Aviat. Med.* 15:381–94
32. Halperin, M. H. 1959. *J. Physiol.* 146:583–93
33. Schulte, J. H. 1963. *Arch. Environ. Health* 7:524–30
34. Bender, W. et al 1971. *Arch. Toxikol.* 27:142–58
35. Groll-Knapp, E. et al 1972. *VDI Berichte* 180:116–20
36. Fodor, B., Winneke, R. 1972. *VDI Berichte* 180:98–106
37. Horvath, S. M., Dahms, T. E., O'Hanlon, J. F. 1971. *Arch. Environ. Health* 23:343–47
38. Hanks, T. G. 1970. *Ann. NY Acad. Sci.* 174:421
39. Grudzinska, B. 1963. *Folia Med. Cracov.* 3:493–515
40. Hosko, M. J. 1970. *Arch. Environ. Health* 21:174–80
41. Forbes, W. H. 1937. *J. Ind. Hyg. Toxicol.* 19:598–603
42. Ray, A. M., Rockwell, T. H. 1970. *Ann. NY Acad. Sci.* 174:396–408
43. Wright, G., Randell, P., Shephard, R. J. 1973. *Arch. Environ. Health* 27:349–54
44. McFarland, R. A. 1973. *Arch. Environ. Health* 27:355–59
45. Paulson, O. B. et al 1973. *J. Appl. Physiol.* 35:111–16
46. Ayers, S. M., Giannelli, S. J., Mueller, H. 1970. *Ann. NY Acad. Sci.* 174: 268–93
47. Aronow, W. S. et al 1972. *Ann. Intern. Med.* 77:669–76
48. Aronow, W. S., Isbell, M. W. 1973. *Ann. Intern. Med.* 79:392–95
49. Anderson, E. W. et al 1973. *Ann. Intern. Med.* 79:46–50
50. Scharf, S. M., Thames, M. D., Sargent, R. K. 1974. *N. Engl. J. Med.* 291:85–86