PB-244 338

GUIDES FOR SHORT-TERM EXPOSURES OF THE PUBLIC TO AIR POLLUTANTS. VI. GUIDE FOR CARBON MONOXIDE

National Research Council

Prepared for:

Environmental Protection Agency

March 1973

NAS/ACT/P-628.7

Guides for Short-Term Exposures of the Public to Air Pollutants

VI. Guide for Carbon Monoxide

by

The Committee on Toxicology
of the
National Academy of Sciences - National Research Council

Washington, D. C.

March 1973

BIBLIOGRAPHIC DATA SHEET	1. Report No. NAS/ACT/P-628.7	2.	PB 244 338

4. Title and Subtitle
Guides for Short-Term Exposures of the Public to Air Pollutants. Vi. Guide for Carbon Monoxide.

5. Report Date
March 1973

6.

7. Author(s)

8. Performing Organization Rept. No. NAS/ACT/P-628.7

9. Performing Organization Name and Address
Committee on Toxicology of the National Academy of Sciences
National Research Council
2101 Constitution Avenue, N.W.
Washington, DC 20418

10. Project/Task/Work Unit No.

11. Contract/Grant No.
CPA 70-57

12. Sponsoring Organization Name and Address
Environmental Protection Agency
4th and M Streets, S.W.
Washington, D.C. 20460

13. Type of Report & Period Covered
Final

14.

15. Supplementary Notes

16. Abstracts

Recommendations are made for limits of air concentrations of carbon monoxide to which the public may safely be exposed for short periods of time. The scientific basis and associated literature references for the recommendations are presented.

17. Key Words and Document Analysis. 17a. Descriptors

Air Pollution
Exposure
Sensitivity
Toxicity
Carbon monoxide

17b. Identifiers/Open-Ended Terms

Air pollution effects (animals)
Air pollution effects (humans)
Short-Term Public Limits (STPL's)
Public Emergency Limits (PEL's)

17c. COSATI Field/Group 13B

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
Release unlimited	UNCLASSIFIED	
	20. Security Class (This Page) UNCLASSIFIED	

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Prepared under Contract No. CPA 70-57
between the the National Academy of Sciences
and the Environment Protection Agency.

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The members of the committee selected to undertake this project and prepare this report were chosen for recognized scholarly competence and with due consideration for the balance of disciplines appropriate to the project. Responsibility for the detailed aspects of this report rests with that committee.

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INTRODUCTION

The Environmental Protection Agency has focused its initial concerns on long-term exposures of the public to air pollutants. Although long-term exposures generally involve exposure to low levels of air pollutants there are occasional circumstances wherein the public may be exposed briefly to relatively high concentrations. For example, batch-process techniques in industries may result in pulses of effluent. The testing and launching of rockets release high concentrations of exhaust products. Rapidly changing meteorological conditions may result in short periods of locally high concentrations of stack effluents. Accidental release of chemicals sometimes occurs in industrial areas or during transport, and may lead to public exposure.

Recognizing that these occasional peak additions to the ambient exposures of the public do occur, the Environmental Protection Agency has requested the assistance of the Committee on Toxicology of the National Academy of Sciences - National Research Council in providing Guides for short-term exposure limits for air pollutants.

In preparing these Guides, the Committee utilized the criteria described in the NAS-NRC document entitled "Basis for Establishing Guides for Short-Term Exposures of the Public to Air Pollutants" (41). Primary consideration was given to literature dealing with single or intermittent brief exposures to the contaminant in question, in this case carbon monoxide.

GENERAL BACKGROUND

Physical-Chemical Properties

Carbon monoxide (CO) is a colorless odorless gas possessing the following physical properties:

Molecular weight: 28
Melting point: -207° C
Boiling point: -190° C
Density (25° C, 760 mm Hg): 1.15 g/l

At 25° C and 760 mm Hg, 1 part of CO per million parts of air (ppm) is equivalent to 1.15 mg of CO per cubic meter of air (mg/m^3).

Sources

Carbon monoxide is produced by the incomplete combustion of carbonaceous materials. A flame in the presence of a sufficient air supply and at temperatures at or above the ignition temperature of the gaseous part of the flame should produce insignificant amounts of CO. Because complete combustion is difficult to attain, varying levels of CO can be expected to form in most combustion processes.

The major man-made source of CO in the environment is the exhaust of motor vehicles, accounting for approximately 60% of the total CO emissions per year. Industrial processes, solid-waste disposal and fuel combustion in stationary sources account for approximately 20% of the total CO emissions while miscellaneous sources account for the remainder of the total emissions (10).

CARBON MONOXIDE AND THE LIVING ORGANISM

Production and Distribution of Carbon Monoxide in Mammals

The first demonstration of small amounts of CO in the blood of experimental animals and humans has been attributed to French scientists (1). The endogenous production of CO is primarily the result of the catabolism of the heme moiety of hemoglobin, although the metabolism of other heme-containing proteins would also be expected to produce CO (2).

Regardless of its source (endogenous or exogenous) CO in the organism is found chemically bound to heme proteins, primarily hemoglobin. Myoglobin, cytochrome oxidase, cytochrome P-450, and hydroperoxidases are other hemoproteins capable of reversibly binding CO although collectively they account for only 10-15% of extravascular CO in

normal man (3, 4). Coburn has reported that under the conditions whereby arterial partial pressures of oxygen (pO_2) are below 40 mm Hg, CO will shift into muscle tissue to bind with myoglobin to yield carboxymyoglobin levels about three times greater than found at ambient arterial pO_2 (4). The full significance of the carboxymyoglobin complex is not known, and may be important in regard to myocardial oxygen exchange (5).

Carbon monoxide binds reversibly with hemoglobin (Hb) forming carboxyhemoglobin (Co Hb). The affinity of Hb for CO is approximately 200-250 times its affinity for oxygen. CO Hb is incapable of carrying oxygen, so that the effect is a reduction of the tissue partial pressure of oxygen. An additional effect is that when CO Hb is present the dissociation of the remaining oxyhemoglobin (HbO_2) is altered in the direction of impairment of release of O_2 to the tissues. The decrease in oxygen-carrying capacity of the blood together with the impaired release of oxygen to the tissues results in a greater tissue oxygen deficiency than is produced by an equivalent reduction in ambient pO_2 (as at altitude) or an equivalent reduction of hemoglobin (as in anemia) (3, 6).

Factors Affecting the Rate of Carboxyhemoglobin Formation

The uptake of CO in the blood is dependent on a number of physiological parameters such as endogenous production of CO, activity (alveolar ventilation) of the exposed individual, and duration of exposure. Although a number of mathematical models have been reported to describe the rate of COHb formation in persons exposed under specific conditions (7, 8) Coburn et al. (56) developed a mathematical model that can be generally applied to consider nine variables that can influence the rate of COHb formation. Appendix 1 contains a representation of the "Coburn equation" applicable to exposure conditions at sea level (760 mmHg).

At equilibrium, when a subject is breathing atmospheric air containing CO at concentrations < 100 ppm, the level of COHb above background has been expressed by the following formula:

% COHb = 0.16 x [CO], the CO concentration being expressed as ppm (8).

According to Forbes (9) the uptake of CO will vary almost in proportion to the rate of ventilation up to minute volumes of 20 liters. Above 20 liters the uptake will be 10 to 15% less than expected from true proportionality. Individual variation among apparently normal, healthy, young adults was about 25% between the fastest absorber and the slowest. These differences, apparently due to differences in dead space and diffusion coefficients, can be greater in pathological conditions.

Goldsmith (8) reports ventilation to be six liters per minute at rest and 18 liters per minute during light work with a somewhat less than three-fold increase in the rate of uptake of CO observed with the three-fold increase in ventilation during light work.

Effects on Animals (Long-Term)

Although the primary concern, for the purposes of this document, is short-term exposures to carbon monoxide, a brief consideration of the long-term exposure effects is important for comparative purposes.

Stupfel and Bonley (12) exposed rats at concentrations of 50 ppm continuously for 4-1/2 days/week, 95 hr/week, for periods ranging from 30 days to 2 years. Some of the observations made on the animals include CO_2 emission, ECG, conditioned behavior, and a variety of biochemical, hematological, bacteriological, and immunological tests. During the first three months of exposure the following functions were not altered: fecundity, reproduction, growth, CO_2 emission, weight of organs, water percentages of organs, hemoglobin, serum protein, lipids, calcium, magnesium, transaminases, hematological data, bacteriological and immunological parameters. Blood cholesterol levels, heart rate, ECG tracings, and avoidance conditioning appeared to be slightly altered at the beginning of exposure. Mortality and aging processes were not altered during the two-year study. Essentially similar findings over a two-year period were recently reported in cynomolgus monkeys (57).

Jones et al. (13) exposed rats, guinea pigs, dogs, and monkeys to 51 ppm CO for 90 days continuously and reported no significant changes in the hematocrit or hemoglobin concentration in any of the species. At CO concentrations of 96 and 200 ppm for 90 days, the hematocrit and hemoglobin were significantly elevated in rats, guinea pigs, and monkeys. Repeated 8 hr/day, 5 days/wk, 6 wks exposure of the same species of animals to a CO concentration of 106 ppm caused a significant increase in hemoglobin and hematocrit in rats only.

Vernot et al. (14) exposed rhesus monkeys continuously for 100 days to a concentration of 57.5 mg/m^3 CO and rhesus monkeys and beagle dogs to CO concentrations of 115, 230, 460, and 575 mg/m^3 continuously for 77 to 182 days. The barometric pressure was maintained at 260 mm Hg with an atmosphere of 68% O_2 and 32% N_2. They observed an increase in red blood cell counts, hemoglobin, and hematocrit that at equilibrium appeared to be a linear function of the CO concentration. In the dogs the red blood cell counts increased 44%, the hemoglobin 41%, and the hematocrit 38% over controls during exposure to 575 mg/m^3 CO. In the exposed monkeys the respective increases were 60%, 58%, and 59%. The polycythemia was normocytic and normochromic. Total blood volume increased in both species while plasma volume remained constant. Equilibrium COHb levels in the monkeys were 12, 21.3, 31.6, and 38.5 respective to the four exposure levels. The COHb levels in the dogs were comparable.

Back (15) conducted an experiment on monkeys exposed continuously to CO at a concentration of 220 mg/m^3 for 103 days under conditions similar to those reported by Vernot (260 mm Hg, 68% O_2, 32% N_2). The monkeys, however, were trained to perform discrete avoidance tasks by both visual and audio cues. Under these conditions COHb was reported to plateau at 22% with increases in hematocrit and hemoglobin similar to those observed by Vernot. Back reported no detectable performance changes in any of the monkeys tested.

MacKenzie et al. (16) and Theodore et al. (17) exposed mice, rats, dogs, baboons, and rhesus monkeys to CO at a concentration of 460 mg/m^3 for 71 days followed by exposure to a CO concentration of 575 mg/m^3 for 97 days (in conjunction with and under the conditions of the Vernot experiment). Although at the 460 mg/m^3 exposure level the COHb level was 32% in the monkeys and 33% in the dogs and, at the 575 mg/m^3 level, the COHb levels were 38% and 39% in monkeys and dogs respectively, the only significant finding was a "marked erythrocytosis" in the experimental animals. Animal survivability, growth rates, clinical chemistry, and pathology were not apparently different from the control animals (17). Anatomic changes found were confined to rodents and consisted of an increase in heart and spleen weight. The authors explain this is due to increased red blood cell volume and blood viscosity (16).

Preziosi et al. (18) reported ECG changes in dogs exposed to CO concentrations of 50 and 100 ppm for 6 hr/day, 5 days/wk for 6 weeks, or continuously for 6 weeks. At autopsy the most frequent finding was dilation of the right heart or thinning of the myocardial wall and flattening of the papillary muscles and trabeculae. He observed dilation of the ventricular system of the brain, particularly of the lateral ventricles in 50% of the animals exposed continuously to CO concentrations of 50 ppm. A similar finding was observed in the animals exposed at 100 ppm either continuously or intermittently. Histological examination revealed mobilization of glial cells and thinning of the white matter in the centrum semiovale in the brain. Heart histology reportedly revealed old scarrings in some cases and fatty degeneration of the heart muscles in others. The blood cytology, hemoglobin, and hematocrit showed no deviation from the control animals.

Summary of Long-Term Exposures

Animals exposed for more than 2-3 weeks to CO concentrations greater than 100 ppm show an increase in red blood cell count, hematocrit, and hemoglobin. Evidently these hematologic changes are the only effects of long-term CO exposures agreed upon by the various researchers. While neural and cardiac lesions or changes are reported by some, others have not reported observing such changes at similar or even higher CO exposure levels.

Short-Term and Repeated Exposure Effects on Animals

Beard and Wertheim (19) exposed rats to CO concentrations of 100, 250, 500, 750, and 1,000 ppm for time periods up to 48 minutes and reported the effects of such exposures on the performance of Skinnerian operant behavior schedules of reinforcement. For a fixed interval (30 sec) reinforcement test, perceptible effects due to CO were reported by the authors to be observed at 100 ppm CO after 11 minutes of exposure. Increasing concentrations produced proportionately greater effects.

Montgomery and Rubin (20) exposed rats to CO concentrations ranging from 250 ppm to 3,000 ppm for 90 minutes and then challenged the animals with hexobarbital or zoxazolamine in order to measure the rate of recovery from the effects of these drugs by the CO-pre-exposed animal. Prolongation of pharmacologic response to hexobarbital and zoxazolamine was observed when the pre-exposure CO concentration was 1,000 ppm and 250 ppm respectively. The authors report that these data do not allow a conclusion to be made regarding the mechanism involved since the duration of response to these drugs is known to be influenced both by alteration of the microsomal drug-metabolizing system and by tissue hypoxia.

Mazaleski et al. (21) exposed rats to CO at 50 ppm for 5 hr/day, 5 days/wk for 12 weeks and measured the concentrations of zinc, copper, cobalt, iron, and magnesium in various liver fractions prepared from the exposed and control animals. The authors report significant variations in all the metals, measured at 3-wk intervals; however, only the cobalt content of the nuclear fraction of the liver of the exposed animals was consistent and significantly lower than controls over the 12-wk exposure period. The authors state that their results suggest that chronic exposure to 50 ppm CO produces an effect on trace metals at the sub-cellular level with a possible reduction in cellular respiration and nucleoprotein synthesis.

Xintaras et al. (22) exposed rats to concentrations of CO over the range of 50 - 1,000 ppm for periods of 1-2 hr. The animals were conditioned to respond to a light stimulus by pressing a lever. Recording electrodes, for EEG recording from the visual cortex and superior colliculus, were used to observe any neurological changes in the exposed animals. No effects attributable to CO exposure were obtained in regard to the conditioned response; however, progressive dose-related changes were observed in the electrical recordings from the cortical and collicular areas of the brain. Similar changes were induced by pentobarbital.

Astrup et al. (23) reported increases in the cholestrol content of the aorta of cholesterol-fed rabbits exposed for 8 hr/day for 10 weeks to concentrations of CO causing 20% COHb (~170 ppm). The exposed animals had as much as five times the aortic cholesterol concentration as was observed in the control animals. Exposing cholesterol-fed rabbits to an atmosphere containing 10% O_2 (hypoxia) for 8 weeks resulted in aortic levels of cholesterol 3.5 times higher than those found in the control animals. An atmosphere of 28% O_2 (hyperoxia) produced an aortic cholesterol concentration of one-half that observed in the control animals. The authors report that both microscopically and macroscopically there was no difference between the arterial lesions in animals exposed to CO and the animals exposed to hypoxia.

Preziosi et al. (18) exposed dogs to CO at concentrations ranging from 1,280 ppm to 17,000 ppm for time periods ranging from "less than 15 minutes" to "60 minutes or more". The sequence of physiological changes observed by the authors in dogs having 40-50% COHb was depressed respiration, rise in cerebrospinal fluid pressure, rise in venous pressure, a secondary rise in cerebrospinal fluid pressure, a rapid irregular respiration, and a decrease in arterial pressure. Electrocardiographic changes included depression of R wave, elevation of ST segment, occasional increases in the T wave, deepening of the Q and S wave, and partial heart block with premature ventricular contractions "at the height of exposure". The authors exposed "control" dogs to hypoxic conditions in order to simulate the O_2-deficient conditions of the CO-exposed animals. These "controls" exhibited changes identical in kind but less in degree than the CO-exposed group.

Estler et al. (24) exposed mice on either a single 4-hr occasion or on repeated occasions (9 hr/day for 35 times in 7 weeks) to a CO concentration of 1,000 ppm. The animals were examined for changes in brain glycogen, pyruvate lactate, ATP, phosphocreatine, and blood glucose concentration. They reported increased pyruvate levels in the brain and a decrease in blood-glucose levels following the 4-hr exposure period. Brain pyruvate and lactate were increased. Blood glucose and brain phosphocreatine were decreased. The COHb levels were reported to be 35% for the single 4-hr acute exposure and 35% after a 9-hr exposure, which terminated the 7-week study.

It is important to note that the COHb levels reported by Estler et al. are unusually low. Rose (25) reported that exposure to CO concentrations of 2,070 mg/m^3(1,882 ppm) for 4 hours was the LC_{50} in rats, and the COHb levels had a mean of 57.5%. Astrup (23) found COHb levels in rabbits to be about 20% after exposure to CO at 170 ppm.

Stupfel et al. (26) observed sex-related differences in the mortality of rats and mice exposed to lethal doses of CO. For male and female mice

exposed to CO at levels of 3,300 ppm for 35 minutes at 13° C the lethality was 32% (16/50) in the males and 0% (0/50) in the females. For a 25-minute exposure to the same concentration of CO at 20°C the lethality was 89% for males and 39% for females. Similar significant sex-related susceptibility was also observed in rats exposed under similar conditions.

Castrated male mice were significantly less susceptible to CO lethality than normal males (31% dead and 80% dead respectively), although the castrated male deaths were still significantly greater than female deaths (9.6%) and castrated female deaths (13%). The difference between normal female deaths and castrated female deaths was not significant.

Effects on Humans

The effects of CO on human function, and indeed on animal function generally, can be classified into two main categories. The first of these is the effect of CO on the oxygen-carrying function of the blood, and any hemodynamic changes associated with alterations of this function. The second classification, the effects of CO on psychomotor functions, will be considered separately for ease of discussion. It is not at this time known whether the neurological effects of CO are entirely secondary to 0_2 deprivation of the nervous system.

Permutt and Farhi (27) have discussed some of the physiological changes that would be expected from a COHb level of approximately 9% (expected from prolonged exposure to CO at 70 ppm). Assuming no changes in blood flow, Hb concentration, or alveolar ventilation, a COHb of 9% could be expected to cause a decrease in venous pO_2 of 4-6 mm Hg, which would represent a percentage change of 8-40% depending on the magnitude of arteriovenous (A-V) 0_2 differences. The authors state that to achieve similar effects without CO the blood flow would have to be lowered by 13-37% or hemoglobin concentration reduced by a similar percentage.

The effects of the decreased oxygen-carrying capacity of the blood together with the relative impairment of oxygen delivery to the tissues caused by COHb may be manifest most markedly in the coronary circulation and myocardial oxygen extraction. In the sedentary man, peripheral tissues extract about 25% of the oxygen present in arterial blood. The remaining 75% serves as a reserve supply. In heavy exercise the tissue uptake can result in an increased extraction of oxygen from the perfusing blood (from the 75% reserve) and an increase in blood flow through the tissue (5, 27). The coronary circulation differs significantly from this aforementioned scheme in that the myocardial tissue extracts about 75% of the 0_2 from the perfusing blood in the resting individual, leaving essentially no reserve 0_2 in the blood. During times of stress, therefore, the increased demand of the myocardium for 0_2 is not met by an appreciable increase in coronary oxygen extraction from the perfusing blood (5).

Ayres (5) observed that a rapid increase in COHb caused by inhalation of 50,000 ppm CO in air for 30-120 seconds resulted in an increased cardiac output in humans although inhalation of 1,000 ppm for 8-15 mins. did not significantly alter cardiac output even though the COHb levels produced were essentially the same.

To examine the effects of rapid COHb production of myocardial function in 11 human patients, Ayers et al. (37) placed catheters in the ascending aorta, pulmonary artery, and proximal coronary sinus and obtained arterial, mixed venous, and arterial coronary sinus blood prior to exposing the patients to enough CO in air for 30-120 seconds to cause a COHb of about 9% with continuous ECG monitoring. Coronary blood flow was measured immediately before and 10 mins. after CO exposure. Oxygen and carbon dioxide tension were measured in a similar sequence as was also blood lactate and pyruvate. Expired breath samples were also analyzed.

In patients with no evidence of coronary heart disease, Ayers observed that increasing the COHb from a control level of 0.95% to 9.0% over the aforementioned time periods resulted in increased coronary blood flow, increased 0_2 extraction ratio by the myocardium (arterio-coronary sinus O_2 difference/arterial concentration), increased oxygen extraction, and an insignificant decrease in coronary sinus O_2 tension. As indicators of anaerobic/aerobic myocardial metabolism, lactate, and pyruvate extraction ratios did not change significantly.

In patients with coronary heart disease, an increase in COHb from 0.66% to 8.69% in 30 to 120 seconds did not result in a significant increase in coronary blood flow, although O_2 extraction and O_2 extraction ratio both increased. The coronary sinus O_2 tension decreased significantly and significant decreases in the lactate-extraction ratio and the pyruvate-extraction ratio were reported.

Ayers concludes that a potentially critical state or condition may result from inhalation of CO in the patient with coronary heart disease due to failure of the patient to respond to the stress by increasing coronary blood flow. Because of the lack of O_2 reserve in the myocardial circulation, a decrease in O_2 extraction (to maintain physiologically sound tissue 0_2 tension) must be balanced by an increase in coronary blood flow in order to maintain the myocardial 0_2 requirement. A normal coronary circulation could adequately increase coronary blood flow but a diseased coronary circulation might not be able to develop an adequate coronary blood flow response.

Knelson (38) has measured the effects of relatively low levels of CO on patients having coronary disease. Using 50 or 100 ppm CO in air over time periods of four hours, Knelson reports that the time of onset of

angina pectoris in exercising patients is significantly less in the presence of the CO than in ambient air. The duration of the anginal pains was significantly longer in the CO environment after ceasing the exercise than it was in ambient air. The COHb levels in those patients exposed to CO were 3 to 4.5%. The author indicates that levels of about 4% COHb add significant stress on persons whose myocardial circulation is already impaired.

In 1944, the theory that acute anoxia due to carbon monoxide poisoning produces less effect on respiration, circulation, mental function, and fine muscular movements than does acute anoxia produced by breathing oxygen at low pressures was challenged by McFarland and co-workers (28). Using human volunteers breathing various levels of CO through a face mask, McFarland compared the results of visual-discrimation tests to the results from tests performed using various levels of oxygen. The tests were run for time periods up to 4 hours. The authors report that effects are observed with COHb levels as low as 5% at sea level. It was concluded that the change in oxygen tension in the blood was the determining factor in elevation of the visual threshold whether this was brought about by loss in oxygen capacity due to CO saturation or loss in arterial 0_2 tension due to altitude (28, 29).

Beard and Wertheim (19) observed the effects of various levels of CO on human volunteers for the effects on discrimination of time intervals. The authors used electronically generated tones of 1,000 Hz to present a reference signal of 1-second duration followed by a variable signal to the subjects. The signal was varied in 18 steps between 0.675 seconds and 1.325 seconds.

Eighteen subjects were tested in at least 15 sessions (600 trials per session). CO was administered in concentrations of 0, 50, 100, 175, and 250 ppm in an audiometer booth. The authors reported significant decrements in performance at all levels of CO exposure. The time of onset of the decrement ranged from 90 minutes with a CO exposure of 50 ppm to 20 minutes with a CO level of 250 ppm.

In more recent reports, Beard and Grandstaff (30) found significant dose-related performance decrements with exposures of 64 minutes at 50 ppm CO and at proportionally shorter periods with higher CO concentrations (less than 20 minutes at 250 ppm CO). The experiments consisted of estimation of the passage of 30 seconds. The exposure chamber was an audiometer booth.

A doubling of error rate in visual function tests by human volunteers exposed for 90 minutes to 250 ppm CO was reported by Beard (31) when the results were compared to results of the tests performed under control conditions.

Schulte (35) examined the effects of levels of CO producing 0 - 20% COHb in 49 volunteers by administering 100 ppm CO in air for various time periods. He reported no uniform physiological changes but he demonstrated decrements in psychological tests at levels near 5% COHb. There was a 10-fold increase in the number of errors in choice discrimination when the COHb levels reached 20%. No differentiation between smokers and non-smokers was made.

Mikulka et al. (32, 33) observed the effects of CO on the performance of a number of tests by human volunteers. Ten university students were exposed to CO levels of 0, 50, 125, 200 and 250 ppm for 3 hr in 12-ft diameter transparent "domes". During test periods the windows of the domes were covered so that the subjects could not see out, but during rest periods the subjects were allowed to look out of the windows. Performance of Time estimation(10 sec.), Critical Instability Tracking Task, and the Pensacola Ataxia Battery (balancing tasks) were measured in the subjects. Mean COHb levels were 0.96% for 0 ppm CO, 2.98% for 50 ppm, 6.64% for 125 ppm, 10.35% for 200 ppm, and 12.37% for 250 ppm. No consistent effects attributable to CO were observed by the authors. The authors attribute the differences between their findings and those reported by Beard et al. (30, 31) to the fact that sensory and motor deprivation was greater in the experiments performed by Beard.

Hosko (34), in a series of 25 experiments, examined the effects of CO on the visual evoked response (VER) in human volunteers. CO concentrations of <1, 25, 50, 100, 200, 500 and 1,000 ppm for time periods ranging from 0.50 to 24 hours were used and the VER and EEG were recorded. No detectable EEG changes were reported for 24, 50 and 100 ppm CO for 8 hrs. Levels of 500 and 1,000 ppm CO for 2 hrs (COHb$\sim$25%) likewise were reported to cause no alteration of EEG patterns. COHb levels in excess of 20% were reported to cause VER alterations although lower levels did not produce these changes. The author comments on the difficulty of analyzing VER data because of the great variation from subject to subject; each subject served as his own control.

The clinical laboratory and psychomotor test results from this experiment were reported by Stewart et al. (36). Eighteen male volunteers ranging in age from 24 to 42 were used as subjects. Clinical laboratory tests consisting of blood cell counts, sedimentation rate, sodium, CO_2, chloride, potassium, calcium, total serum protein, alkaline phosphatase, bilirubin, blood urea nitrogen, glucose, SGOT, and COHb were performed before and after exposure to CO concentrations of 100 ppm or more. Psychomotor tests included hand and foot reaction time, AAA driving simulator, Crawford collar and pin test, and time estimation-hand reaction time.

Stewart reports that no untoward symptoms were noted during, or in the 24-hr period following, the exposures to 25, 50, and 100 ppm. No detectable changes from control values for the clinical tests were observed by the authors except the predictable rises in COHb during exposure. The only psychomotor test to indicate a significant relationship to CO exposure was the Crawford collar and pin test. The authors maintain that this correlation is spurious in light of the lack of correlation in other similar tests and the lack of significance of the paired t-tests for the pin and collar task.

Four-hour exposures to 200 ppm produced headaches by the end of the third hour in the three subjects exposed. Clinical laboratory tests were normal. After 1-hour exposure at 400 ppm, mild exertion produced a 10% increase in heart rate which was observable clinically and subjectively. At the end of 90 minutes a frontal headache was reported by one of the two subjects. In a second experiment using 500 ppm, over a 2-3 hours total exposure period, two exposed subjects had mild frontal headaches after 1 hour of exposure. After the exposure interval the headaches were reported to intensify to "very severe," reaching a pain peak 3-1/2 hours post-exposure and accompanied by mild nausea. These symptoms persisted for 7 hours. Repeating the 500-ppm experiment a third time, Stewart observed similar symptoms in the subjects during exposure, but the post-exposure symptoms were alleviated with hyperbaric 0_2 immediately after CO exposure.

An experiment involving the exposure of two subjects to CO at concentrations increasing from 1 ppm to 1,000 ppm during a 2-hour period resulted in COHb levels in excess of 30% and in frontal headaches becoming "incapacitatingly severe" 6 hours post-exposure and still noticeable after a night's sleep (12 hr post-exposure). Clinical tests and ECG's were normal although visual evoked response changes were observed at COHb levels at or in excess of 20%. These changes returned to normal when COHb saturation fell below 15%. The results of hand reaction time-time discrimination tests indicated an increase in reaction time 2 hr post-exposure, but no impairment of time-estimation ability. Performance of manual-dexterity tests decreased at the high exposure and hand fatigue was noted by the subjects.

Horvath et al. (43) observed the effects of CO on visual discrimination (vigilance) in human volunteers exposed at levels of 26 ppm (30 mg/m^3) or 111 ppm (128 (mg/m^3), which caused COHb levels to average 2.3% and 6.6%, respectively, for 135-140 minute exposure. Vigilance tests were performed in a double-walled booth (4x4x6 1/2 feet) under "single blind" conditions. The authors reported that there was a significant decrease in vigilance at the 111-ppm level (6.6% COHb), but no decrease in vigilance when exposures were to 26 ppm (2.3% COHb).

Summary of Short-Term Effects on Humans

The question of changes in psychomotor performance with levels of COHb between 2% and 3% has yet to be resolved.

Experiments reporting effects at levels of 2-3% COHb (19, 30, 31) should be verified by independent research groups using "double blind" studies and giving careful attention to control of parameters not easily measured, such as motivation of the subjects and extraneous stimuli. Interpretation of the results of such studies should focus on determining if the observed effects are applicable generally to the public involved in tasks such as driving a car, or if the effects are applicable only to specialized groups of persons such as radar operators or persons involved in critical but "non-stimulating" tasks.

Effects of CO on myocardial function in normal persons and persons with coronary and non-coronary heart disease have been examined by at least two experimenters. Ayers (37) found that increasing COHb fairly rapidly to 9% caused changes in coronary blood flow and myocardial function. Although as little as 4% COHb correlated with a decrease in mixed venous O_2 tension, significant myocardial changes were seen in patients with elevation of COHb above 6% (5).

Knelson (38) reported decreased tolerance to exercise in angina patients exposed to CO (50-100 ppm) for 4 hours, which resulted in COHb levels of 3-5%. Perusal of this yet unpublished work is in order before any conclusions can be drawn for purposes of this document.

Epidemiology

Hexter and Goldsmith (39) and Cohen et al. (40) have reported significant correlation between CO concentrations and mortality.

Hexter and Goldsmith in their study involving deaths from all causes in Los Angeles County during a 4-year period reported a significant regression coefficient associating excess mortality from all causes with CO concentration. Although the logarithm of the CO concentration used in their statistical model did not provide a direct measure of the contribution of CO to mortality, the authors reported that comparisons between concentrations could be made. Using the 4-year high 24-hr average concentration (20.2 ppm) and comparing this to the four-year low (7.3 ppm) 24-hr average concentration, the estimated CO contribution to mortality is reported to be 11 deaths, all other factors being equal. Cohen et al. studied the relationship of CO and survival from myocardial infarction in a number of patients admitted with myocardial infarcts to 35 hospitals in the Los Angeles area. They reported that a significant correlation could exist between fatalities and CO levels of 7.7 to 14 ppm.

However, the authors caution against drawing conclusions without further studies to verify their findings.

Effects on Plants

At the concentrations and for the time intervals with which this guide is concerned, CO has not been reported to have a significant effect on plant life.

It has been reported that 100 ppm (115 mg/m^3) caused a 20% inhibition of nitrogen fixation in red clover plants inoculated with Phizobium trifolii and exposed to the CO for 1 month. Concentrations of 500 ppm (575 mg/m^3) for 1 month caused 100% inhibition.

A 4-hour exposure at 6,000 ppm (6,900 mg/m^3) (No. 11 44) caused some inhibition in nitrogen-fixing ability in Azotobacter vinelandii (45).

There is some evidence that certain soil fungi may act as a "sink" for CO, converting the CO to CO_2 (46).

Analytical Methods

The reference method for the continuous measurement of CO in the atmosphere as recommended by the Environmental Protection Agency is non-dispersive infrared spectrometry (47). An extensive description of this method is contained in the reference.

An evaluation of alternative methods for CO analyses and a brief evaluation of the parameters to be considered in using these methods is contained in Air Quality Criteria for Carbon Monoxide (48).

Short-Term Public Limits (STPL's) and Public Emergency Limits (PEL's)

Short-term public exposures are those occurring at predictable times and arising from single or occasionally repeated events. Where exposure can be predicted, there is no justification for subjecting the public to any appreciable risk (41).

"The importance of CO in the ambient air lies principally in the ability of CO to combine with hemoglobin." (49). "Exposures to increased CO concentrations for relatively short periods, such as one or two hours, are innocuous unless or until the cumulative effect is such that the blood COHb level has been raised appreciably." (49).

Because the absorption of CO in the blood is dependent on the duration of exposure, the concentration of CO in the inspired air, the activity or respiratory rate of the exposed individual and a number of other

variables, the setting of acceptable exposure limits is complicated by the fact that all exposed persons will not necessarily be involved in the same physcial activities. Therefore, they would be expected to absorb CO at different rates although exposed to essentially the same level(s) of CO for the same time periods.

For purposes of setting public limits, the Panel on Carbon Monoxide and the Committee on Toxicology assumed that during an exposure period persons exposed could be engaged in "light work" (see Appendix 1) and would therefore be expected to have a ventilatory rate greater than sedentary persons (8, 9). Consequently, it would be expected that the CO-absorption rate would be greater during the initial part of the exposure periods although at equilibrium the COHb levels would be the same for both resting and active individuals.

The Committee on Toxicology recommends the following STPL's and PEL's based on the avoidance of significant myocardial changes in persons having pre-existing coronary heart disease. It is the opinion of the Committee that these persons represent the most susceptible segment of the general public.

It is believed that the levels recommended below (STPL's) would cause COHb levels of about 2% in non-smoking persons engaged in "light work" (See Appendix 1 for parameters assumed). Levels of COHb in excess of 2% may result under conditions of heavy exercise depending on variations between humans and the extent of their physical activity. In no instance would these levels significantly exceed 3%. The recommendations, including the ten-minute levels are considered to be time-weighted averages. Any excursions above these levels would be limited to a factor of 1.5 and would be compensated for by an equivalent reduced exposure during the period.

Recommended Short-Term Public Limits for CO

10 min	90 ppm
30 min	35 ppm
60 min	25 ppm
4-5 hr/day, 3-4 days/mo	15 ppm

PEL's

Emergency exposure limits for the public are intended for situations in which pollutants escape in an uncontrolled manner at unpredictable times and places as the result of accidents such as damage to transportation equipment or fire.

Differing from the optimal conditions of the short-term public limits, which require that there be no adverse health effects, public emergency limits envision the possibility of some temporary discomfort, provided the effect is reversible and that no injury results from it. With respect to CO exposure, it is believed that persons with myocardial disease would be most susceptible to the effects of increased COHb.

The following PEL's are recommended as "Ceiling Limits" in order to prevent the COHb levels from exceeding 5% in persons engaged in "light work" and 6% in persons engaged in "heavy work". Persons at rest would be expected to never exceed 3% COHb during exposure to the PEL concentrations for the times given.

Recommended Public Emergency Limits

10 min	275 ppm
30 min	100 ppm
60 min	60 ppm

A margin of safety may be assumed in the aforementioned PEL's only insofar as one would not expect a person having myocardial difficulties, such as recurring angina, to participate in "light work" for durations of time that could precipitate anginal pains even in the absence of CO.

Appendix 1

The following figures are graphic representations of the formula: (56)

$$\text{CO in air (PPM)} = \frac{1316\,(AC - V_{CO}B + \alpha\,(V_{CO}B - AD))}{1 - \alpha}$$

where $A = \dfrac{P_{C-O_2}}{M[O_2Hb]}$

$B = \dfrac{1}{D_L} + \dfrac{P_L}{Va}$

$C = [COHb]_+$ = COHb concentration (mlCO/ml blood) at time t.

$D = [COHb]_0$ = "background" [COHb] (mlCO/ml blood) at time = 0.

V_{CO} = Rate of endogenous CO production (ml/min)

$\left(\dfrac{-tA}{VbB}\right)$

$\alpha = e$

Vb = blood volume

$P_{C-O_2} = PO_2$ in capillaries (mmHg)

$[O_2Hb]$ = oxyhemoglobin conc. (ml/ml blood)

M = CO/O_2 affinity for Hb

D_L = diffusion rate of CO through lungs (ml/min/mmHg)

P_L = dry barometric pressure in lungs (mmHg)

Va = ventilation rate (ml/min)

Assumptions (Constants)

$D = 0.0015, (0.76\%)$

$V_{CO} = 0.007$ ml/min

$Vb = 5,500$ ml

$P_C - O_2 = 100$ mmHg

$[O_2Hb] = 0.2$ ml/ml blood

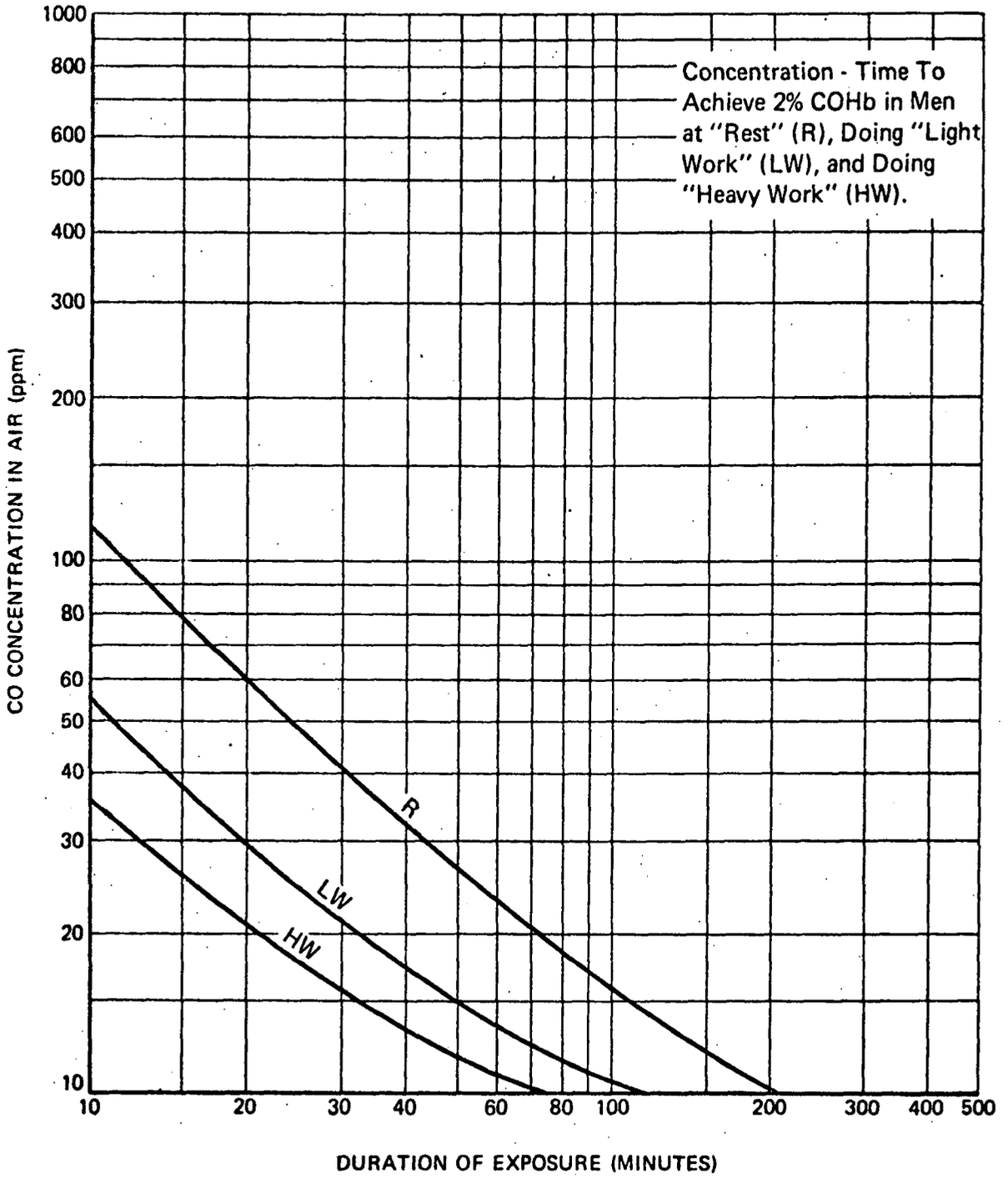
$M = 218$

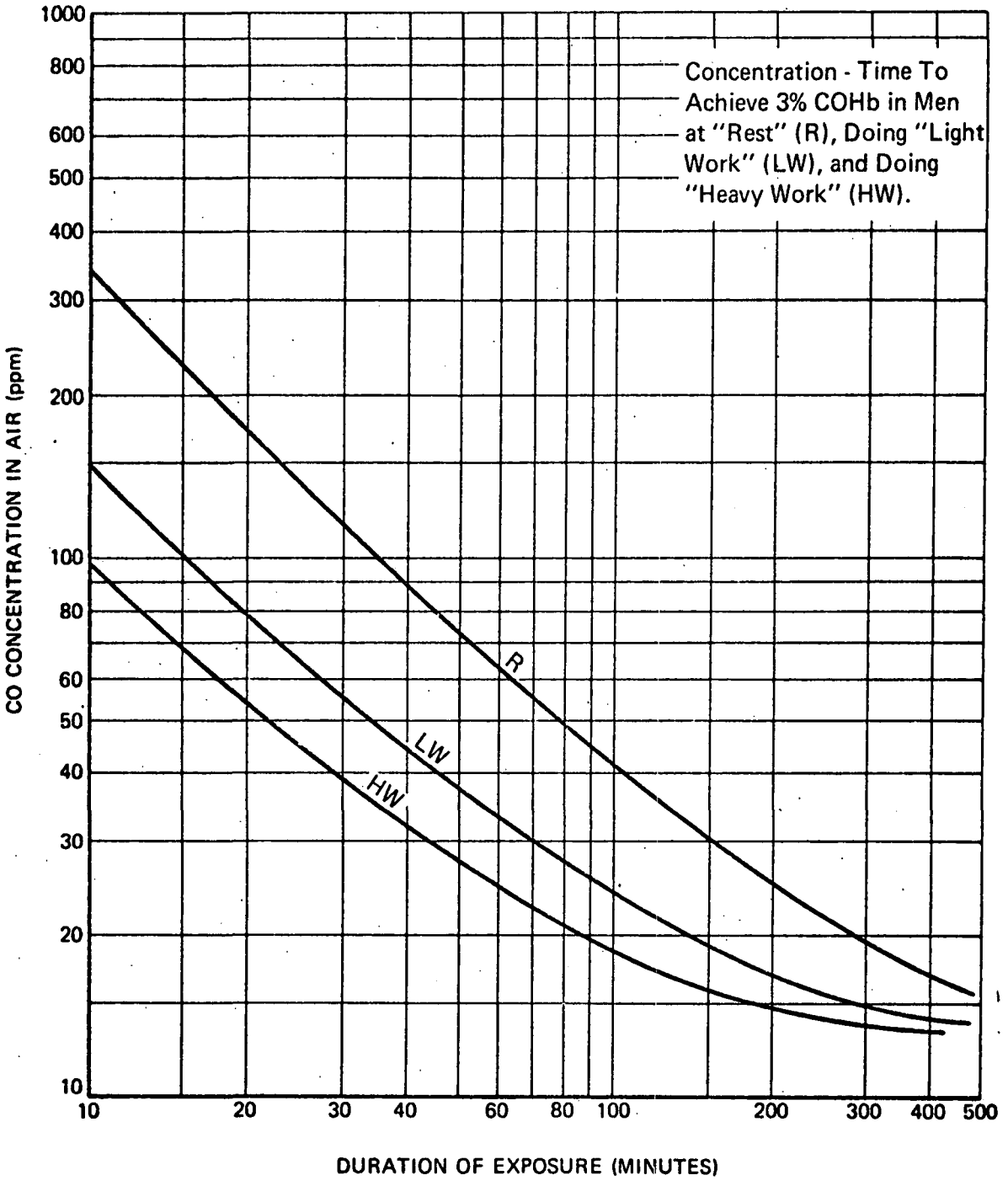
$P_L = 713$ mmHg

Assumptions (Variables)

	Rest	Light Work	Heavy Work
D_L =	30.	40.	60.
Va =	6,000	18,000	30,000

Equation was solved for light work, heavy work, and rest at COHb levels of 2%, 3%, 4%, 5%, 6%, 8%, and 10% for times ranging from 10 minutes to 8 hours.


Concentration - Time To Achieve 2% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
200
100
80
60
50
40
30
20
10
R
LW
HW
10
20
30
40
60
80
100
200
300
400
500
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 3% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
200
100
80
60
50
40
30
20
10
R
LW
HW
10
20
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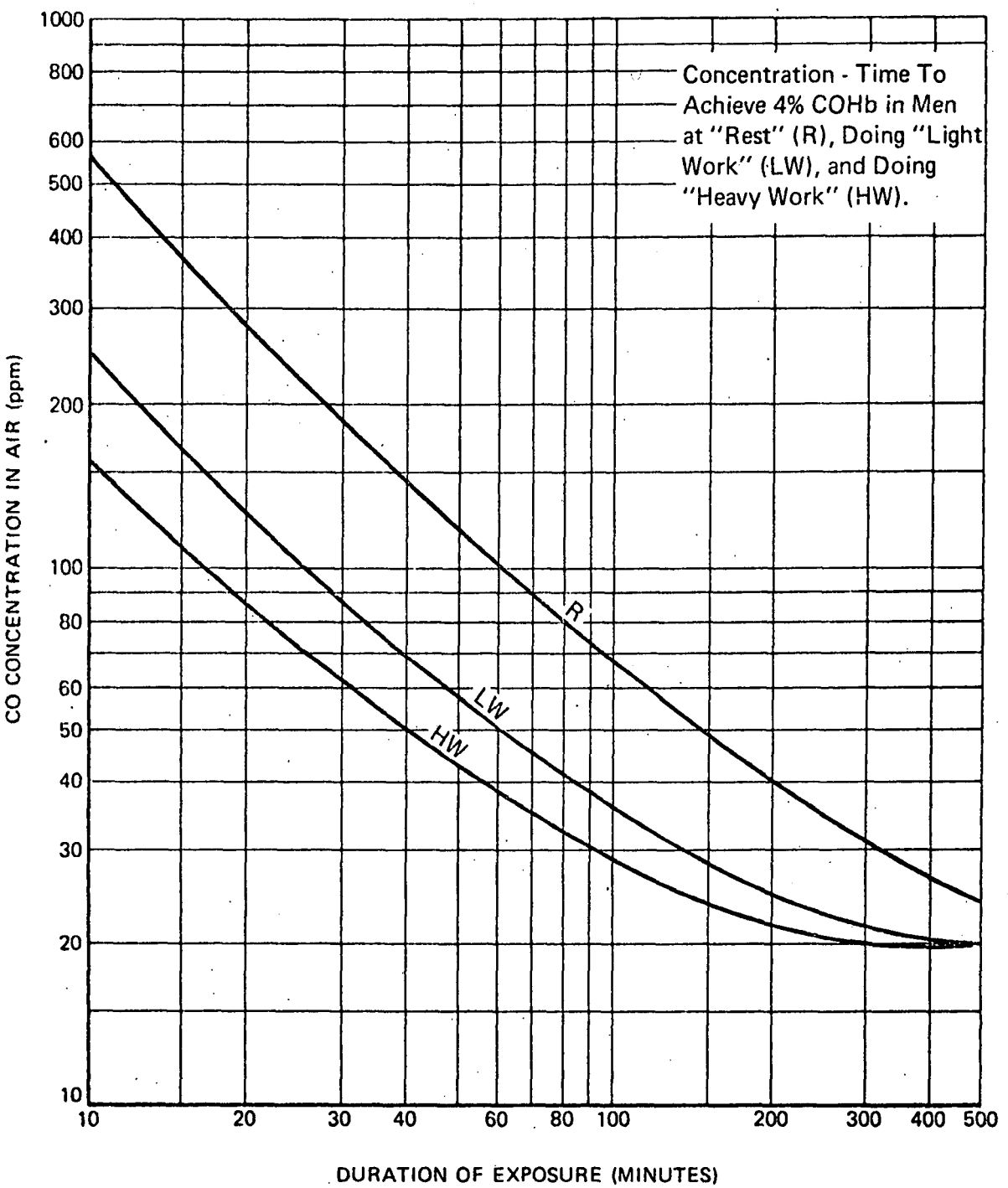
200
300
400
500
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 4% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
R
LW
HW
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
200
100
80
60
50
40
30
20
10
10
20
30
40
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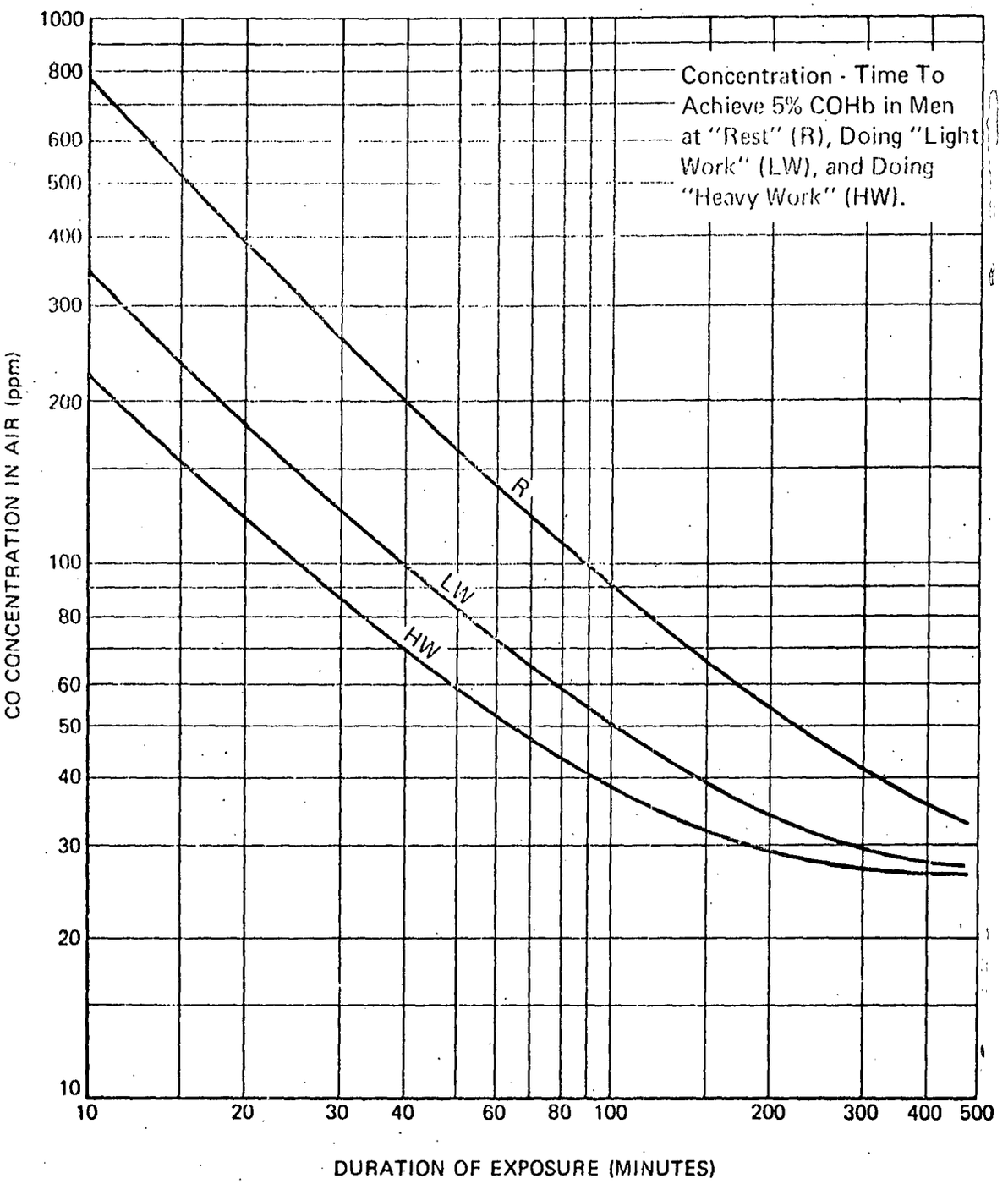
80
100
200
300
400
500
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 5% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
R
LW
HW
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
200
100
80
60
50
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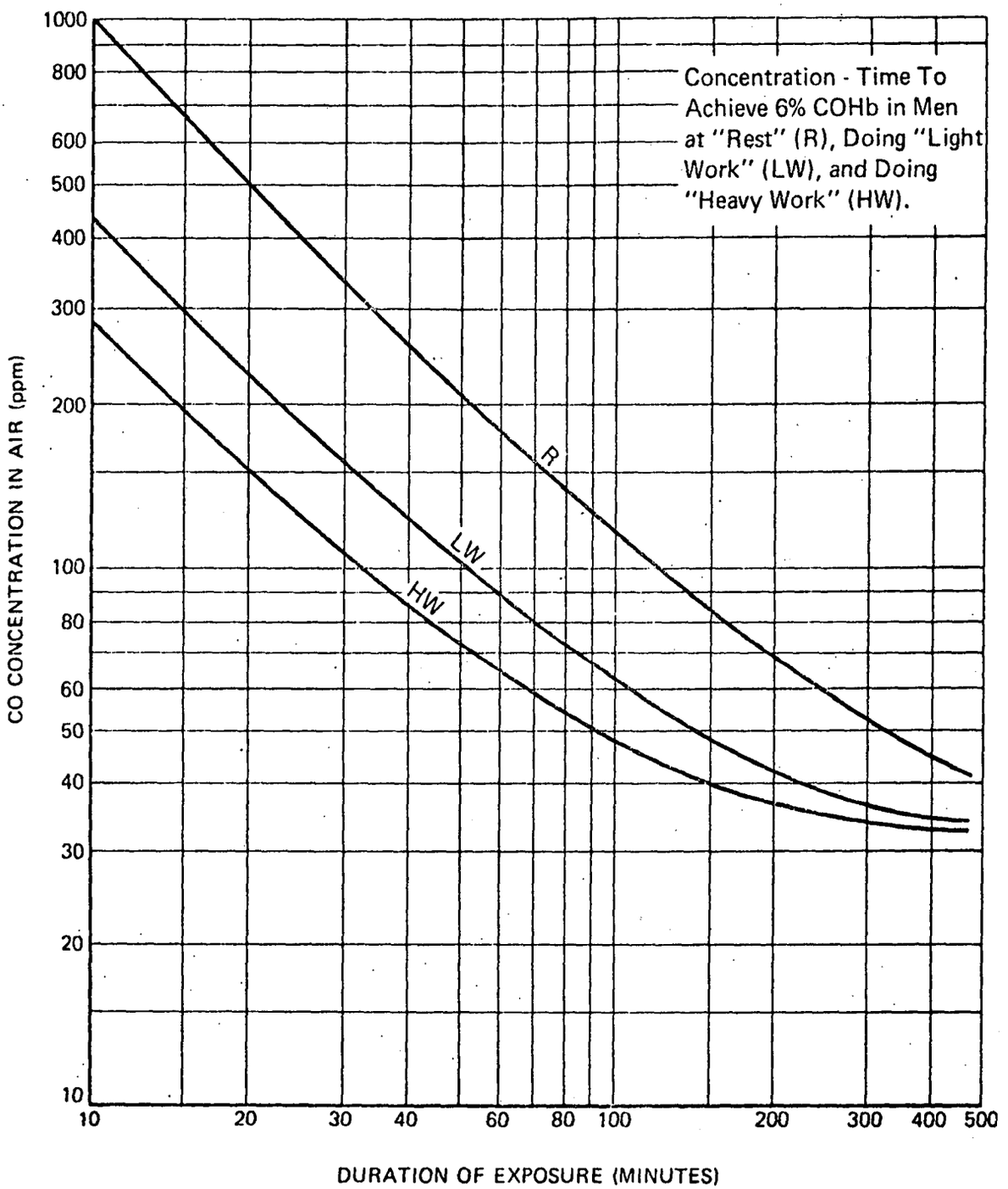
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 6% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
R
LW
HW
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
200
100
80
60
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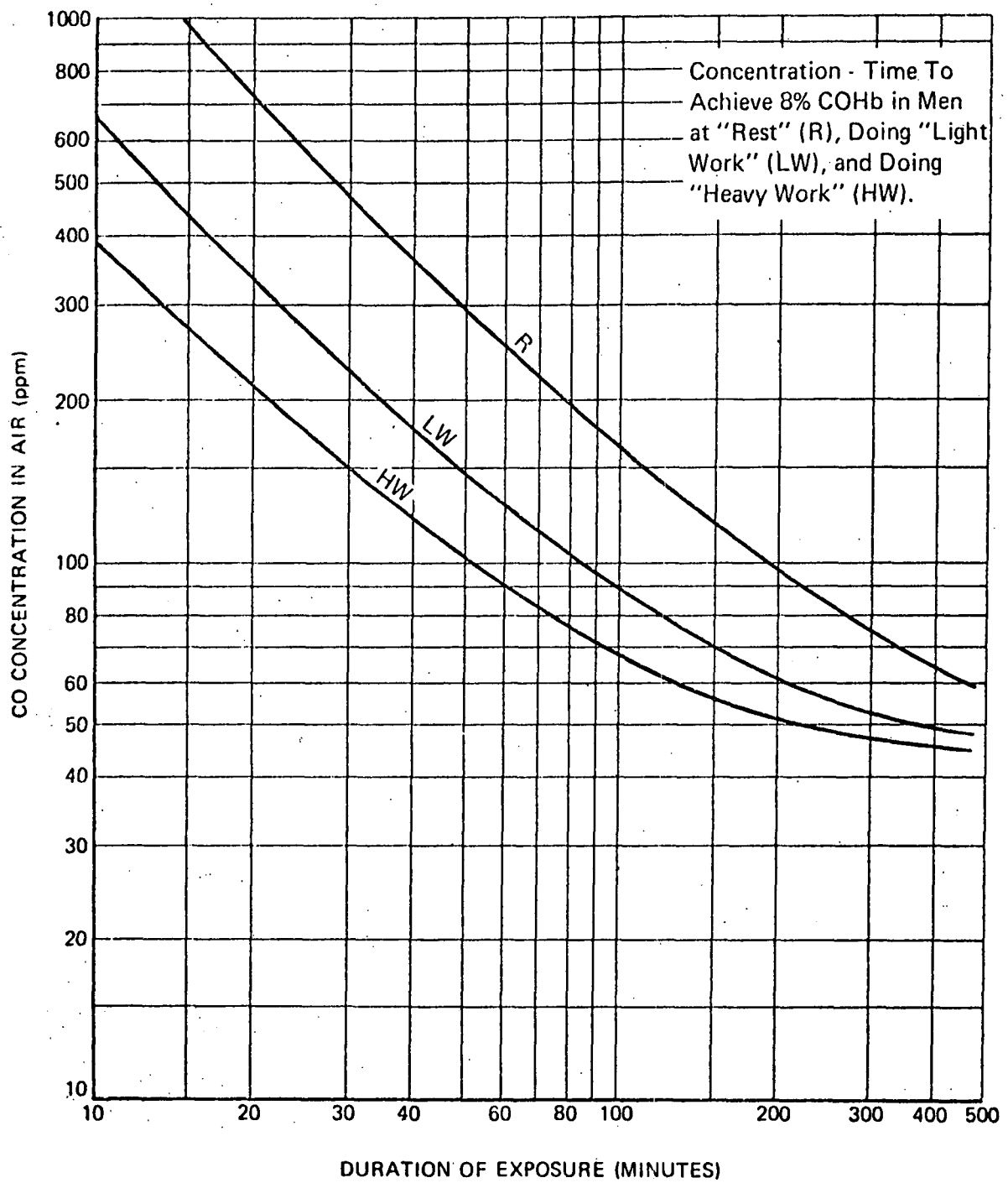
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 8% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
R
LW
HW
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
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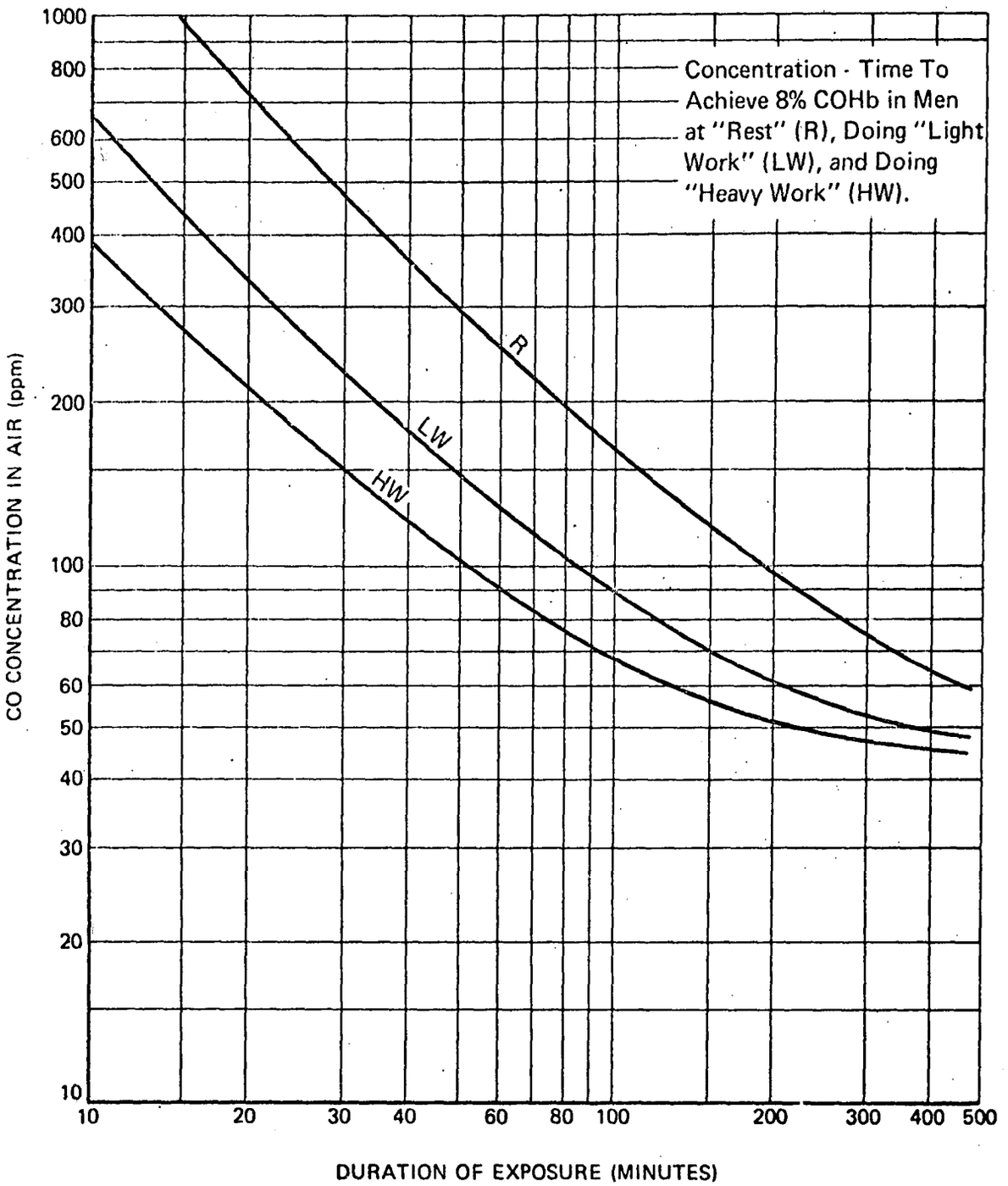
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 8% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
R
LW
HW
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
200
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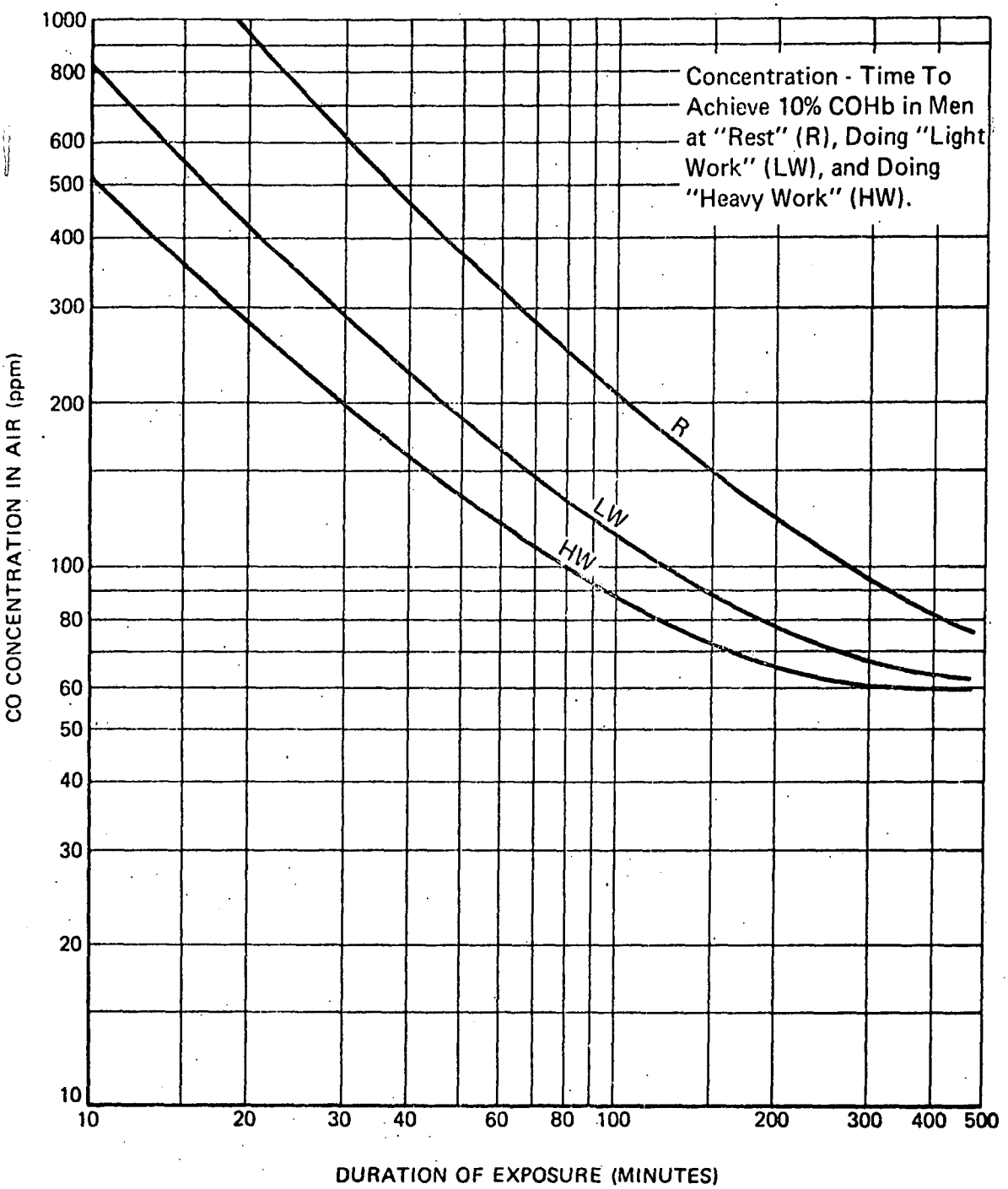
DURATION OF EXPOSURE (MINUTES)


Concentration - Time To Achieve 10% COHb in Men at "Rest" (R), Doing "Light Work" (LW), and Doing "Heavy Work" (HW).
R
LW
HW
CO CONCENTRATION IN AIR (ppm)
1000
800
600
500
400
300
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DURATION OF EXPOSURE (MINUTES)

APPENDIX 2–Table I

[CO] in ppm	Length of exposure	Species	Effects	Comments	Ref. No.
50–500	77–182 days	Monkeys Dogs	Exposed continuously showed increased RBC, hemoglobin and hematocrit. Total blood volume increased in both while plasma volume remained constant.	The polycythemia was normocytic and normochromic.	14
50	5 hrs/day, 5 days/week, × 12 weeks	Rat	Zinc, copper, cobalt, iron, and magnesium were seen to be altered by CO exposure. Cobalt exhibited a massive and consistent loss from rat liver fractions.	The consistent trace metal loss in the mitochondrial fraction indicates an overall reduction of cellular respiration and ATP production.	21
50	3 mo–2 yrs	Rats	Exposed 95 hrs/week. No changes were noted that could be due to CO; studies were done on fecundation, reproduction, growth, CO_2 emission, weights and water percentages of different organs, hemoglobinemia, protidemia, lipemia, calcemia, magnesesemia, serum transaminases, hematological data, infection & immunization, and Guerin's grafted tumor's evolution.	It was noted that just putting the rats into an enclosure (i.e., chamber-held, but no CO) affects body growth, heart rate, ECG, and avoidance conditioning.	12
51 96 200 106	90 days, cont. " " 8 hrs/day, 5 days/week × 6 weeks	Rats, g. pigs, dogs, monkeys	In the continuous exposure, COHb levels were: dog, 51 ppm:5.7–6.2%; monkey, 51 ppm:5.3%; rat, 51 ppm:5.1%; g. pig, 51 ppm:3.2%. At 96 ppm, dog:12.5%; monkey:10.3%; rat:7.5%; g. pig:4.9%. At 200 ppm, dog:20.8%; monkey:20.0%; rat:16.4%; g. pig:9.4%. At 96 and 200 ppm, there was an increase in hematocrit and hemoglobin. In the repeated exposure, the rat hemoglobin and hematocrit were increased.	No toxic signs were noted in any of the studies.	13
100 200	Egg incubation period "	Chicken "	Egg hatchability was 61.7%, as compared to 78.8% for the control eggs; embryonic death appeared to be earlier in exposed chicks. 4/30 chicks were alive at time of shell opening; many eggs dead-in-shell showed symptoms similar to acute CO intoxication (petechial hemorrhage and visceral blood clotting).		50
400 500	71 days 97 days	Monkeys, dogs in both groups	COHb in monkeys:32%; in dogs:33%. COHb in monkeys:38%; in dogs:39%.	No effects seen on survival, growth rate, clinical chemistry. Little of significance seen on pathological exam. There was a marked erythrocytosis. Animals appeared able to perform learned tasks at COHb levels of 30%.	17
191	103 days	Monkeys	Developed an increased RBC, hemoglobin, and hematocrit. COHb mean level was 22%. There was no detectable change in performance.	COHb level was essentially 0% at 1 day post exposure; other hematological changes were normal after 1 month.	15

[CO] in ppm	Length of exposure	Species	Effects	Comments	Ref. No.
400 500	for 71 days for 97 days	Rats, mice, baboons, monkeys, dogs	Heart and spleen were heavier in rats. Two rats died with a possible contribution from circulatory failure. No other significant pathology was seen.	Immediate response was depression of activity and decreased food consumption. Recovery was complete in 2 weeks. There was a reddening of unpigmented areas of the skin.	16
1,000	90 min	Rats	Enhanced the sleeping time response to hexobarbital in rats.	Perhaps due to effect of CO on P-450.	20
250	90 min	Rats	Prolonged muscle paralysis seen after zoxazolamine.		
3,000	90 min	Rats	No deaths in 15 rats.		
3,400	<90 min	Rats	10/10 died during exposure.		
1,000	4 hrs	Mice	COHb was 35%; the pyruvate content of the brain was increased and the blood glucose was decreased.		24
1,000	9 hrs/day X 35 days	Mice	COHb was 35%; brain pyruvate was increased; blood glucose was decreased; brain lactate was increased; brain phosphocreatine was decreased.	These effects were only partially reversible after 15 hrs in room air.	
1,280–17,000	varied	Dogs	Those dying during or shortly after exposure exhibited extensive coagulation necrosis in the CNS or no definable pathology. They consistently developed respiratory arrest, cardiac arrest, and a rapid fall in blood pressure. Surviving animals were examined for changes in the CNS and heart. Changes were seen clearly only in those animals exposed to CO in lower concentrations, with a COHb of 40–60%. Short duration—<15 min—and higher conc. did not produce any pathology (1%).	Physiologically, respiration was first depressed; then there was an abrupt rise in CSF pressure. Venous pressure rose to >25% above the base line level, and this was followed by an additional rise in CSF pressure. (To 100% greater than base line.) ECG changes consisted of depression of R wave, elevation of ST segment, occasional increases in T wave, deepening of Q and S, and partial heart block with PVC's. The severe changes persisted to sacrifice. EEG changes of severe depression of voltage or absence of activity was noted in animals with CNS pathology.	18
1,500 3,000	30 min 30 min	Dogs	Showed striking increases in coronary blood flow, which was linear with % COHb. (The COHb increased about 1%/min at 1500 ppm.) Coronary stroke volume also increased linearly with %COHb, as did heart rate.	There was no significant change in left ventricular pressure or dP/dt, nor in arterial pO_2.	51
1,600	4 hrs	Monkeys	LC50 for squirrel monkeys.	COHb varied from 45.6% for animals surviving 1601–1800 ppm to 62.7% for animals dying at this level.	52
3,000	45 min	Rats	Immediately after exposure, showed a significant decrease in DNA, by 14%, and of gangliosides, by 8%. There was no significant change seen in cerebrosides. There was a distinctly red coloration to the brain, and a marked engorgement of the superficial blood vessels. Histologically there were no changes.		53

[CO] in ppm	Length of exposure	Species	Effects	Comments	Ref. No.
0–8,695	4 hrs	Rats, mice, g. pigs	Results of LC50 determinations at 0–100 psig didn't vary significantly within species. The COHb levels for rats & g. pigs also showed little variation with total pressure.	Partial pressure of O_2 was maintained between 140–160 mm Hg.	25
230,000	several minutes, one time or 5 times	G. pigs	Functional and structural changes of the retina were seen; there was inhibition of succinic acid dehydrogenase, and alkaline phosphatase; increased activity of acid phosphatase was interpreted as a sign of enhancement of autolytic process.	Toxic effect was long lasting.	54
10,000	10 min	Rats	Cardiac ultrastructural changes consisted of intracellular edema, swelling of mitochondria and sarcoplasmic reticulum, disruption and reduction of cristae, disappearance of mitochondria, appearance of lipofuscin pigment granules & lysosomes, increase of glycogen granules and fat droplets.	These changes were evident 10 min after exposure ceased, and became most prominent in 30 min to 1 hr. In 24 hrs the hearts appeared essentially normal.	55

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