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BEHAVIORAL EFFECTS OF CARBON MONOXIDE ON ANIMALS AND MAN[1]

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Victor G. Laties and William H. Merigan

Environmental Health Sciences Center and Department of Radiation Biology and Biophysics, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642

INTRODUCTION

Even though experimental observations of the behavioral effects of carbon monoxide (CO) date back to J. S. Haldane (35) in 1895, until recently there had not been enough literature on this subject to warrant an entire Annual Review chapter. Haldane, in order to ascertain the relationship between the carboxyhemoglobin (COHb) level and symptomatology, exposed himself to the gas and recorded his own behavior. He described deficiences in vision, audition, balance, reading, and writing at COHb levels ranging from 25 to 50%.

Surprisingly little more was done during the next half century. It was only during World War II that work on the behavioral effects of CO started in earnest. For instance, the work of McFarland and his colleagues (36, 63, 68), treated below, dates from that time. Then followed almost 20 years of relative inactivity disturbed only when governments became concerned with the possible effects of CO levels in aircraft, spaceships, and nuclear submarines [e.g. Malorny (62); Theodore et al (105); Schulte (91)]. Finally, a surge of interest in the environment led to the very influential "Restoring the Quality of Our Environment" report by the Environmental Pollution Panel of President Lyndon B. Johnson's Science Advisory Committee in 1965 (22), to a comprehensive CO bibliography published in 1966 [Cooper (18)], to a report on the health effects of CO by the National Research

[1]This review covers the literature through July 1978.

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Council in 1969 (73), to a New York Academy of Sciences symposium in 1970 [Coburn (16)], and especially to the passage by the US Congress of legislation that mandated air quality standards. This set the stage for the proliferation of research in this area in the 1970s.

Studies of the behavioral effects of CO have been briefly reviewed several times in the past ten years, usually in the context of a general review of the CO literature [Laties et al (50); Lawther (54); North Atlantic Treaty Organization (75); Stewart (99); and US Department of Health, Education, and Welfare (107, 108)]. A recent monograph [National Research Council (74)] contained a broad examination of CO's behavioral effects on humans by one of the present authors [Laties (49)]. The subsequent appearance of much new behavioral material prompted the present effort, which attempts a comprehensive treatment of both animal and human behavioral studies of CO.

With few exceptions, this review is confined to experimental laboratory studies. We do not discuss the epidemiologic literature [Goldsmith, Beard & Dinman (29)]. Nor do we generally consider studies of the behavioral sequelae of either acute or chronic high concentration CO exposures [e.g. Culver & Norton (19); Grut (32)].

We also do not consider studies of the behavioral effects of engine exhaust gases or tobacco smoke, both of which, while containing CO, also contain much else. Such work is of great relevance to an important societal problem, but it is difficult to separate the effects of the components of these complex mixtures [cf e.g. Dorcus & Weigand (21); Fristedt & Akesson (26); Johnson et al (42)].

Mechanism of the toxic effects of CO Physiological changes associated with exposure to CO are described at length in the recent NRC monograph (74). The most prominent of these are due to CO's reversible binding with hemoglobin, its affinity for hemoglobin being more than 200 times that of oxygen. The formation of COHb produces hypoxia by reducing oxygen transport by the red blood cell and impeding the dissociation of oxygen from hemoglobin in the capillaries. The percentage of hemoglobin bound as COHb is thus the most important index used to characterize the magnitude of CO exposure.

However, some investigators [e.g. Goldbaum, Orellano & Dergal (27); Lilienthal (55); Plevová & Frantík (81); and Sokal (98)] maintain that specification of both CO exposure concentration and duration better predicts toxicity than does COHb level. If this is true, it could reflect the operation of other mechanisms of CO toxicity (e.g. interference with cellular respiration). A second possibility is that deviations from expected effects might be due to rapid oscillations of cerebral levels of COHb [cf Abboud, Andersson & Coburn (1)]. For example, brief exposure to high concentrations of CO might produce very high momentary cerebral levels of COHb that would be inadequately reflected by venous COHb levels measured minutes after exposure. In this review, we describe concentration and duration of exposure to CO as well as COHb level, the traditional measure of CO exposure. COHb levels also provide checks on measures of atmospheric concentrations of CO during exposure and they reflect the rate of CO uptake by the organism.

ANIMAL PERFORMANCE

The effects of CO exposure have been studied on a wide variety of behaviors, but with only a very few species. Most investigators have worked with rats; a few have used mice, pigeons, or monkeys. Because of the small number of nonrodent studies and the absence of direct comparative investigations we consider the results for all species together.

Unconditioned Behaviors

Several unconditioned behaviors in rodents are disrupted by exposure to CO, including food and water intake, running, swimming, and digging. Annau (3) and Koob et al (45) reported decreased food and water intake and lowered body weight in rats exposed to at least 250 ppm for 24 hr. Following exposure to 50 ppm CO for 120 consecutive hr per week, Stupfel & Bouley (103) found decreased water consumption and slight decrements in weight gain, which were made up during weekends. Theodore, O'Donnell & Back (105) found slight decreases of weight gain in rats exposed continuously to 400 or 500 ppm CO. However, the body weights of the exposed rats had reached control levels by the end of the 168 day exposure. These studies suggest that CO primarily decreases food and water intake, thereby reducing body weight, and that this decreased consumption is not maintained during extended exposures.

Two quite different techniques have been used to study running in rodents during CO exposure. Plevová & Frantík (81) measured the length of time rats could keep pace with a treadmill that forced them to run 21 m per min. Three groups of rats were tested after each of two CO exposure conditions and an air control, which were presented in a counterbalanced order across groups. One CO condition involved a brief exposure to a high concentration (700 ppm for 30 min) resulting in a 19.6% COHb level, while in the second, rats were exposed for a longer period to a lower CO concentration (200 ppm for 24 hr) producing 22.8% COHb. Running performance declined after both exposures, but was twice as low following use of the higher CO concentration. This result was somewhat surprising since the greater effect occurred at the slightly lower COHb level, suggesting that the COHb level is not invariably the best index of CO toxicity, and that CO concentration and exposure duration must also be considered. Malorny (62) studied spontaneous wheel running in the white mouse during the final 3 hr of a 17 hr exposure to CO. The distance traveled decreased by one third after exposure to 55 ppm, one half after 84 ppm, and three quarters after 160 ppm CO. When the exposure started just before the test period, the observed decrements were small, and occurred only at greater than 100 ppm CO.

Malorny (62) also reported that members of his laboratory found that swimming by rats and sand hauling by hamsters were very sensitive to the effects of CO. Following fur degreasing with detergents, rats were placed in lukewarm water, and the length of swimming time was recorded. One hour of exposure to 300 ppm CO (8 to 13.5% COHb) reduced swimming time to less than half of control values. Dramatic decreases in swimming time were also found after 7 hr of exposure to 100 ppm CO. Syrian golden hamsters dig impressive quantities of sand during burrowing. As little as 4 hr of exposure to 50 ppm reduced the amount of sand that was dug to about one fourth that of control hamsters.

Conditioned Behaviors

Most animal studies of the behavioral effects of CO have used operant (i.e. reinforced or rewarded) behavior as an assay. Animals are typically trained until behavioral performance reaches a stability criterion, at which point CO exposure is initiated. The operant behaviors studied to date range from performance on the simplest reinforcement schedule, in which every response is reinforced (fixed-ratio 1 or FR 1) to complex discriminations.

Three studies examining the behavioral effects of CO in the rat have used the FR 1 schedule. Teichner (104) trained rats to press a lever for food pellets in daily 3 min sessions. On days 23 through 27, rats were exposed to 500 ppm CO for 5 hr prior to the experimental session. Although the data were highly variable, a significant reduction in responding occurred on the days of CO exposure. A similar CO-induced reduction in FR 1 responding maintained by electrical brain stimulation was found by Annau (3). In this study, rats were exposed throughout the 2 hr test sessions and significant reductions in response rates occurred following exposure to 500 and 1000 ppm but not 100 or 200 ppm. Goldberg & Chappel (28) reported that exposures to 250 and 500 ppm produced lower response rates during a 55 min session on days 10 through 12 of training. Another group of rats responded less than controls when tested during the second hour of a 2 hr exposure on training days 1 through 4.

Other reinforced behaviors studied have included running in the straight-alley maze, and escape and avoidance performance. Teichner (104) trained rats to leave a start box and run 66 in. (168 cm) along a straight alley to a goal box where they received food; a session consisted of five trials a day. Rats exposed to 500 ppm CO for 1 hr prior to testing on days 30 through 34 of training showed a small increase in the time required to leave the start box, and a slight reduction in running speed. In a second experiment, rats housed in a 60°F (16°C) environment showed an increase in shuttle-box shock escape latency when exposed to 300 ppm CO for 1 hr immediately prior to being tested in an 80°F (27°C) chamber, whereas those initially housed at 74°F (24°C) did not show this effect. Both groups, however, showed increased escape latencies after 500 ppm CO.

Back and his colleagues [Back & Dominguez (7); Theodore, O'Donnell & Back (105)] examined the effects of CO on monkeys that worked on an avoidance schedule requiring several concurrent performances. Each of two levers, one on the right and the other on the left of the response panel, had to be pressed before 15 sec elapsed to avoid shock. In addition, occasional auditory and visual signals required responses on designated keys within 2 sec to avoid other shocks. In the first experiment, 12 rhesus monkeys were continuously exposed for at least 7 days to each of several CO levels of up to 383 ppm (resulting in 27 to 34% COHb) as well as to reduced atmospheric pressure (5 psi, 68% O_2, 32% N_2). Decreased response rates were shown by two of the monkeys at the higher CO levels. In a subsequent experiment, exposure to the two highest conditions in 12 additional monkeys for 100 days led to no performance changes. The interpretation of these studies is complicated by the addition of low atmospheric pressure and high oxygen concentration to the CO exposure. However, under these unusual conditions, the behaviors Back and colleagues studied were quite insensitive to CO.

Interval and ratio schedules of reinforcement have often been used to assess behavioral effects of various toxicants, including CO. On interval schedules, a reinforcement follows the first response occurring after a specified time period, resulting, following adequate training, in a distinctive pattern of increasing response rate throughout the interval. Ratio schedules require the completion of a specified number of responses for reinforcement. We have discussed the FR 1 schedule above. Larger ratios typically generate a pause after reinforcement followed abruptly by a high rate of responding until the next reinforcement. Carter et al (14) showed that a 1.5 hr exposure to 1000 ppm CO (51.6% COHb) essentially eliminated the responding of rats working on a FR 15 schedule. However, concentration-related protection from the disruptive effects of CO occurred if the rats were concurrently exposed to carbon dioxide.

McMillan & Miller (69) studied the effects of CO alone and in combination with drugs on both the fixed-interval (FI) and FR schedule performance of pigeons by having these components alternate during a session (multiple FI FR). Exposure began 1 hr before the session and continued throughout the 1 hr session. Decreased response rates on both schedules were produced by 490 ppm (32% COHb) but not by 380 ppm (29.8% COHb) exposure to CO alone. Amphetamine potentiated the rate-decreasing effect of CO in a dose-related fashion on both reinforcement schedules. The same effect on response rate was found with pentobarbital on the FR schedule. However, on the FI schedule, an intermediate dose of pentobarbital (10 mg/kg) elevated the response rate well above levels seen with no exposure or with CO exposure alone.

An extensive study of CO and interval and ratio schedules was briefly reported by Beard & Wertheim (10). Concentration effect curves (250–1000 ppm CO) were determined for fixed-interval 3 min, fixed-ratio 25, variable-interval 25 min, variable-ratio 25, and variable-ratio 15 schedules of reinforcement. The magnitude of response rate attenuation went from greatest to least in the order listed above. Unfortunately, since no statistics were reported, the reliability of the data is unclear.

Recently, Ator (4) examined the effects of CO on the performance of rats working under either an FR 30 schedule, an FI 3 min schedule, or a procedure in which the FR 30 and FI 3 min schedules alternated after each reinforcement (multiple FR 30 FI 3 min). Three groups of rats experienced each of these conditions in counterbalanced order. The rats were exposed throughout the 75 min test session to 500, 700, or 900 ppm CO. Response rates were most profoundly decreased under the FR schedule when it stood alone, with consistently smaller decreases seen under the FR schedule which alternated with the FI schedule. These overall rate decreases were due to complete cessations of responding. Responding before cessation remained brisk and the pattern of responding in individual ratios remained intact.

Response rates were decreased less under the FI schedule both in isolation and in alternation with the FR schedule. The first effect seen on FI responding was a disruption of the typical pattern of increasing response rate throughout the interval: This pattern was replaced by intermittent periods of responding between extended pauses. The extended pauses occurred much later in the session under the FI than under the FR schedule.

Thus, this study demonstrated both a greater sensitivity of FR than FI and a different pattern of disruption under these two schedules. The attenuation of CO effects when the schedules alternated appeared to be due partly to the alteration of the stimuli associated with the two schedules. When Ator tested the rats under the FR schedule but alternated stimuli after each reinforcement (multiple FR 30 FR 30), performance was also less disrupted by CO.

On the progressive ratio schedule, the response requirement increases with each successive reinforcement, and the session is terminated when the animal ceases responding for some period of time. The size of the last completed ratio and response rates are the basic performance measures with this schedule. Merigan & McIntire (70) presented a detailed analysis of CO effects on the progressive-ratio performance of rats exposed for 30 min before and throughout testing to 155, 330, 520, and 700 ppm. The size of the last completed ratio decreased for some rats with over 1 hr of exposure to 330 ppm CO (23% COHb). In addition, the response rate decreased slightly and the pause time from reinforcement to the subsequent response increased slightly at the higher levels of CO. However, these latter effects were quite small and the pattern of responding remained intact even at 700 ppm CO (46% COHb).

Only responses separated by more than a specified interval are reinforced on the DRL (differential reinforcement of low rate) schedule. Beard & Wertheim (10) reported response rate decreases in rats working on DRL schedules following exposure to CO concentrations as low as 100 ppm for 12 min. This paper was a conference report with no details of methodology or data analysis described, and the results for DRL were presented in a single figure. Despite these limitations, the results have been strongly emphasized in reviews of CO effects, and are therefore discussed here.

The first issue of importance is the reported sensitivity of performance on DRL schedules to the effects of CO. The data shown are quite extensive, with each data point in the summary figure representing the mean of 60 determinations (a total of 1620 determinations). The authors did not provide the absolute values of response rates, but instead graphically presented the time required for the rate to fall two standard deviations below controls. This is an unusual measure, especially for the DRL schedule, which often produces a low and variable response rate. The resolution with which these determinations could be made was not specified although very fine resolution would be required to detect the decrease after 5 min of exposure to 1000 ppm CO on the DRL 30 sec schedule. It should be noted that a well-trained rat working on this schedule would emit only 2 to 3 responses each min. In addition, no measures of variability were reported, and COHb levels were not measured. For the above reasons, we feel that the dramatic response decreases reported by Beard & Wertheim should be considered preliminary until replicated.

A second issue raised by this study concerns the interpretation of the data. From the response rate decreases the authors concluded that temporal discrimination was readily impaired by CO. However, it is preferable [Kramer & Rilling (46)] to describe DRL responding in terms of the intervals between responses (inter-response times or IRTs). The reported response rate decreases might have been due to a decreased frequency of very short IRTs ("bursts" of responding), decreases in schedule-appropriate IRTs (disordered "timing"), or to a complete cessation of responding. The reader would have benefited greatly from knowing the IRT distributions resulting from control and CO sessions.

Ator, Merigan & McIntire (6) presented a more detailed analysis of DRL performance effects following exposure to CO. Rats working on a DRL 21 sec schedule were exposed to CO during both a 30 min presession and during a 60 min test session. Response rate decreases were found at minimum CO levels of 500 to 750 ppm, which produced COHb levels of 35 to 50%. An analysis of IRT distributions showed that the modal IRT was not moved, indicating that "timing" was unimpaired. Decreased response rates seen at the higher CO levels were due to extended pauses. Contrary to the conclusions of Beard & Wertheim, these findings suggest that the accuracy of DRL performance on "timing" is unimpaired even during CO exposures which almost abolish responding, a finding that resembles what occurs after ethanol (51, 96).

Smith, Merigan & McIntire (97) studied CO effects on the performance of rats working on a fixed consecutive number (FCN) schedule of reinforcement that required at least 20 consecutive responses on one lever before a single response on a second lever was reinforced. Premature switches to the second lever reset the requirement to 20. The control performance was characterized by sequences of consecutive responses (run lengths) appropriate to the schedule requirement, with the modal run length on the first lever at or above 20 responses. Exposure to 200, 400, and 600 ppm of CO during either a 30 or 60 min presession period, as well as during the 45 min test session, reduced the response rates of all rats. The subjects differed greatly in sensitivity, however, with one rat showing reliable rate decreases after exposure to 200 ppm (15 COHb) while the least sensitive of four subjects was only affected at 600 ppm (37 COHb). The reductions were due both to slight decreases in the maximum response rates seen and to extended pauses. CO also impaired the accuracy of responding, shifting the mode of the run length distribution to below the 20 responses required for reinforcement. This type of shift also occurs after drugs such as scopolamine and amphetamine (47, 111) and represents the only instance of a CO effect that does not appear to be explainable as a simple consequence of a rate decrease.

Psychophysical procedures can be used to test explicitly discriminations that may be involved in the schedules described above. Johnson et al (41) studied temporal discrimination performance during CO exposure in three highly trained rhesus monkeys. On each trial, the monkey was presented with an auditory or visual stimulus of 1.0 to 3.5 sec duration. The monkey then chose one of three response buttons, to indicate whether the stimulus was shorter than, equal to, or longer than 2 sec. When stable psychometric functions were obtained, the monkeys were tested following at least 10–12 hr exposure to CO levels ranging from 172 to 575 mg/m^3 (150 to 500 ppm), the greatest exposure resulting in a COHb level of 44%. Although response latency increased slightly, there was no impairment of accuracy on the time discrimination. It should be pointed out that 44% COHb is higher than that produced in any human discrimination studies.

Prenatal Exposure

In the only study of the behavioral consequences of prenatal CO exposure [Fechter & Annau (23)], rats were exposed to 150 ppm throughout pregnancy resulting in a 15% COHb level. Spontaneous motor activity of the offspring was assessed at 14 and 21 days of age. Exposure to CO reduced activity on day 14. The activity of other groups of rats was determined at 1 and 4 days of age following L-dopa injections to increase their low spontaneous activity levels. CO-exposed pups were significantly less active than air-exposed controls following the injections and this was correlated with reduced whole brain dopamine concentrations.

Summary of Changes Observed in Animal Behavior

The most consistent CO effect observed in the above studies appears to be an attenuation of the rate of behavior emitted by the organism. This result has been found with species-specific behaviors such as wheel running and sand hauling [Malorny (62)] as well as with treadmill running [Plevová and Frantík (81)] and swimming [Malorny (62)]. Food and water intake has been shown to decrease during CO exposure [Annau (3); Koob et al (45); Stupfel & Bouley (103)], although a rebound of intake has been observed following exposure. When learned behaviors were tested on a trial-by-trial basis as in shuttle box avoidance [Teichner (104)] or temporal discriminations [Johnson et al (41)], increased response latencies were seen during CO exposure. If the response rate of a learned behavior was not constrained by the experimental procedure (i.e. free operant behavior), exposure to CO invariably resulted in decreased response rates. This reduction in responding has been reported both where control rates of responding are typically very high (70) and very low (6, 10) and is due primarily to extended pauses (6, 97) although there may also be a reduction in the ongoing rate of response (3, 4, 70).

Despite decreases in the rate of responding, the behavior that does occur during CO exposure is often difficult to distinguish from control performance. For example, Ator et al (6) and Johnson et al (41) found that the precision with which temporal intervals were produced or discriminated was unimpaired even during CO exposures that slowed responding. However, as seen above, Smith et al (97) found impairment of the accuracy of FCN responding at the same concentrations of CO that reduced response rate.

In the majority of the studies described above, the first indications of behavioral disruption have been found at exposure concentrations of 200 to 400 ppm for at least 1 hr duration. These were associated with COHb levels of 13 to 25%. These studies include Goldberg & Chappell (28), Johnson et al (41), Merigan & McIntire (70), Plevová & Frantík (81), Smith et al (97), and Teichner (104). Two laboratories have reported dramatic behavioral effects with exposure to much lower levels of CO. First, Beard & Wertheim (10) found disruptions of DRL performance with brief exposures to 100 ppm CO. Unfortunately, only preliminary work was presented in this report and the apparatus and procedures were not described in enough detail to make direct replication possible. A later study by Ator et al (6) found DRL performance to be quite insensitive to exposures even at very high levels of CO. Second, Malorny and his colleagues (62) reported several types of behavioral change following extended exposure to low levels of CO: The length of time rats could swim was decreased after a 7 hr exposure to 100 ppm CO; spontaneous wheel running of mice was reduced by one third after a 14 hr exposure to 55 ppm; and the amount of sand moved by golden hamsters declined considerably after a 4 hr exposure to 50 ppm CO. Both methods and results were only briefly described, however, and the experiments have not been repeated in other laboratories.

HUMAN PERFORMANCE

This part of the review is organized into sections on *Vision and audition; Motor behavior: tracking, coordination, and driving; Time discrimination;* and *Vigilance.* This reflects the current state of the literature, rather than the way in which human behavior would most rationally have been examined if such an enterprise had been planned ahead. For instance, there has been very little work on perception, complex intellectual behavior, problem solving, or decision making. Some of the earliest studies reported on these topics [Schulte (92)] suffered from rather cursory descriptions of procedures and apparently faulty measurements of COHb levels [cf Stewart et al (102); Guest, Duncan & Lawther (33); and Mikulka et al (71) for discussion of this latter point]. Later studies [e.g. Bender et al (12); Bender, Göthert & Malorny (11); Seppänen, Häkkinen & Tenkku (95)] yielded some positive results on simple and very short measures of learning and perception. But little has yet been done drawing upon the wide riches of modern psychology [cf Beard & Grandstaff (9)].

Vision and Audition

Although permanent visual and auditory impairment are common sequelae of severe CO poisoning [Lumio (58); Wilmer (117)], the nature of the sensory effects of lower CO concentrations remains controversial. Possible auditory effects of lower concentrations of CO have received little attention. Guest et al (33) found no increase in the auditory flutter fusion threshold (the lowest rate of white noise interruption that would appear continuous) of subjects whose COHb level was increased to 10%. Stewart et al (102) were unable to find any changes in the audiogram of subjects exposed to 100 ppm for 8 hr (12% COHb).

Possible visual effects of low levels of CO have been explored in a large number of studies. In many of these, the visual tests were part of a battery of screening tests, and, typically, only a small number of measurements were made for each of a large number of subjects. In many cases, no description was given of the visual stimuli or the procedure used to gather the data. For these reasons, it is difficult to determine why studies of the visual effects of CO often have produced seemingly contradictory results.

A most provocative study of the visual effects of CO by Wertheim was reported by Beard & Grandstaff (8). The absolute threshold for detecting light, brightness difference thresholds, critical flicker fusion, and vernier (or offset) visual acuity were measured, with the latter three tests made at each of three brightness levels (2.65, 0.255, and 0.0286 fL). The thresholds of four subjects were measured in four blocks in each session and the test blocks were separated by 35 min. Exposure to 50, 150, or 250 ppm CO began after the first test block and lasted 1 hr. The results for absolute threshold were quite variable and they were not reported. However, consistent impairments in thresholds on the other three measures were found following 27 to 50 min of exposure to 50 ppm (3 to 5% COHb estimated from expired air). Higher CO levels produced even greater threshold changes. Unfortunately, the dramatic results of this study would be difficult to replicate, as many aspects of the procedure and data analysis were not described. For example, only one set of data is described for each of the three tests although they were conducted at three different luminance levels.

Other authors have been unable to detect CO-induced threshold changes on either the visual tests described above or other tests. Stewart et al (102) found that visual acuity, depth perception, and color vision, measured with a Bausch and Lomb Ortho-rater®, were not disturbed following 100 ppm CO for 8 hr (12% COHb). CO-induced increases in blood COHb levels to 7% in smokers and 4.4% in nonsmokers were found by Wright, Randell & Shephard (120) not to produce any effects on night vision, glare recovery, or depth perception. Ramsey (86, 87) could detect no changes in brightness increment thresholds or depth perception following exposure to 300 ppm

CO for 45 min (4.5% COHb), or in brightness discrimination, depth discrimination, or critical flicker fusion after a 45 min exposure to 650 or 950 ppm CO (8.5 to 12.1% COHb).

Although many investigators [Fodor & Winneke (24); Guest et al (33); Lilienthal & Fugitt (56); O'Donnell, Chikos & Theodore (76); Ramsey (87); Vollmer et al (109); von Post-Lingen (110); Weber, Jermini & Grandjean (112); and Winneke (118)] have studied critical flicker fusion during CO exposure, producing COHb levels as high as 26%, impairments like those found by Wertheim (115) have generally not been reported. It may be important that von Post-Lingen, at COHb levels of 20 to 26%, only found decreased flicker sensitivity when a single-blind procedure was used, but was not able to replicate the results with a double-blind procedure.

Recently Seppänen and co-workers (95) demonstrated consistent decreases in critical flicker fusion of smokers and nonsmokers with COHb levels of only 5%. Each subject in two groups of 22 smokers and 22 nonsmokers was tested with CO on one day, and air on a second. The order of CO and air exposure was randomized across subjects and was unknown to the individual subjects (single-blind). The test stimulus was a piece of white paper illuminated by a repetitive strobe light. This stimulus was brighter than the brightest stimulus used by Wertheim. The critical flicker fusion thresholds and certain other nonvisual measures were determined in six 5 min test periods each day. The test periods were separated by 5 min periods during which the subjects inhaled air or 1100 ppm CO through a mouthpiece. The five periods of CO exposure resulted in stepwise increases of COHb levels which reached approximately 13% after the last exposure. Flicker thresholds were slightly, but significantly, decreased after the first CO exposure (5% COHb) and the magnitude of these changes increased linearly with each subsequent exposure (up to 13% COHb).

Thus, the results of Seppänen et al (95) and Wertheim (115) seem at odds with most of the remaining literature. An intriguing possibility is that the clear effects found by Wertheim may be a result of testing vision at lower luminances. However, this hypothesis is not supported by studies of the time course of dark adaptation. Abramson & Heyman (2) did find impaired dark adaptation in four of nine subjects, but only with COHb levels greater than 20%. These levels were achieved by introducing 150 to 200 ml of pure CO into the breathing system. Unfortunately, their study was not well controlled and order effects may have confounded the results. McFarland (64), in a study described only vaguely, was unable to demonstrate any changes in dark adaptation in subjects exposed to 700 ppm long enough to produce blood COHb levels of 17%. Recently, Luria & McKay (59) found a 3 hr exposure to 195 ppm CO (9% COHb) did not impair the ability of dark-adapted subjects to locate stimuli in various regions of the visual field. It remains possible that other visual functions may be more susceptible to impairment under lower luminance. This point is illustrated by the finding of McFarland & Halperin (65) that hypoxic impairment of visual acuity was an inverse function of luminance.

Perhaps the most interesting studies of the effects of CO on vision were carried out in the 1940s by McFarland and his colleagues (36, 63, 68). Some unusual features of these experiments included the use of (*a*) a small number (four) of well-trained subjects, (*b*) high concentrations of CO which elevated COHb levels rapidly, (*c*) dark-adapted subjects who viewed dim stimuli, and (*d*) the measurement of thresholds every few minutes to determine the time course of visual changes. It should be noted, however, that these studies were not conducted in a double-blind manner.

A typical result for one subject is shown in Figure 1. CO administrations are marked by the double-headed horizontal arrows, and blood COHb determinations are marked by the vertical arrows. It can be seen that slight elevations of COHb (e.g. 4.5%) produced reliable increases in thresholds. It should be noted that very high momentary COHb levels may have been reached because of the method of administering CO: "the subject wore a closely fitting oro-nasal mask. . . . Measured amounts of pure carbon monoxide (ranging from 100 to 300 c.c.) were administered slowly into the intake tube of the mask, resulting in the absorption of about one-half of the carbon monoxide administered" [Halperin et al (36) pp 584–85]. The visual changes were very small, in some cases less than the day-to-day variability in the threshold of a subject. However, the threshold elevations were stable

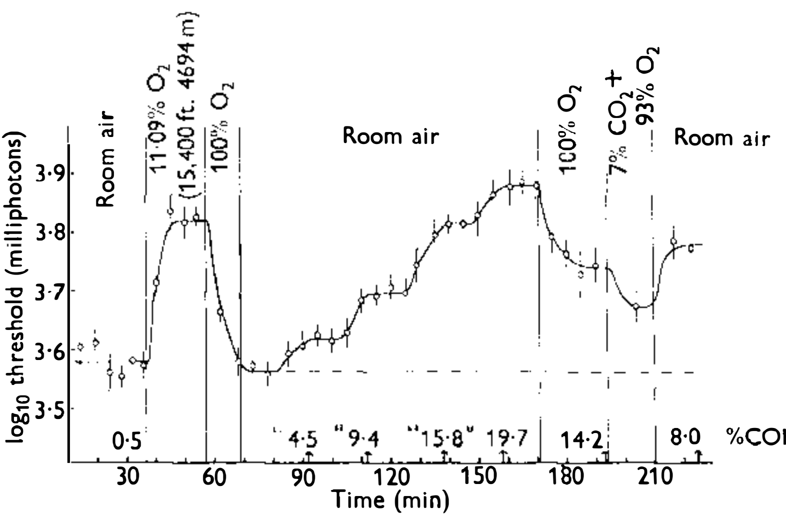

Figure 1 Brightness thresholds of a single human subject. Reprinted with permission from Halperin et al (36).

enough to permit examination of other aspects of CO intoxication, for example, the relative efficiency of pure oxygen and an oxygen-carbon dioxide mixture in combating the effects of CO (cf Figure 1). Using the same technique, McFarland's group later studied the time course of recovery from CO-induced visual impairment [Halperin et al (36)].

Most of the studies described in this section indicate that visual function is quite insensitive to CO. This view is challenged by the great sensitivity of vision reported in the work of McFarland et al (36, 63, 68); Wertheim (115); and Seppänen et al (95). These important studies should be carefully replicated to rule out the possibility of artifactual results (for example, in none of these studies was the double-blind procedure used). Pending such replication, the positive studies suggest the importance of several key variables in determining sensitivity of CO. Certain stimulus parameters, such as illumination level, may be crucial in revealing visual deficits. Use of brief exposures to high CO concentrations may maximize impairment as compared to longer exposures to lower CO levels. Minimizing the variability of measures, for instance, through the use of highly practiced observers, may be necessary to reveal small effects of CO. Explicit parametric examination of the above variables might eliminate much of the present confusion in the visual literature.

Motor Effects: Coordination, Tracking, Driving

COORDINATION Most investigators who have used straightforward measures of coordination report no remarkable effects associated with low levels of CO. For instance, Stewart et al (101, 102), at COHb levels as high as 15%, found negative results with tests requiring subjects to pick up small pins, put them in little holes, and place collars over the pins as rapidly as possible. Work with two subjects at 30%, however, provided evidence that interference with this performance could eventually be produced. Negative results with other coordination and hand steadiness tests have also been reported by Stewart et al (101, 102), as well as by Wright et al (120), Fodor & Winneke (24), and Winneke (118). An exception to this general picture is provided by Bender et al (11, 12). They reported that following exposure to 100 ppm for about 2.5 hr (7% COHb level), subjects showed small but significant degradation of performance on two versions of the Purdue Pegboard test, one of which required them to engage in a concurrent verbal task.

No changes on any of the measures of ataxia included in the Pensacola Ataxia Battery were seen by O'Donnell et al (77). For example, the ability of men with eyes closed to walk a straight line or to stand on one leg was not adversely affected by a 3 hr exposure to 125 ppm, which produced an average COHb level of 6.6%.

TRACKING Two double-blind studies by Putz and his colleagues examined compensatory tracking and vigilance tasks concurrently. In the first experiment [Putz (83); Putz, Johnson & Setzer (84)], 30 healthy young men and women were exposed to 5, 36, and 74 ppm CO for 4 hr producing COHb levels of 1%, 3%, and 5.1%, respectively, at the end of exposure. The tracking task required keeping a small, white spot centered in a target ring on an oscilloscope face by adjusting a hand control to cancel out unpredictable vertical oscillations of the dot. The subjects worked on this tracking task for 16 55-sec trials confined to half of each hour of a 4 hr exposure period. The subject concurrently reported occasional increases in the intensity of two red lights, about 25° to the left and right of the central target ring. (Performance on this part of the dual task is described under *Vigilance* below.) Two distinct levels of tracking difficulty, in which vertical oscillations of the dot that was to be kept centered occurred at either 4 or 7 cycles per min, were examined. Increases in tracking errors appeared during the fourth hour of exposure to CO, but only at the higher oscillation rate. The COHb levels were approximately 5% at this time.

In a second study, Putz, Johnson & Setzer (85) examined the effects of both methylene chloride and CO. A repeated measurements design was used in which 12 subjects performed on three separate days at weekly intervals. Exposure to CO for 4 hr at 76 ppm produced a mean COHb of 4.8% immediately after the exposure while a 195 ppm methylene chloride exposure produced a mean level of 5.1%. For both substances significant decrements in performance appeared, but again only on the more difficult of the two tracking tasks. (Results on the vigilance parts of this dual task are discussed under *Vigilance* below.)

Despite the long history of interest in laboratory-based tracking behavior by workers in applied experimental psychology, little else has been done with CO. O'Donnell, Chikos & Theodore (76) used a task requiring the subject to keep a needle within prescribed limits on a dial for 1 min, while simultaneously monitoring three other dials whose pointers occasionally moved off their null positions. In a second version, the subject also had to count the number of times a light flashed. In each case only two 1-min trials were run and no changes were seen at 12.7% COHb. A more complicated task was also used in another study by this group [O'Donnell et al (77)] in which subjects worked on a compensatory tracking procedure, the difficulty level of which progressively increased until the subjects could no longer compensate successfully for the imposed deviations. A significant decrement was seen about midway through a 3 hr exposure to 125 ppm CO, which subsequently disappeared near the end of the exposure period. After examining the individual performance curves, the authors concluded that the difference was not really trustworthy. It is well known from work with drugs and with sleep deprivation that short tests tend to be less sensitive than longer ones (114, 116), and in their studies tracking never lasted more than about 5 min at a time. This factor may be important in accounting for the difference in results between these three studies and the two by Putz and colleagues described previously.

DRIVING The effects of CO on automobile driving and various simulations of it have been studied since 1937; yet, in that time, only a handful of papers have appeared. In the first, Forbes et al (25) produced COHb levels as high as 30% but failed to find any changes in a variety of reaction time, coordination, and perceptual tests presented within the context of a simulated driving skills test. However, they failed to use a control group, making the results uninterpretable. More recently, two groups studied CO's effects upon actual driving performance but few details have been published by either [Weir & Rockwell (113); McFarland and his colleagues (64, 66, 67)]. Weir & Rockwell made a series of preliminary studies in which the subject drove a car that was yoked by a thin wire to another car so that separation between the two could be monitored. They also measured steering wheel reversals and many other aspects of driving. However, a great deal of intersubject variability led the authors to be very circumspect in their conclusions. It appears wisest to consider these studies as valuable primarily in providing leads for future work.

An imaginative study by McFarland and his group (64, 66, 67) concerned the amount of visual information needed by a driver to maintain his position in his lane on the highway. The driver wore a helmet with a shield that prevented him from seeing the road. By depressing a foot switch he could briefly raise the shield. He was instructed to do this sufficiently often to keep his car within the lane while maintaining a constant speed of either 30 or 50 mph on different trials on the deserted expressway that was the scene of this heroic experiment. [This task was devised by Senders et al (93) and is remininiscent of Katz & Spragg's work on tracking performance in the laboratory under conditions of intermittent illumination (43).] Ten drivers were used, each serving as his own control, and each exposed to air or to enough 700 ppm CO to produce a COHb level of 17%. The results, although not reported in detail, suggested that under CO the subjects required more roadway viewing when driving at the higher speed [cf Safford (90) for another study suggesting the same conclusion, this time measuring how long drivers could close their eyes while maintaining lane position].

Two recent driving experiments used simulated driving tasks. In a study by Wright et al (120), no effects were found of a measured amount of 20,000 ppm CO that produced an increase in COHb of 3.4% over the pre-CO level, smokers averaging 7.0%, nonsmokers, 4.4%. However, when the various performance measures were categorized as either "brisk automatic responses to emergencies" (e.g. braking) or "careful driving habits" (e.g. releasing the parking brake, making turn signals) the authors found a marginally significant deterioration in the latter. Since this was a post-hoc analysis, the finding should be regarded only as a provocative lead for future work.

The other simulator study [Rummo & Sarlanis (89)] nicely illustrates how driving possesses characteristics of both vigilance and tracking tasks. A very realistic driving simulator was made from a two-door sedan with automatic transmission. A series of movable belts and an optical lens system provided the subject with a strong illusion that he was seeing 750 ft (229 m) of roadway ahead of him. His task was to move the steering wheel in order to keep the car within his lane and to stay at a specified distance from a lead car. The lead car's speed was occasionally varied with 40 changes occurring during an uninterrupted 2 hr test period. Acceleration or deceleration of the lead car occurred at a speed of one mile/hr/sec. The time required by the subject to respond to this slight change was recorded. CO at 800 ppm was administered only for 20 min prior to the simulated drive and the seven subjects averaged 7.6% COHb at the beginning and 6.0% by the end of the test period. CO and room air treatments were counterbalanced among subjects, with each subject exposed once to each after two practice sessions. The subjects, but not the experimenters, were unaware of the treatment condition. The mean reaction times to the changes were 7.8 sec under the control conditions and 9.6 sec under CO, a statistically significant effect.

Rummo & Sarlanis (89) saw no change in the way subjects responded to a dashboard warning light that was flashed on at random intervals. This finding agrees with other reports on reaction time to signals during driving simulator tests: Both Wright et al (120) and Stewart et al (102) also failed to find increases. In the former case the COHb level reached was only 3.4% above that shown before CO exposure; in the latter it was about 16%. In all three of these negative studies, the signal was very explicit and greatly above detection threshold. The positive findings of Rummo & Sarlanis occurred with a much more ambiguous stimulus, i.e. a speed change by the lead car.

That the differences in reported reaction times are due to the saliency of the stimulus gathers additional support from a brief report by Ray & Rockwell (88). They examined the effects of 0, 10, and 20% COHb on the actual driving behavior of three men, each of whom was exposed to the three experimental conditions. These levels were attained by having them breathe either 0, 950, or 1900 ppm CO from rubberized canvas bags. The subject rode in an automobile yoked by a taut wire to a lead car driven ahead of it and attempted to detect slight changes in the relative velocities of the two vehicles while the lead vehicle was about 60 m in front. Time required to respond to a velocity change of 2.5 miles per hr was approximately 1.3 sec for the control condition, 3.3 sec when the COHb level was about 10%, and 3.8 sec when it was about 20%, with the changes considered to be statistically reliable. Changes in relative velocity are presumably more difficult to detect than the sudden appearance of a bright dashboard light; said another way, stronger stimulus control is exerted by the dashboard light. It may be that the greater likelihood of CO-induced change shown by behavior under weak stimulus control during these driving tasks is another example of the way that the degree of stimulus control can modulate the effects of chemicals on behavior (37, 52).

Time Discrimination

This section will take as its point of departure a study reported in 1967, which, although flawed in some respects, was very influential in determining the direction of research over the following decade. Beard & Wertheim (10) presented human subjects with a long series of paired tones, the first of which was always 1 sec long and served as the standard. The subject reported whether the second tone was shorter, longer, or the same length as the first by pressing one of three buttons. It took 6 to 7 min to complete each block of 50 trials and the subject then had about 13 min during which he could either read, rest, or watch television, while remaining isolated in the small (110 ft^3) sound-insulated audiometric booth used as an exposure chamber. This cycle of working approximately one third of the time and resting the other two thirds was repeated three times per hour for 4 hr so that a total of 600 judgments were made during each experimental session.

These details are given in an effort to emphasize an aspect of the experiment that was not originally recognized as important, namely that the testing conditions themselves, especially the isolation of subjects from the experimenter, may have been important in determining the results. Eighteen university students were exposed to 0, 50, 100, 175, and 250 ppm CO three times each. The subjects but not the experimenters were blind as to the particular exposure condition, which started after the subjects had worked in the booth for 30 min and continued for the next 2.5 hr. The mean percentage of correct responses averaged about 78% at 0 ppm. The authors measured the time required for each concentration of CO to produce a decrement in performance greater than two standard deviations in magnitude. Exposure to 50 ppm CO for only 90 min produced a statistically significant decrement while it took 50 min with 100 ppm, 32 min with 175 ppm, and 23 min with 250 ppm CO to produce similar changes. COHb levels were not measured and can only be estimated at this time. According to the equations of Coburn, Forster & Kane (17), these levels should have ranged from 2.5 to 5%.

Two groups immediately attempted to replicate these important findings on the same time discrimination task. In one case, O'Donnell, Chikos & Theodore (76) used an experimental design involving incomplete counterbalancing (the 0 ppm exposure condition was always administered last) and this diminished the value of the study. In addition, the task was embedded within a 1.5 hr series of tests that included measures of tracking, vision, time estimation, and mental arithmetic. Subjects thus spent approximately 6 to 7 min twice during that time on the replication of the Beard and Wertheim experiment, making the context of testing very different in the two studies. However, no trend could be seen in values reported for the two exposure conditions of 75 and 150 ppm for 7.5 hr, which resulted in COHb levels of 5.9 and 12.7%, nor did the values differ from the control level.

A second group, Stewart et al (100), used the same auditory time discrimination task in different ways that resulted in different effects. The experiment was originally done in a large room with subjects seated on one side of a table while they all listened to the tones and made their judgments. Under these conditions, no differential effects were seen with COHb levels that went up to almost 20% (all exposures were double-blind). Nor were effects seen when subjects were studied one at a time in the large experimental room. However, when the men were tested in an audiometric booth similar to that used by Beard & Wertheim (10) a statistically significant decrement in performance appeared, associated with a mean COHb saturation of 9.7%. (The exact exposure parameters that led to this level were not given, but most exposures in this work were to 100 or 200 ppm for from 2.5 to 5 hr.) The performance decrement of 2.9% was a far cry from the large drop in performance reported by Beard & Wertheim at a level estimated to be much lower. Possibly important is the fact that in the Stewart et al experiment, subjects did not experience the same degree of isolation as they did in Beard and Wertheim's since they were free to interact between brief periods of testing in the isolation booth. However, a recent attempt to replicate the Beard & Wertheim experiment, using a very high degree of social isolation, also failed to show CO effects [Otto, Benignus & Prah (79)].

Thus the picture is still unclear regarding the specific time discrimination task first studied by Beard & Wertheim. Regardless of the outcome of subsequent attempts at replication of the findings with this precise experimental paradigm, it is quite unlikely that these results are typical of the effects of CO on timing behavior in general. Several other studies have shown that CO, even at COHb levels high enough to produce headaches, does not have marked effects upon ability to reproduce intervals from 1 to 30 sec, either by matching the length of an auditory or visual stimulus or of a verbally specified interval by holding down a button for the indicated amount of time [Stewart et al (99, 100, 102)], or by repetitively responding every *n* sec [O'Donnell, Chikos & Theodore (76); Mikulka et al (71)]. Such findings fit quite well with the available animal data on timing behavior and discrimination (see *Animal Performance*).

We suggested above that Beard & Wertheim's (10) use of *isolated* subjects working on a rather boring task was a potentially important feature of their experiment. This isolation made their situation resemble one that psychologists have investigated extensively, called watchkeeping, monitoring behavior, or, most commonly, vigilance [Davies & Tune (20); Holland (38); Mackworth (60, 61)]. It is to this topic that we now turn.

Vigilance

On this type of task the subject is asked to detect and report small environmental changes ("signals") occurring at infrequent intervals and therefore requiring continuous attention. These signals may or may not be embedded among closely similar stimuli that are not signals. Characteristically, the subject's response does not itself affect the occurrence of the signals.

The term *vigilance* refers to an area of behavior rather than to a specific procedure. In discussing its literature we cite more details concerning tasks than would be necessary if we were dealing with standardized test procedures. While there are many similarities, there are also large differences among tasks. By specifying these differences, we hope to sensitize potential researchers to parameters that may determine the effects of CO. The importance of the length of the task has been mentioned in connection with other tests; it is no less important here. Both the signal rate and the relative number of signals among the stimuli presented may influence performance on these tasks, with rare signals making the task more difficult [Davies & Tune (20); Mackworth (61)]. It is quite likely that sensitivity to chemical agents interacts in complex ways with such parameters. This is certainly the lesson that has been learned on the animal level in behavioral pharmacology, where a detailed examination of the controlling variables has proved the most powerful approach to an understanding of drug effects on behavior (44, 53).

DETECTION OF AUDITORY SIGNALS Three types of auditory vigilance tasks have been studied. Groll-Knapp et al (31) presented subjects with pairs of tones of unspecified intensity, the second shortly after the first. If the second tone was "slightly weaker," it was a signal and was to be reported. Neither the frequency of nonsignals nor the time interval between pairs was specified. However, in a 90 min test period, 200 signals of this type appeared, making the mean signal rate 2.2 per min. (Table 1 summarizes the details of the parameter values that seem most important for this and other studies.) Exposure to CO at 0, 50, 100, or 150 ppm started 0.5 hr before the test and lasted for a 2 hr period. COHb concentrations were not

Table 1 Some characteristics of the auditory vigilance tasks

Studies	Signals per min	Percentage of stimuli that were signals
Groll-Knapp et al (31)	2.2	not specified
Fodor & Winneke (24)	1.0	3
Winneke (118)	not specified	3
Putz et al (85)	2.8	11
Putz et al (84)	8.7	36

measured but were estimated to have reached about 3% with 50 ppm, 5.4% with 100 ppm, and 7.6% with 150 ppm by the end of the period. Whether or not smokers were excluded was not specified. Under control conditions, subjects detected an average of 87% of the signals during the test. For the three CO levels, this figure dropped to 82% with 50 ppm, 80% with 100 ppm, and 78% with 150 ppm, with all three CO groups differing significantly from controls. However, the reliability of the results has been brought into question by the authors' later report that they were unable to replicate their finding; unfortunately, no further data have actually been published [Groll-Knapp et al (30); cf Haider et al (34)].

A second type of auditory vigilance task was described by Fodor & Winneke (24). In this procedure, short pulses of noise were presented at 2 sec intervals. Three percent of the pulses, spaced randomly so as to occur at about 1 per min, were slightly less intense than the others. These were the signals the subjects were to report. Exposure to either 0 or 50 ppm CO was started 80 min before the first of three 45 min vigilance tests that were separated by 5 min intervals. COHb levels were not measured but were predicted to reach 3.1% at the end of the first, 3.7% at the end of the second, and 4.3% at the end of the last test. The subjects detected 80 to 88% of the signals under control conditions. Many more signals were missed under CO exposure but the effect lasted only for the *first* 45 min test, during which time subjects detected only 67% of the signals. Differences did not persist during the final two tests even though the COHb levels presumably continued to rise.

A few years later, Winneke (118) reported another study of CO with substantially the same auditory vigilance task, in which signals were either 3.8 or 4.8 db less intense than the nonsignals (in unspecified proportions) rather than the uniform 3.8 db of the previous study. Exposures to 0, 50, or 100 ppm CO for 4 hr had no effect, with differences not even in the expected direction, even though COHb (not measured directly) was estimated to have reached about 9%. It is unclear what caused the failure to replicate. The use of the slightly more detectable signal may have been important. When this type of auditory vigilance task was also used by Putz et al (85), it proved quite sensitive to CO and to methylene chloride, both given in quantities sufficient to produce COHb levels of about 5% (76 ppm CO, 195 ppm MeCl for 4 hr). Rather than two different intensities, three were used, with 40 db and 44.5 db being the nonsignals, while 35.5 db noises constituted the signals. Under control conditions the subjects averaged 63% correct detections, whereas they averaged only 40% correct after CO or methylene chloride exposure. The significant effects occurred while they were working on the third 30 min vigilance session, which occurred at the beginning of the last of 4 hr of exposure. Response latencies also increased significantly at this time.

The final type of auditory-vigilance task investigated with CO utilized a frequency discrimination procedure [Putz et al (84)]. Three 1.5-sec tones of equal intensity (80 db) but different frequencies 400, 1000, and 2000 Hz, were presented in a scrambled order every 2.25 sec for 15 min every hr. The middle frequency, presented 36% of the time, was the signal. At other times during the hour, subjects worked on the dual task described above under *Tracking* [Putz (83)]. The frequency discrimination procedure proved completely insensitive to disruption by CO, with the level of correct detections remaining at about 80% throughout exposures to 5, 36, and 74 ppm for 4 hr. Response time for correct detection also did not change. The highest COHb levels reached were about 5%.

Summary and further comment Groll-Knapp et al (31), at an estimated 3% COHb level, obtained positive results using a task on which subjects reported whether the second of two brief tones was slightly weaker than the first. They subsequently reported difficulty in replicating the earlier findings. Fodor & Winneke (24) described some detection deficits at an estimated 3% COHb level when subjects were to report less intense than usual noises. While Winneke (118) could not replicate this with subjects at an estimated 9% COHb, Putz et al (85), using a modification of the procedure, did succeed in finding an effect of CO at about 5% COHb. Putz's version differed, however, in several ways from Fodor & Winneke's, perhaps most importantly in the level of difficulty of the task. Despite a higher signal rate and a greater percentage of signals, the detection level was only 63% under control conditions as compared to 84 to 88% in the earlier studies. Putz et al (84) also used a different type of auditory vigilance procedure in which the subject was required to report the intermediate of three frequencies. The higher signal rate and greater percentage of signals combined to produce an easier task: 80% of signals were detected under control conditions. They failed to find any changes after exposure to enough CO (74 ppm for 4 hr) to produce about 5% COHb.

DETECTION OF VISUAL SIGNALS Four distinct methods have been used to study the influence of CO on the detection of visual signals. Already described above (under *Driving*) was a study of how CO modified the ability of men to detect apparent separation of simulated automobiles on a highway [Rummo & Sarlanis (89)]. The resemblance of this 2 hr driving simulation task to the vigilance situation was deliberate. In fact, the authors remarked that the task "was designed as a vigilance task that closely simulated a real-life situation of prolonged driving on a little-traveled road under twilight conditions. Nearly all the subjects remarked that the driving was realistic but boring" (p. 129).

The most common method involves the use of a light that occasionally increases in intensity above a background luminance. In addition, the detection of slightly briefer than normal visual stimuli, and the detection of triads of odd or even numbers embedded within long strings of numerals presented one at a time have been investigated.

Increases in intensity In the first published study of CO and vigilance, Horvath et al (40) [cf O'Hanlon (78)] placed a dimly lit 1 in. (2.5 cm) in diameter ground-glass disk about 3 ft (0.9 m) away from their subjects. Every 3 sec the disk brightened slightly for 1 sec. The increment used to change a nonsignal into a signal was determined first for each subject, with the criterion being a detection level of 80 to 90% correct, with fewer than 5% false detections. Two types of tests were then made. First, in a 3 min test the light brightened 60 times but on ten randomly interspersed occasions became slightly brighter than usual. Then, after a minute's rest, a 60 min vigilance test was conducted during which the subject was shown 1200 of the 1 sec disk brightenings and on 40 randomly interspersed occasions slightly brighter "signals" appeared. (Details of the signal frequencies for this and other studies are summarized in Table 2.) Before these tests started, each subject was exposed for 1 hr to either 0, 26, or 111 ppm CO. They were then exposed further to CO during the vigilance tests. Measured COHb levels with 26 ppm were 1.6% after the first and 2.3% after the second hr; with 111 ppm they were 4.2% after the first and 6.6% after the second hr.

Performance on the short 3 min test with the high signal rate was not modified by these exposures, whereas that on the low rate vigilance test was significantly degraded by 111 ppm. The largest effect was seen three quarters of the way through the test, when correct signal identifications dropped from about 70% under control conditions to about 53%. It is tempting to conclude that the difference between the two tests with different signal rates argues that the signal rate contributed to CO's effects; unfortunately, the higher rate was also associated with a shorter duration test. In addition, a reversal of the sequence of tests would be required to rule out a possible

Table 2 Some characteristics of the visual vigilance tasks

Studies	Signals per min	Percentage of stimuli that were signals
Horvath et al (40)		
Initial 3 min test	3.3	17
Vigil	0.67	3
Christensen et al (15)		
Initial 5 min test	3.3	17
Vigil	0.67	3
Winneke et al (119)		
Initial 5 min test	3.3	17
"Less monotonous" vigil	2.0	10
"Monotonous" vigil	0.67	3
Putz (83)	4.4	25
Putz et al (85)	4.4	25
Beard & Grandstaff (9)	0.33	1.4
Benignus et al (13)	1.6	50
Rummo & Sarlanis (89)	0.33	not relevant

order effect. The relative importance of these factors cannot be determined from the data at hand.

Two attempts to confirm the results of Horvath et al (40) have been made, but both have been unsuccessful. Christensen et al (15), from the same laboratory, used approximately the same CO exposure level (114 ppm), but added two conditions, both a 17% O_2 exposure and a combination exposure to 113 ppm CO and 17% O_2. Exposures were for a slightly shorter duration and consequently CO exposure alone did not produce a COHb level as high as that in the previous experiment (4.8% versus the 6.6% of Horvath et al). Signal detection was not significantly impaired by CO. The only statistically significant performance decrement occurred with low oxygen alone. Somewhat surprisingly, the combination of 113 ppm CO plus 17% O_2 produced performance that did not differ from that found with 21% O_2.

In their replication of the Horvath et al experiment, Winneke et al (118) added an intermediate monotony level by using an intermediate signal rate. (This was not a direct test of the influence of signal rate since the subjects were also given both feedback on their detection rate and short rest pauses.) Exposures were to either 0 or 100 ppm for 2.5 hr, or to 200 ppm for 1 hr followed by 150 ppm for 1.5 hr, producing COHb levels of 1.0, 7.5, and 11.3%, respectively, at the end of the exposure periods. No behavioral changes appeared under any treatment.

Figure 2 contains curves plotted from data culled from these three quite similar vigilance studies. The figure illustrates the difficulties encountered by workers in this area when they have attempted to replicate either their

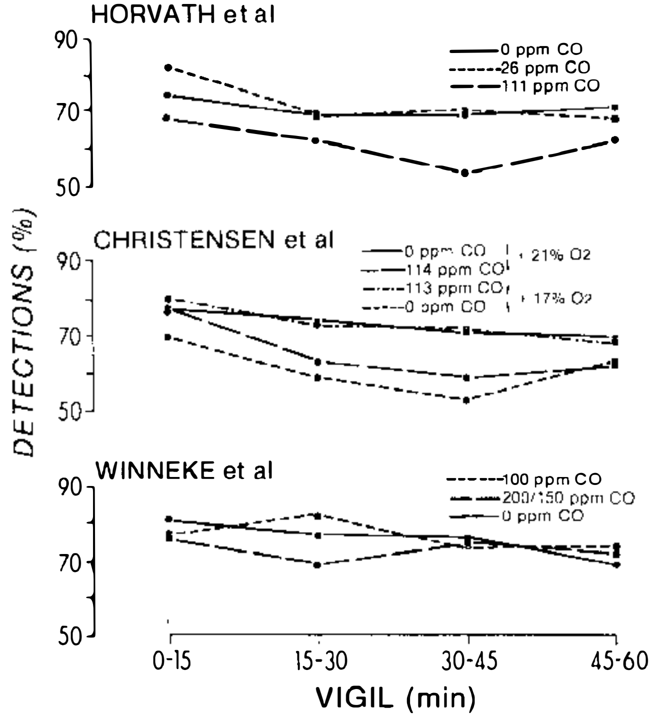

Figure 2 Three experiments on carbon monoxide and visual vigilance, all of which used the same basic methodology. The curves have been plotted with data taken from the curves presented by Horvath et al (40), the histograms of Christensen et al (15), and the tables of Winneke et al (119).

own or their colleagues' results. Particularly striking is the way in which the 114 ppm CO results from Christensen et al (15), though failing to reach statistical significance, followed the pattern of the earlier 111 ppm CO curve of Horvath et al (40).

One factor common to all three studies, and indeed to all vigilance studies that work with near threshold stimuli, was an aspect of the procedure that may have introduced a confounding variable: If CO influences the threshold for brightness, as it very well could, it would have modified detection levels in a way that would be unrelated to the vigilance dimensions that most interested the investigators. The importance of this factor cannot be assessed from the published papers.

Putz (83) studied visual vigilance with the context of the dual task described under *Tracking* above: Subjects worked on a compensatory tracking task while simultaneously monitoring the intensity of lights that occasionally flashed in the periphery. Exposure to 74 ppm CO produced about

5% COHb and did not change detection levels. However, response latencies to detected signals increased reliably with increasing exposure duration. In the second study of CO, which also included work on methylene chloride, Putz et al (85) substantially replicated the earlier findings using concurrent tracking and visual vigilance tasks. Subjects again took significantly longer to report signals after exposure to CO (76 ppm for 4 hr) or methylene chloride (195 ppm for 4 hr) that produced COHb levels of about 5%, while the detection rate itself did not change. This study permitted analysis of the influence of tracking difficulty on vigilance performance. The change in latency of response appeared only when the subject worked on the more taxing of the two difficulty levels.

Decreases in duration Beard & Grandstaff (9) reported positive results with a visual vigilance task in which the signal consisted of a slightly shorter duration light flash than was usually programmed to occur. The subject, seated in a small audiometric booth, faced a 3 X 3 in (7.6 X 7.6 cm) electroluminescent panel 2 ft (0.6 m) from his eyes. Every 2 sec this panel was lit, usually for 0.5 sec, but occasionally only for 0.275 sec, a signal to be reported by the subject.

Four 30-min vigilance periods occurred during an experimental session, the first before gas exposure had started and the last after it had ceased. Exposure to either 0, 50, 175, or 250 ppm CO (double-blind) began at the beginning of a 10 min rest period that separated the first and second vigils. After the second vigil, another 10 min rest preceded a third vigil, following which the gas exposure terminated and the last vigil occurred. COHb levels were estimated from alveolar breath samples taken before testing and after the last vigilance test, i.e. 30 min after exposure to CO had ceased. The pretest levels were always below 1%, whereas the post-test levels averaged 1.8% for 50 ppm, 5.2% for 175 ppm, and 7.5% for 250 ppm exposures.

Subjects who had been exposed to only room air detected about 74% of the signals during the last three vigils. Both the 50 and 175 ppm exposures produced detection rates of 64%, while the 250 ppm exposure yielded a rate of about 70%. The decreases following the exposure to 50 and 175 ppm were reported to be statistically significant with a one-tailed t-test. In this case, the authors speculated that at the 250 ppm exposure level, compensatory physiological reactions may have partially counteracted the deficit produced by the gas.

Triads of numerals Benignus et al (13) [cf Otto et al (80)] used a procedure that had many of the characteristics of the vigilance test but which featured a more complicated signal than usual. Subjects were presented with a sequence of single numerals flashed on a screen for 0.05 sec every 1.5 sec, and instructed to report any appearance of three odd or three even numbers in a row. A total of 27 such triads occurred during each 16.7 min test period. On 27 other occasions, runs of two odd or two even numbers appeared. Following a short rest, the test was repeated and this sequence continued until ten such tests were made over a 3 hr 20 min session. Exposures (double-blind) to either 0, 100, or 200 ppm CO (yielding COHb levels of 0.01, 4.6, and 12.6%, respectively) were started after a single practice period and a preexposure baseline period and continued until eight more test periods had been completed. Absolute error scores were not reported. Instead, difference scores, expressing changes from the preexposure baseline performances, were given. These did not change reliably with the possible exception of a transient increase in error rate during the first two testing periods after exposure to 100 ppm. However, after considering the possibility of this being a true early effect subsequently erased by some sort of compensatory mechanism, such as the CO-induced increases in cerebral blood flow described by Traystman (106), the authors decided that the lack of a similar change after 200 ppm exposure made this unlikely. They perhaps were influenced in this decision by the results of a pilot study that had been completely negative, with not even a trend in favor of a CO effect [see Exp. 1, Otto et al (80)].

Summary and further comment Four studies were concerned with the detection of occasional brightness increments. At about a 5% COHb level, Horvath et al (40) found positive results while Christensen et al (15) found, if anything, only marginal effects. An attempt by Winneke et al (119) to replicate these findings at COHb levels as high as 11% failed. Finally, at a 5% COHb level, positive results on a peripheral-brightness-monitoring task that occurred in conjunction with a tracking task were found twice by Putz et al (83, 85). Beard & Grandstaff (9), using a technique that required detection of occasional shorter-than-usual stimuli, obtained positive results at about 2% COHb. In a simulated-driving vigilance task, Rummo & Sarlanis (89) found an effect at a COHb level of about 7% upon ability to detect changes in the relative speed of automobiles. On the other hand, Benignus et al (13), with as high as 13% COHb, found no change in the detection of runs of three odd or three even numerals that appeared amid long trains of digits flashed one at a time.

While we fully recognize the dangers of post hoc analysis, we suggest two ways that the studies reporting positive findings differed from those with negative results. The Beard & Grandstaff (9) and Rummo & Sarlanis (89) studies had the lowest signal rates (see Table 2), which may be the source of their sensitivity if, indeed, their findings prove to be replicable. Similar reasoning would at first glance seem to make the Putz et al (83, 85) studies very insensitive as their signal rates were the highest of all. But, in both Putz studies, visual vigilance tasks were run concurrently with a tracking task.

This may have more than compensated for the rather unfavorable signal rates. It is quite likely that concurrent performances are more easily influenced by CO just as they are by alcohol [Moskowitz (72)].

Changes Observed in Human Behavior

Some behavioral changes seem to be associated with COHb as low as 5 to 8%; the scattered reports of impairment at lower levels of COHb are not very compelling. The strongest evidence for such effects comes from work on vigilance (83, 85), driving (89), tracking (83, 85), and vision (36, 68, 95, 115). Even here, however, our confidence would be greater if the findings were buttressed by independent confirmation.

The most common impairment is a depression or slowing of responding, an effect similar to that found in animals. No studies describe CO-induced increases in rate, accuracy, quality, or intensity of behavior. Although the observed response depression may reflect a variety of changes in CNS function, it is common to many of the behaviors investigated, with the magnitude of observed slowing depending upon the precise way performance was tested. For example, compensatory tracking was degraded only when the vertical oscillations to be matched by subjects occurred at the higher of two rates used. In driving studies, slowed reactions were often found only to less salient stimuli: Reactions to gradual increases in the speed of a lead automobile were slowed by CO whereas reactions to a dashboard warning light were not. Subjects also reacted more slowly when they detected signals on a vigilance task that was part of a dual procedure that included compensatory tracking. The only measure of coordination on which performance was impaired was the timed Purdue Pegboard test of the rate of assembly of pegs, bushing, and rings.

A general depression of responding may also partially account for decrements in vigilance performance: Fewer observing responses by subjects could lead to fewer detected signals (38). There may, however, also be direct effects on other aspects of vigilance performance, such as changes in sensory thresholds or decision criteria. Changes in visual threshold, even though small, may have important consequences for other types of performance. For instance, if visual function during CO exposure is impaired primarily at low luminance levels, then already marginal night vision might be critically degraded.

DIRECTIONS FOR FURTHER RESEARCH

To date, the animal literature has clearly demonstrated response-rate-decreasing effects of CO and has suggested an approximate range of minimally effective CO concentrations. However, other major issues in the behavioral toxicology of CO have scarcely been broached in animal studies. The differential sensitivity of various types of behavior to disruption by CO has not been systematically explored in comparative studies that could point to behaviors most at risk (e.g. high vs low response rate, learned vs unlearned, or performance under strong vs weak stimulus control). Despite the absence of such systematic studies, some hypotheses can still be derived from a comparison of the available data. The studies of McIntire and his colleagues (4, 6, 70, 97) suggest that performance maintained by reinforcement schedules generating high rates of responding (e.g. FCN or progressive ratio) may be more readily disrupted than those producing low response rates (e.g. DRL). Malorny's finding (62) that several unconditioned behaviors were sensitive to CO disruption could reflect either a greater sensitivity of unlearned behaviors or the greater physical exertion involved in unlearned behaviors such as swimming, digging, and running [cf Seppänen (94)]. The dependence of CO effects on amount of physical activity has been recognized since Haldane (35) [cf National Research Council, pp 152–60, (74)].

A second unresolved issue is the relative importance of various parameters of CO exposure (concentration, duration, COHb level) in determining the extent of behavioral impairment. Plevová & Frantík (81) demonstrated that COHb level was not the primary determinant of an observed decrement in treadmill running. This result, which should be replicated and extended, is consistent with other evidence that suggests COHb level is not related in a simple fashion to CO toxicity. Both continuous and repeated exposures to CO need to be examined over prolonged periods to determine whether significant behavioral adaptation occurs. There are hints of such adaptation in the data of Annau (3) and Goldberg & Chappell (28), and in a recent study in which behavioral adaptation was found in the FCN performance of rats [Ator & Merigan (5)]. It is not known whether this phenomenon differs from the adaptation seen with other aspects of the biological response to repeated or chronic exposure to CO [National Research Council, pp 160–64 (74)].

There is also a great need to continue the work of Fechter & Annau (23) in examining the behavioral consequences of prenatal exposures to CO. This study, as well as the work of other investigators [cf Longo (57)], suggests that the developing organism may face grave risks when the mother is exposed to CO from cigarette smoke or other sources. Careful behavioral research could help delineate the extent of the hazard and the precise nature of possible behavioral sequelae.

As we have seen, the human literature is replete with contradictory findings. Some investigators have reported that low levels of CO influence a particular aspect of human behavior, whereas others, and on occasion the same investigators at a later time, have reported completely negative results. However, the following generalizations about the literature seem warranted.

First, there are undoubtedly interactions between the effects of CO and various characteristics of the particular behavior under study, e.g. parameter value, test length and complexity, presence of a concurrent activity. In studies of vigilance, signal rate may be of particular importance. The role of social and motivational variables has also been mentioned. Very few investigators have attempted to explore any of these systematically, despite their known importance in the study of other environmental stressors such as sleep deprivation, drugs, vibration, and noise (114, 116).

Second, most CO effects appear to be truly marginal. CO probably does not have large and consistent effects upon behavior when given for short periods at low levels. Therefore, the ease with which effects can be established is heavily dependent on such factors as the reliability of tests used, amount of practice, the number of subjects, their physical condition, and the adequacy of the data treatment. In animal research the usual functional relationship established between dose or exposure level and effect provides a guarantee that the techniques used were sensitive to the agent in question. In work with humans, however, levels high enough to produce unambiguous effects are rarely used. Consequently, investigators are often unsure whether they observed an impairment, and, if so, its precise nature. The determination of dose-effect relationships would certainly help bring order to this area. Whenever this proves impossible, standard or reference substances should be included in research protocols to provide a positive control as evidence of task sensitivity, which would especially aid in the interpretation of negative results (39, 48).

Third, the dose-effect and time-effect relationships for CO may not be monotonic. Several investigators have reported CO effects that appeared only transiently, diminishing in magnitude or disappearing completely as exposure continued [e.g. Fodor & Winneke (24); Benignus et al (13)]. Others have reported reversals, with higher exposure levels apparently producing less effect than lower ones [e.g. O'Donnell et al (77); Beard & Grandstaff (9)]. The possibility of physiological compensatory mechanisms, triggered when certain levels are reached, has been discussed by Fodor & Winneke (24), Bender et al (11, 12), Christensen et al (15), and Benignus et al (13), among others. Behavioral compensatory adjustments might also be occurring, and even improvements in performance from seemingly noxious environmental agents cannot be ruled out a priori. There are, for example, many reports of noise and vibration actually improving performance [Poulton (82)]. We hasten to point out that explanation in terms of compensatory mechanisms should not be too readily seized upon since such anomalies in the dose-effect curve are not at all well established. They may result from procedural mishap, poor design, sampling error leading to the inclusion of some especially resistant or susceptible subjects, etc. Replication of these findings with larger and more well defined samples and tighter experimental protocols would be advisable before great effort is invested in their explanation.

A particularly powerful approach that might help to explore the three issues raised above would be the use of single subjects and highly reliable measures. The inclusion of these features facilitates the examination of the time course of effects, a type of analysis that may provide valuable insights into the mechanisms involved in CO-related impairments. For example, Halperin et al (36) showed that following a pulsed exposure to CO, visual thresholds remained elevated while COHb levels declined. This result suggested that the CO effect was not due simply to the reduction of the oxygen-carrying capacity of the blood and the shift of the oxyhemoglobin dissociation curve. The precise mechanism responsible for the impairment might be isolated by comparing the time course of other physiological changes (e.g. cerebral metabolism) with the time course of visual recovery.

Finally, since the behavioral effects of CO are usually studied in healthy young subjects, judicious extrapolation is needed in using these results for the establishment of permissible exposure levels for the general public. For instance, effects may be exaggerated in utero, in the elderly, or in persons with cardiovascular or respiratory insufficiency. Also the possible interactions of CO with drugs such as alcohol, nicotine, and tranquilizers, with other toxic gases, and with altitude have not been adequately explored.

In conclusion, we have found the literature on the behavioral effects of CO to include an enormous range and variety of experiments. Unfortunately, the great majority of these report isolated observations rather than systematic extensions of previous findings. For this reason, the conclusions we have reached about CO effects as a function of subject, task, and exposure parameters are quite tentative. Future experimental work, rather than simply adding new observations, should emphasize parametric investigations of those variables that the currently available literature suggest are the most crucial contributors to the behavioral toxicity of CO.

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