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Carbon monoxide – Addendum for re-evaluation of the BAT value

Assessment Values in Biological Material – Translation of the German version from 2021

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Keywords

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the biological tolerance value (BAT value) of carbon monoxide (CO) [630-08-0].

Exercising healthy test persons became statistically significantly faster exhausted at CO exposures resulting in a CO-Hb content of 3.35 to 5.1%. This was only observed with very high physical activity (minute volume of 100 l/min) which is much higher than that assumed to be realistic in workplaces (20 l/min). Moreover, specific parameters such as heart rate, oxygen intake and oxygen partial pressure as well as blood pressure, haemoglobin content and lactate values were unchanged by CO exposure.

Adverse neurobehavioural effects in humans were reported in some, but not all, studies at a CO-Hb value of about 5%. Furthermore, in some studies no behavioural effects were described at far higher CO-Hb values of up to 17%. In most studies using within-subject design, which is more meaningful than between-subject design, no behavioural effects were demonstrated. Data from a review indicate that a 10% change in adverse behavioural effects can only be expected at concentrations of 15 to 20% CO-Hb. The current BAT value of 5% CO-Hb is therefore confirmed. The BAT value corresponds to an 8-hour exposure to the current maximum workplace concentration (MAK value) of 30 ml/m^3 with moderate physical work. It is derived as ceiling value because of acute toxic effects. The BAT value only applies to non-smokers.

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BAT value (1982)	**5% CO-Hb** BAT value derived as ceiling value because of acute toxic effects evaluated for non-smokers Sampling time: at the end of exposure or end of shift
MAK value (1981)	**30 ml/m³ ≙ 35 mg/m³**
Peak limitation (2011)	Category II, excursion factor 2
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (1985)	Pregnancy Risk Group B
Germ cell mutagenicity	–

Re-evaluation

The biological tolerance value (BAT value) for carbon monoxide (CO) of 5% CO-Hb was derived in accordance with the existing maximum workplace concentration (MAK value) of 30 ml CO/m³. Based on the formula of Coburn et al. (1965), a CO-Hb value of 4.1% was calculated for an 8-hour exposure to 30 ml/m³ at physical rest, and a CO-Hb value of 4.94% during moderate physical work. Since the last documentation (Bolt 1994), new data have been published that make a review of the BAT value necessary.

1 Critical Toxicity

In addition to the concentration in the air, other factors have an effect on the severity of CO poisoning: exposure duration, breathing activity, air circulation, air pressure, previous cerebral and cardiovascular diseases and lung function. The unborn, new-born, as well as children and old people are particularly sensitive. The affinity of CO for human haemoglobin is 240 times as high as that of oxygen, depending on temperature and pH. CO binds to cytochrome oxidases and thus intervenes in the oxidative metabolism. Due to the binding to cytochrome oxidases, the electron transport is disturbed and the formation of adenosine triphosphate (ATP) is inhibited. Cerebral hypoxia leads to increased amounts of glutamate and nitrite, as well as to the degradation of unsaturated fatty acids and further to oxidative stress, necrosis and apoptosis. CO increases the activity of soluble guanylate cyclase, which leads to activation of various protein kinases, phosphodiesterases and affects ion channels. Furthermore, CO acts directly on the membrane-bound Na^+-K^+-ATPase. Endogenously formed CO also acts as a second messenger by stimulating guanylate cyclase, which leads to an increased intracellular level of cyclic guanosine monophosphate. This causes smooth muscle relaxation and vasodilation, similar to the effect of nitrogen monoxide (NO). Further oxidative damage in the central nervous system is triggered by the activation of neutrophils, which in turn produce increased myeloperoxidase, proteases and reactive oxygen species, leading to lipid peroxidation in the brain. CO induces hypoxia-inducible factor 1α (Hif-1α), which is involved in gene regulation (Sykes and Walker 2016).

The mechanisms of action described can lead to behavioural toxicity and disturbances of brain functions, which, however, occur only above approx. 18% CO-Hb (Benignus and Coleman 2010).

2 Kinetics

Nine men and nine women (all non-smokers, healthy, normal lung function) were exposed to CO concentrations in the range of 900 to 1300 ml/m^3 for 30 to 60 minutes on three different days until CO-Hb values of 10 to 12% were reached. After adjustment to total haemoglobin content, the half-life correlated with inverse alveolar ventilation in both males and females. A gender difference was no longer observed after this adjustment (Zavorsky et al. 2014).

3 Experimental Studies

Table 1 details the studies in test persons that were conducted with CO concentrations up to 100 ml/m^3. Studies using higher concentrations are listed in the documentation of the Nordic Expert Group (Stockman-Juvala 2012).

3.1 Studies on exercise capacity performance

CO-Hb values between 4.8 and 21.2% were set in ten well-trained test persons aged 22 to 34 years. CO concentrations were not reported (exposure design see Table 1). The CO-Hb levels were positively correlated with the percentage decrease in exercise capacity (time to exhaustion, exercise duration) and maximum oxygen uptake (Ekblom and Huot 1972). As no individual data are reported in the study, it is not included in the evaluation.

During exposure to 50 ml CO/m^3 and an ambient temperature of 35 °C, a decrease in treadmill exercise duration of one minute on average was observed in 10 healthy non-smokers. A mean CO-Hb level of 2.5% was reported four minutes after exposure. No change in exercise duration was observed in smokers. Reaching exhaustion was reported subjectively by the test persons (Drinkwater et al. 1974).

In 10 test persons aged 45 to 55 years, a statistically significant faster exhaustion of 35 seconds on average was measured after one-hour exposure to 100 ml CO/m^3 and subsequent exercise on the treadmill. CO-Hb levels averaged 3.95% (3.0 to 4.9%) after the one-hour exposure. No effects were observed on blood pressure and heart rate (Aronow and Cassidy 1975). Subsequently, the decrease in exercise duration was calculated from the individual data and plotted against the CO-Hb values. There was no correlation.

In four healthy test persons (24 to 33 years, three non-smokers and one pipe smoker), the maximum oxygen uptake capacity (VO_{2max}), heart rate, exercise duration, haemoglobin level, CO-Hb values and blood lactate level were determined in a single-blind study after three exposures, each at an interval of one week, to 0, 75 and 100 ml CO/m^3. Information on the exposure design is given in Table 1. The VO_{2max} was slightly lower, the heart rate, the haemoglobin level and the lactate levels were without any noticeable findings compared to those found in the controls without CO exposure. A statistically significant decrease in exercise duration was observed at CO-Hb levels of 3.35 and 4.3% after exposure to 75 and 100 ml CO/m^3, respectively (Horvath et al. 1975). It cannot be inferred from the publication how exhaustion was defined. In an earlier publication by the authors Drinkwater and Horvath (1971) it is described that in this test the persons decided subjectively when the exercise was stopped.

In a blinded cross-over study, 15 non-smokers were exposed for three to four minutes to room air or to 100 ml CO/m^3 at an interval of one month. Immediately after exposure, exercise was performed on a treadmill according to the Bruce protocol, increasing the load (speed or inclination angle of the treadmill) every three minutes. The time to exhaustion was determined, although the publication does not state whether the end of the load was determined by the test persons themselves or by objective changes in the electrocardiogram (ECG) or heart rate. After exercise on the treadmill, no effects on heart rate, blood pressure, concentrations of pyruvate and lactate in the blood and no cardiac arrhythmias were caused by CO exposure compared to the control condition. ECG changes were observed only in one person. CO-Hb levels averaged 0.51% before exposure and 0.54% after exposure to clean air. After exposure to CO, 5.1% (2.3 to 8.9%) CO-Hb was determined. After exposure to CO, test persons experienced statistically significantly faster exhaustion (13.7 minutes, 95% confidence interval (CI): 13.2 to 14.3) than after exposure to clean air (15.3 minutes, 95% CI: 14.7 to 15.4). Myocardial perfusion was not affected (Adir et al. 1999). From the data, the difference in exercise duration with

and without CO exposure was subsequently calculated and plotted as a function of the CO-Hb level. Figure 1 shows that there is no correlation between the CO-Hb level after exposure to CO and the difference in exercise duration.

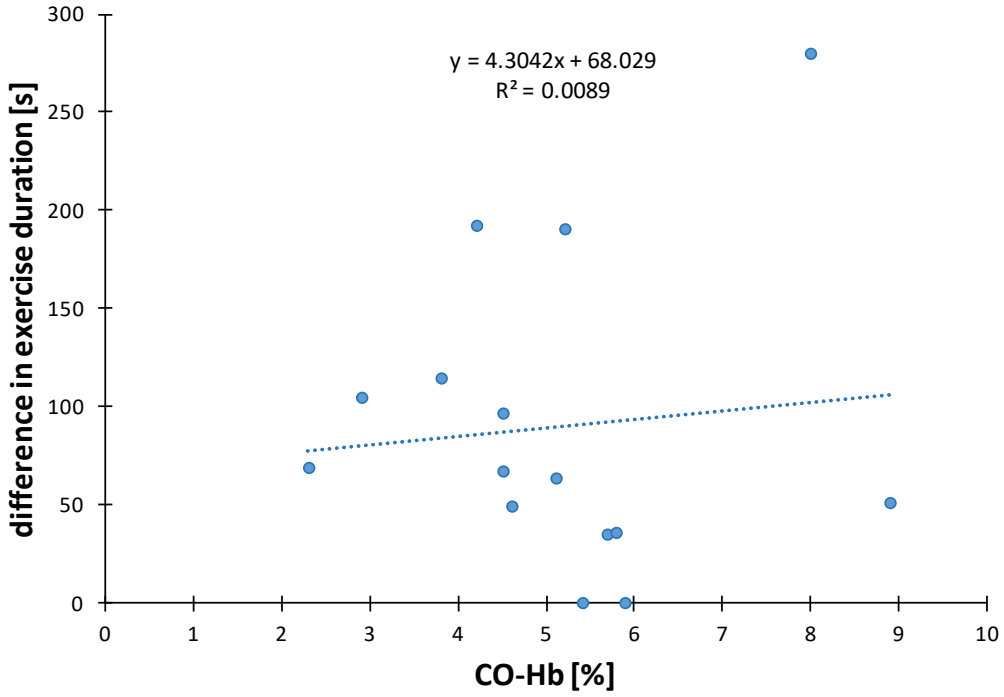

Fig. 1 Difference in exercise duration with and without CO exposure and CO-Hb levels, calculated from data of Adir et al. (1999)

No decrease in exercise capacity performance was observed in further studies:

In nine test persons, no effects on heart rate, blood pressure, respiratory minute volume and respiratory volume occurred after 15-minutes exposures to 320 ml CO/m^3 on a bicycle ergometer (6-minutes rest, then increase in load by increments of 50 watt (W) at 3-minutes intervals from 50 to 150 W (submaximal load)) compared to control exposure without CO. No decrease in performance was observed either. The CO-Hb value after exposure and concurrent exercise was 6.9% (Turner and McNicol 1993).

Nine test persons were exposed to 18.9 ml CO/m^3 for two hours during physical exercise. A decreased oxygenation was observed in the skeletal muscles, but this did not lead to a decrease in exercise duration (power load: 112 ± 5 W; end of exercise: below 70% of the preferred speed of 60 to 90 rpm for more than 5 seconds). In the frontal cortex, too, there was no effect on delivery and utilisation of O_2 (Keramidas et al. 2012).

Nine trained test persons were exposed to 1.2 ml CO/kg body weight for 30 seconds per day on 10 sequential days. 16 hours after the last exposure, they exercised on a bicycle ergometer starting with 50 W, increased by 30 W every four minutes. No effects on haemoglobin, lactate levels, O_2 uptake or exercise duration were observed compared to a control group of nine unexposed test persons. The increase in the CO-Hb level was given as 4.4%. In the control group the increase was 0% (Ryan et al. 2016).

Tab. 1 Studies on exercise performance after CO-exposure of healthy test persons

Test persons, age	Study design	CO in air [ml/m³]	CO-Hb [%]	Effects	References
10 (non-smokers, well trained) 22–34 years	**test 1** (n = 5): submaximal load (6 min bicycle ergometer): low (30% VO_{2max}), high (70% VO_{2max}) maximum load (bicycle ergometer, treadmill)	n. d.	control (n. d.) 7 20	at 30% VO_{2max}: 7% CO-Hb: no statistically significant effects, 20% CO-Hb: HR ↑* (14 beats/min) no effect: VO_2, lactate at 70% VO_{2max}: 7% and 20% CO-Hb: V_E ↑*, HR ↑* no effect: VO_2, 20% CO-Hb: lactate ↑ maximum load: 7% and 20% CO-Hb: VO_2 ↓, exercise duration ↓, 20% CO-Hb: HR ↓	Ekblom and Huot 1972
	test 2 (n = 10): maximum load treadmill (15 min warm-up, 15 min exposure until exhaustion)	n. d.	3 different CO-Hb levels between 4.8 and 21.2	exercise duration ↓, VO_2 ↓ correlates with CO-Hb level, individual data not reported	
20 ♂ (10 smokers, 10 non-smokers)	temperature 35 °C, treadmill (94 m/min; inclination ↑ by 1%/min), end of stress given subjectively, RMV up to 112 l/min double-blind	control 50	non-smokers: 0.9 smokers: 2.6 non-smokers: 2.5 smokers: 4.1	non-smokers: exercise duration ↓*, exhaled CO_2 ↑, smokers: exercise duration unchanged, ventilation equivalent ↑, RR ↑ than in non-smokers, ventilation volume ↑ non-smokers and smokers: respiratory quotient ↑*	Drinkwater et al. 1974
4 ♂ (3 non-smokers, 1 smoker, not smoked 12 h before the test)	treadmill (3.45 mph, inclination ↑ by 1%/min) until subjective exhaustion, RMV up to 120 l/min, single-blind			no statistically significant effect: VO_{2max}, HR, haemoglobin level, lactate	Horvath et al. 1975
	test 1: CO exposure 15 min before exercise and during exercise	control 75 100	post: 0.33 post: 3.35 post: 4.3	 exercise duration 4.9% ↓* exercise duration 7.0% ↓*	
	test 2: bolus exposure before exercise with maintenance concentration during exercise	control 17.7 23.6	post: 0.35 post: 3.18 post: 4.25	 exercise duration ↓* exercise duration ↓*	
9 ♂, 1 ♀ (non-smokers), 45–55 years	treadmill, maximum load pre and post 1 h CO exposure, n. d. on RMV double-blind cross-over	0 100	1.67 3.95	faster exhaustion[a]: 697.7 sec down to 662.7 sec (11.63⟶11.1 min*) no effect: BP, HR, no ST segment depression, no correlation of exercise duration ↓ with CO-Hb level	Aronow and Cassidy 1975
9 ♂ (4 non-smokers, 3 former smokers, 2 smokers), 21–31 years	15 min, (6 min without load, 9 min bicycle ergometer (50 W up to 150 W))	0 320	2.41 6.9	no effects on BP, HR, respiratory volume, RMV and exercise duration	Turner and McNicol 1993

Tab. 1 *(continued)*

Test persons, age	Study design	CO in air [ml/m³]	CO-Hb [%]	Effects	References
15 ♂ (non-smokers)	treadmill, 4 min CO exposure double-blind cross-over	control 100	pre: 0.51 post: 0.54 pre: 0.59 (0–1.2) post: 5.1 (2.3–8.9)	no effect on HR, BP, concentration of pyruvic acid, lactic acid, no cardiac arrhythmia, faster exhaustion*: control: 15.3 min (95% CI: 14.7–15.9); exposed: 13.7 min (95% CI: 13.2–14.3), not dependent on CO-Hb level, see Figure 1 ECG changes in one test person	Adir et al. 1999
9 ♂ (non-smokers)	bicycle ergometer, 85% of maximum load (~ 300 W, RMV ~ 115 l/min) **control**: 3 h air **exposure 1**: 1 h air, 2 h CO **exposure 2:** 2 h CO, 1 h 100% O_2	control 18.9	n. d. not measured (approx. 1.6% above background level (Carlisle and Sharp 2001))	**exposure 1 and 2:** oxygen content in the M. vastus lateralis (thigh) and M. serratus anterior (intercostal) during exercise 25–30% ↓, brain deoxyhaemoglobin ↓, **exposure 1**: deoxyhaemoglobin not increased, total haemoglobin ↓, **exposure 2:** deoxyhaemoglobin ↑, **no effect** on O_2 and CO_2 end-tidal partial pressure, VO_2, V_E, HR, exercise capacity performance, respiration, cerebral oxygenation of the frontal cortex region	Keramidas et al. 2012
18 ♂ (non-smokers for at least 3 months)	bicycle ergometer (50 W, every 4 min 30 W ↑ until volitional exhaustion) > 16 h post CO exposure, CO exposure for 30 sec per day on 10 sequential days	control 1.2 ml/kg body weight (weight: 76 ± 12 kg)	0% increase 4.4% increase	no effect: haemoglobin, VO_2, lactate, output power (W), exercise capacity performance	Ryan et al. 2016

[a] exhaustion: > 80% of the maximum attainable heart rate (208 – 0.7 × age)
*p < 0.05; BP: blood pressure; CI: confidence interval; ECG: electrocardiogram; HR: heart rate; n. d.: no data; RMV: respiratory minute volume; RR: respiration rate; V_E: expired respiratory minute volume; ventilation equivalent: ratio of ventilation volume and oxygen uptake; VO_2: oxygen uptake; VO_{2max}: maxiumum oxygen uptake

3.2 Cardiotoxic effects

A total of 55 test persons, half of them smokers, were divided into four exposure groups in the study by Davies and Smith (1980). Exposure was continuous to 0, 15, 50 or 75 ml CO/m³ for seven to eight days. The test persons had a regular daily routine, including physical activity. CO-Hb levels measured during exposure were 0.5% (0.1 to 2.1%) in the control group, 2.4% (0.9 to 3.1%) in the lowest exposure group and 7.2% (6.4 to 8.9%) in the middle exposure group. In the highest exposure group, tested in a pilot study only (10 test persons: 14 days fresh air, 7 days 75 ml CO/m³, 7 days recovery), CO-Hb levels were determined separately for smokers and non-smokers. In the unexposed non-smokers and smokers, 0.5 and 5.1% CO-Hb, and in the CO-exposed test persons, 10.9 and 14.9% CO-Hb, respectively, were determined. After exposure to 15 ml CO/m³, non-specific P-wave changes in the ECG occurred in 3 of 15 test persons. This effect was also observed at 50 ml/m³ in 6 of 15 test persons (Davies and Smith 1980). In the Nordic Expert Group document, the non-specific P-wave changes in the ECG were considered non-adverse (Stockman-Juvala 2012).

3.3 Studies on behavioural and neurotoxicity

Table 2 shows the human studies on behavioural toxicity after exposure to CO.

In the studies by Putz et al. (1976, 1979) and Putz (1979) effects are described after exposure to 35 ml CO/m³ and above in the following tests: auditory vigilance task and a performance test for two tasks performed simultaneously measuring

eye-hand coordination and reaction time to detect a peripheral light (dual task). The CO-Hb levels after exposure were in the range of 5%.

Behavioural toxicity was studied in 12 test persons (6 men, 6 women) exposed to 70 ml CO/m^3 or room air for four hours in a repeated-measures design. Two neuropsychological tests served as dependent variables and were completed by the test persons a total of three and six times, respectively. In a dual task, a tracking task was paired with a visual reaction time task (simple reaction time; SRT) and five performance parameters were recorded (including tracking errors). The second task was an auditory vigilance task in which a rare tone had to be recognised in a continuous sequence of tones. Both tasks were performed statistically significantly worse and slower by the test persons under exposure. Especially in the dual task, performance deteriorated during the four-hour exposure phase. Under CO exposure, statistically significantly more errors were made after four hours and the SRT was statistically significantly longer. In the auditory vigilance task, there was a statistically significant decrease in performance compared to that in the control condition (Putz et al. 1979). The study by Putz et al. (1979) is extremely sensitive (see MAK value documentation of dichloromethane (Hartwig and MAK Commission 2016)), as the variances in the tests were low (coefficient of variation: 7%).

The two publications by Putz (1979) and Putz et al. (1976) describe the same double-blind study in a between-subject design. Twenty men and ten women were exposed in three groups of ten to concentrations of 5, 35 or 70 ml CO/m^3 for four hours. Tests included the same tests as in Putz et al. 1979. The CO-Hb level was less than 1% in the control group (5 ml CO/m^3), 1.5% before exposure to 35 ml CO/m^3, 3% after exposure and 5.1% after 70 ml CO/m^3. Also, in these studies, the effects as a function of time show a clear dependence on the CO concentration. However, the effects were also dependent on task difficulty. This is plausible to some extent, since complex cognitive performance is probably more dependent on a reduction in blood oxygen.

In another study, seven men and eight women were exposed to 100 ml CO/m^3 for 2.5 hours (within-subject design), with the CO-Hb level increasing to approx. 6% within this period. The tests were a compensatory tracking task, a visual signal detection task and the combination of these tasks (dual task performance). During exposure, these tasks were performed individually (single attention) or combined (divided attention) and this factor was taken into account in the statistical analyses. Behavioural toxicity was observed at the end of exposure, characterised by a reduction in performance in the visual signal detection task when both tests were combined (divided attention). Performance in the tracking task was not affected (Gliner et al. 1983). The described effects on the combination of these tasks are consistent with the results of Putz et al. (1979).

The study by Wright et al. (1973) is not suitable for the assessment of behavioural toxicity due to methodological shortcomings (non-validated test systems). Smokers and non-smokers were examined, who clearly differed in their CO-Hb levels before and after exposure. However, the evaluations were not carried out separately for smokers and non-smokers.

However, there are also some studies in which no behavioural toxicity was observed at CO-Hb values in the range of 5% (Benignus et al. 1990; Christensen et al. 1977; Harbin et al. 1988; Mihevic et al. 1983; Roche et al. 1981):

After exposure to 114 ml CO/m^3 for 50 or 120 minutes (double-blind, within-subject design), no effects were observed in the attention test, on heart rate, blood pressure and ventilation in five men and five women. No effects were also observed in combination with 17% oxygen compared with exposure to fresh air. However, after exposure to 17% oxygen alone, a decrease in vigilance performance was observed, indicating hypoxic effects. This result is explained by the fact that the oxygen partial pressure decreases more after exposure to 17% oxygen alone than after exposure to the gas mixture with 17% oxygen and CO (Christensen et al. 1977).

Also, in twelve men and six women (double-blind, within-subject design) exposed for one hour to 28 ml CO/m^3 to maintain the CO-Hb level of 5% achieved after inhalation of a CO bolus (40 to 60 ml CO depending on the individual blood volume of the test persons, ten minutes rebreathing), no effects on heart rate, blood pressure, ventilation, respiratory volume, in alert and visual vigilance tests were observed. During CO exposure, the exposed reported mild irritation of the throat and eyes (Roche et al. 1981).

No effects on motor performance and reaction time (reciprocal tapping task, digit manipulation) were observed in eight males and eight females after exposure to 100 ml CO/m^3. However, as in Putz et al. (1976) and Putz (1979), performance and reaction time depended on the difficulty of the task (Mihevic et al. 1983).

In a random sample, younger (mean 22.8 years) and older (mean 68.7 years) men were exposed to 200 ml CO/m^3 for one hour and, after adjusting the CO-Hb level to approximately 5% (see Table 2), they were then exposed to 50 ml CO/m^3 for a further two hours. In the course of this two-hour exposure a multiple reaction time task and electroencephalogram (EEG) measurements to record visual-evoked potentials (VEPs) during an oddball task were performed. Compared to a control exposure, only age-dependent effects on test performance and VEPs were observed (Harbin et al. 1988). Age differences in CO uptake were reflected in statistically significantly higher CO-Hb levels in younger men (mean 5.6%) compared with those in older men (mean 5.0%).

In the study by Benignus et al. (1987), the experimental design of Putz et al. (1976) was repeated to verify the observed effects in this study. Healthy men (non-smokers) were exposed to 0 or 100 ml CO/m^3 for four hours. The study was conducted in a between-subject design as in Putz et al. (1976). CO-Hb levels before exposure were in the range of 0.9 to 2.32% in the control group and in the range of 1.07 to 1.57% in the exposed group. After exposure, CO-Hb levels were 0.87 to 1.55% (control group) and 7.57 to 9.03% (exposed). The observed effects in the compensatory tracking task were smaller compared with those in the study by Putz et al. (1976). In the visual signal detection task, no prolonged reaction times were observed as a function of exposure duration and compared to the control group (Benignus et al. 1987). The authors explained the differences in the results with the large variability between the test persons, which could be explained by the different training status. Due to the higher CO-Hb level (8.2%), the effects should actually have been stronger than those found in the study by Putz et al. (1976) (CO-Hb level: 5.1%).

In another study, 74 well-trained men were exposed to high CO for four to five minutes (see Table 2) in order to achieve CO-Hb levels of approx. 5%, 12% or 17%. This was followed by 4-hour exposure to CO concentrations of 32 to 149 ml CO/m^3, in order to maintain the corresponding CO-Hb levels. The test persons were divided into five groups according to their CO-Hb level (0.4 to 1.2% (control), 4.6 to 7.2%, 4.9 to 6.3%, 10 to 12.8%, 15.6 to 17.9%). In the compensatory tracking task and the visual signal detection task (dual task), no statistically significant effects were found in the group comparison, even at a CO-Hb value of 16.6% (Benignus et al. 1990).

Conclusion: Comparing the different studies is difficult because not only the method of blinding varied, but also the general design of the studies. There are studies that were conducted completely in a repeated-measures design (within-subject design), others in a group comparison (between-subject design). Benignus et al. (1987) used a combination with an exposure-free phase for baseline correction between groups. The exposure durations and the type of exposure are also not well comparable (see also Benignus et al. 1990). The studies with within-subject design are to be rated higher in terms of reliability, since there are no latent group differences. In most studies using within-subject design, no behavioural toxicity could be detected in the range of a CO-Hb level of 5%.

In a meta-analysis by Raub and Benignus (2002) on CO and neurotoxic effects, it is pointed out that only at a level of 15 to 20% CO-Hb a 10% change in behavioural toxicity indicators, such as reaction time in attention tests, is to be expected. The basis for this statement was a critical review and quantitative summary of the literature on behavioural and sensory effects, on the interpretation of physiological effects of CO-Hb in the central nervous system, on the extrapolation of effects due to hypoxia to effects after CO-hypoxia and on the extrapolation of behavioural effects in rats to humans. In addition to CO-induced hypoxia, intracellular effects such as binding to cytochrome oxidases and activation of soluble guanylate cyclase with activation of various protein kinases, phosphodiesterases and ion channel changes could also contribute to neurotoxicity. There are reliable studies describing behavioural toxicity in the range of 5 to 10% CO-Hb as well as those describing no effects.

Tab. 2 Studies on behavioural toxic effects in test persons after CO exposure

Test persons, age, exposure time, study design	CO in air [ml/m³]	CO-Hb [%]	Tests	Effects	References
20 ♂, 10 ♀, non-smokers, 18–26 years, 4 h, between-subject design, double-blind	5 (control)	< 1	dual task: tracking task and peripheral light detection, auditory vigilance test, auditory evoked potentials	**at 35 and above:** reaction time ↑ in light detection task **70:** 30% impairment in the tracking task[a], no impairment in the auditory vigilance test, different ratios of the P1 and N1 amplitudes in EEG [a]	Putz 1979; Putz et al. 1976
	35	pre: 1.5 post: 3.03			
	70	pre: 1.3 post: 5.1			
5 ♂, 5 ♀, non-smokers, 22–34 years, 0, 50, 120 min, within-subject design, double-blind	21% O_2	50 min: 0.54 120 min: 0.54	visual vigilance task	no effects on HR, BP, respiration and in visual vigilance task	Christensen et al. 1977
	114	50 min: 2.53 120 min: 4.76			
	17% O_2	50 min: 0.48 120 min: 0.49			
	113 + 17% O_2	50 min: 2.62 120 min: 5.12			
6 ♂, 6 ♀, non-smokers, 18–40 years, 4 h (3 × with 7 days interruption), test phase in each case 3 × 80 min, within-subject design	6 (control)	pre: 1.6 post: 1.4	dual task: tracking task and peripheral light detection, auditory vigilance test	tracking errors ↑, reaction time ↑, correct responses ↓ in the course of time	Putz et al. 1979
	70	pre: 1.5 post: 4.9			
12 ♂, 6 ♀, non-smokers, 20–30 years, within-subject design, double-blind	0	1.01–1.07	visual alert test, visual vigilance test	no effects on HR, BP, respiratory rate, V_E, in the alert and vigilance test, slight irritation in throat and eyes	Roche et al. 1981
	40 to 60 for 10 min, then 28 (maintaining dose)	pre-test: 5.25 ± 1.01 post-test: 4.95 ± 0.87			
7 ♂, 8 ♀, 20–32 years, 2.5 h, within-subject design, single-blind	0	1	tracking task, peripheral light detection single tasks and dual task	decrease in performance in both tests	Gliner et al. 1983
	100	pre-test: 3.45 post-test: 5.78			
8 ♂, 8 ♀, non-smokers, 20–36 years, 2.5 h, within-subject design	0	1.5	reciprocal tapping task, digit-manipulation	no effects on motor performance and attention	Mihevic et al. 1983
	100	pre-test: 4.33 post-test: 5.67			
24 ♂, non-smokers, 19–31 years, 4 h, between-subject design, double-blind	0	pre: 1.42 post: 1.22	dual task: tracking task and peripheral light detection, auditory vigilance test	smaller effects on performance in the tracking task, no effects in the light detection task	Benignus et al. 1987
	100	pre: 1.36 post: 8.24			

Tab. 2 *(continued)*

Test persons, age, exposure time, study design	CO in air [ml/m³]	CO-Hb [%]	Tests	Effects	References
11 ♂, 7 ♀, non-smokers, 18–29 years, 9 experimental runs: rest or load 50 min with 35% or 60% of VO_{2max}, treadmill 3.5 mph, within-subject design, single-blind	0	0.7–1 rest: 0.66 35% of VO_{2max}: 0.82 60% of VO_{2max}: 0.7	5 cognitive tests: Manikin spatial processing, Sternberg memory, Stroop word-color interference, visual search, dual axis tracking with and without subsequent mathematics tests	no increase in symptoms depending on the CO-Hb level, no statistically significant effect on absolute and relative O_2 uptake, respiratory volume, HR ↑ (rest and exercise), no effects on Manikin task, Sternberg task, tracking/divided attention task, effects at 7 and 10% CO-Hb: in the Stroop task, visual search task (also at high workload)	Bunnell and Horvath 1988
	45	7 rest: 6.74 35% of VO_{2max}: 7.16 60% of VO_{2max}: 7.4			
	65	10 rest: 9.31 35% of VO_{2max}: 9.99 60% of VO_{2max}: 10.2			
33 ♂, 18–28 years, 22 ♂, 60–86 years, 2 experimental runs, within-subject design, double-blind	200 (1 h), then 50 (2 h)	pre: 1.3 post: young: 5.6; old: 5.0	visual oddball task, reaction time task	changes only dependent on age, not on CO	Harbin et al. 1988
74 ♂, well trained, 18–35 years, 4 h, between-subject design, 5 groups, double-blind		entire group pre-exposure: 1.11 (0.6–1.9)	dual task: tracking task and peripheral light detection; auditory vigilance test	no statistically significant effects	Benignus et al. 1990
	0	0.9 (0.4–1.2)			
	70	6.1 (4.6–7.2)			
	2600 (5 min), then 32	5.6 (4.9–6.3)			
	6000 (5 min), then 86	11.4 (10.0–12.8)			
	9600 (5 min), then 149	16.6 (15.6–17.9)			

[a] statistically significant

BP: blood pressure; EEG: electroencephalogram; HR: heart rate; RR: respiration rate; V_E: expired respiratory volume; VO_{2max}: maximum oxygen uptake

4 Epidemiological Studies

A population-based cohort study in Sweden examined the association between CO-Hb levels in 4111 smokers, 1229 former smokers and 2893 never-smokers and the risk of cardiovascular disease. The geometric mean CO-Hb levels were 0.59% (maximum 5.47%) for non-smokers and 0.61% for former smokers, which were thus in the same order of magnitude. For smokers, the geometric mean values increased up to 2.22% (at > 20 g tobacco/day) depending on the number of cigarettes smoked per day. The sometimes very high CO-Hb levels of up to 5.47% in non-smokers are explained by exposure to second-hand smoke. The authors state that in sidestream smoke the concentration of CO is 2.5 times as high as that in mainstream smoke. Among non-smokers, the risk of myocardial infarction and death from chronic ischaemic heart disease increased with increasing CO-Hb levels, statistically significant above 0.7% CO-Hb (relative risk 3.34 to 3.71, 95% CI: 1.82 to 7.03 depending on model and adjustment) compared to those with CO-Hb levels < 0.5%. Adjustments were made for age, one-second capacity (FEV1), body mass index, diabetes mellitus, blood pressure, cholesterol, sedentary occupations, drinking habits and history of angina pectoris. In an additional analysis for non-smokers excluding those with CO-Hb levels greater than 1.7%, the relative risk of myocardial infarction, death

from chronic ischaemic heart disease and all-cause mortality were increased. In the group with CO-Hb levels of 0.66 to 1.66%, the risks were increased in a statistically significant manner. The authors discuss a contribution of passive smoking to the increased risks of disease and to the increased mortality (Hedblad et al. 2006). It cannot be assumed that the cause of the increased risks is solely due to exposure to carbon monoxide.

A meta-analysis included ten studies on immediate and delayed neuropsychological effects after acute CO poisoning. The authors pointed out that the neuropsychological effects weakened over time and thus caused no permanent damage to the brain. Since no information was given on exposure levels and CO-Hb levels, the study is not relevant for evaluation (Watt et al. 2018).

5 Background Exposure

Carbon monoxide is also formed endogenously, so that the CO-Hb level in non-smokers is 0.4 to 0.7%. During pregnancy, the level can rise up to 2.6%. In patients with haemolytic anaemia, the CO-Hb levels are in the range from 4 to 6%. In the urban population, an average CO-Hb level of 1 to 2% has been determined. Smokers have much higher CO-Hb levels which can range from 5 to 9%, depending on the number of cigarettes smoked per day. The CO-Hb level varies greatly in both non-smokers and smokers (ACGIH 2001, 2015).

6 Re-evaluation of the BAT Value

Overall, the study results do not show consistent effects at a CO-Hb level of 5%. In some studies, a statistically significantly faster exhaustion was observed at a CO-Hb level of 5.1% (2.9 to 8.9%, without concentration dependence) (Adir et al. 1999) or a statistically significant decrease in exercise duration at CO-Hb levels in the range of 3.35% and 4.3% (Aronow and Cassidy 1975; Horvath et al. 1975). However, specific parameters such as heart rate, oxygen uptake and oxygen partial pressure as well as blood pressure, haemoglobin level and the lactate values were unchanged by CO. The decrease in exercise duration was observed under very high physical activity (about 100 l/min respiratory minute volume), which is much higher than that assumed to be realistic in workplaces (20 l/min). In a study with a CO-Hb level of 6.9%, no decrease in exercise duration was observed (Turner and McNicol 1993).

There are studies describing behavioural effects at CO-Hb levels in the range of 5 to 10% as well as studies in this range without effects. Furthermore, no behavioural effects were described at much higher CO-Hb levels of up to 17%. The studies in the within-subject design are more reliable because there are no latent group differences. In most studies in the within-subject design, no behavioural effects could be detected in the range of 5% CO-Hb. In a review publication by Raub and Benignus (2002) it is pointed out that a 10% change in behavioural effects can only be expected at a level of 15 to 20% CO-Hb.

The available data confirm the evaluated BAT value of 5% CO-Hb.

The BAT value of 5% CO-Hb is therefore confirmed.

Due to acute toxic effects, the BAT value is derived as a maximum value. The BAT value of 5% CO-Hb corresponds to an 8-hour exposure to the current maximum workplace concentration (MAK value) of 30 ml/m³ with moderate physical work. It applies only to non-smokers. The sampling time is at the end of exposure or end of shift.

Prenatal toxicity

Carbon monoxide was assigned to Pregnancy Risk Group B. Since the BAT value for carbon monoxide was derived in accordance with the MAK value of 30 ml/m³, prenatal toxicity cannot be excluded even if the BAT value of 5% CO-Hb is observed.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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