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TOXICOLOGY UPDATE

Title:	**CARBON MONOXIDE**
Synonyms:	Carbonic Oxide, Carbon Oxide, Flue Gas, Exhaust gas
CAS NO:	630-08-0
Boiling point:	-191.5°C
Color:	Colorless gas.
Conversion Factor:	1 ppm = 1.25 mg/m3 @ 25°C
Dot designation:	Poison Gas , Flammable gas
Flammability:	Flammable gas. Burns in air with a bright blue flame. In the presence of certain metal oxides such as iron or silver, CO can react with explosive force.
Autoignition:	609°C (1128°F)
LEL:	12.5% by volume
UEL:	74% by volume
Henry's law constant:	NA
Melting point:	-205°C
Molecular formula:	CO
Molecular weight::	28.01
Odor:	odorless
Solubility	
water:	3.3 ml/100 ml water @ 0°C 2.3 ml/100 ml water @ 20°C 2.14 ml/100 ml water @ 25°C
Kow:	NA
other:	Soluble in acetic acid, benzene, ethyl acetate and chloroform.
Koc:	NA
Specific gravity:	(gas) 1.250 g/L @ 0°C, (liq. 0.793 @ 0°C

Specific volume:	13.8 cu ft./lb. @ 70^{o}F
Taste:	Tasteless
Vapor density:	0.968 (air=1)
Vapor pressure:	greater than 1 atm @ 20^{o}C
Viscosity:	16.62 μN s/sq. m @ 273^{o}K

NA = not available
(References: 1-4)

COMPOSITION: Carbon monoxide (CO) is readily produced by the incomplete combustion of hydrocarbon materials (e.g., fires). Significant quantities are produced during the operation of internal combustion engines due to the incomplete combustion of the fuel. CO is also produced by natural metabolic processes and is a major product of methylene chloride metabolism. On a commercial scale, CO can be prepared by the partial oxidation of hydrocarbon gases from natural gas or by gasification of coal or coke (1).. For industrial purposes, CO is supplied as a compressed gas or liquid in three grades: Commercial, 98 - 99.0% pure; Ultra-high purity, 99.% and Research Grade, 99.97% -99.99% pure.(1-4)

USES: CO is finding increased use in the production and manufacture of commodity chemicals and production of synthetic fuel (syngas: carbon monoxide and hydrogen). It is used as a reducing agent in blast furnaces, production of phosgene, purification of metals, and in the production of acetic acid and formic acid (1-4).

ACUTE TOXICITY: The primary health effects associated with overexposure to carbon monoxide appear to be related to the condition of hypoxia or oxygen deprivation (5). Carbon monoxide combines with the hemoglobin of the blood to form carboxyhemoglobin (COHb). This action interferes with the oxygen carrying capacity of the blood and the tissues experience the condition of hypoxia. Exposures that typically generate COHb blood levels of 10-30%, can produce a throbbing temporal headache, shortness of breath on exertion and dizziness. Moderate intoxication (COHb levels of 30 - 50%) may produce severe headache, weakness, dizziness, nausea, vomiting, syncope, tachycardia and tachypenea. Severe toxicity (typical COHb levels of 50-80%) produce syncope, seizures, coma, cardiovascular toxicity, respiratory failure and death (Table 1).

Acute CO exposure can also mimic acute gastroenteritis or food poisoning with accompanying nausea and vomiting. Rapidly fatal cases of CO poisoning are characterized by congestion and hemorrhages in all organs. The extent of the tissue and organ damage is related to the duration of the post-hypoxic unconsciousness. Sudden Infant Death Syndrome (SIDS) may be a misdiagnosis of CO poisoning (7). The acute toxicity values for CO in some mammalian species are listed in Table 2.

The relationship between air concentration, duration of exposure and COHB formation in humans and monkeys is presented in Table 3.

The relationship between air concentrations of CO and COHb levels I the blood has been rendered mathematically predictable by the "Coburn-Foster-Kane" (CFK)[1] equation (11). However, this equation tends to over-predict COHb levels. As a result, calculations derived from the CFK equation need to be interpreted with care (11,12).

[1] A presentation and discussion of the CFK equation is beyond the scope of this review. Please refer to the appropriate references indicated for details.

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Ingestion: At ordinary temperatures and pressure, carbon monoxide is a gas. Therefore, ingestion of this material is not a likely route of exposure.

Inhalation: Exposure to carbon monoxide can result in immediate effects and, depending on the severity of the exposure, delayed effects. These delayed effects may occur days to weeks after the initial exposure(13) and are discussed in the section below entitled CHRONIC TOXICITY.

The initial effects of overexposure to carbon monoxide may include a throbbing headache and dyspnea upon exertion, tachypenea and lethargy. This may be followed by dizziness, nausea, vomiting, weakness, tachycardia, and hyperventilation. During more severe exposures, the victim may show EKG changes suggestive of cardiac ischemia (heart attack), atrial or ventricular arrhythmias, visual field deficits, confusion, syncope, coma, seizures, respiratory failure and death (14).

When carbon monoxide levels in air exceed 3% (30,000 ppm), death occurs almost at once. Lower levels are associated with vertigo, muscular weakness, rapid and stretorous breathing, intermittent heart beat, loss of sphincter control, coma and death (15).

Eye Toxicity: Direct contact with the liquefied gas may cause skin injury, burns or frostbite (3). Exposure to CO by inhalation can also lead to decreased light sensitivity and dark adaptation (16).

Skin Toxicity: Direct contact with the liquefied gas may cause skin injury, burns or frostbite (3). Other manifestations of skin toxicity in cases of CO poisoning, include the occurrence of skin bullae especially over pressure areas, alopecia and sweat gland necrosis. The manifestation of the bullae appears to be associated with the severity of the toxicity. Cherry red skin, lips and mucus membranes are characteristic of nonsurvivors because the high COHb levels required to produce this appearance are not compatible with life. Carboxyhemoglobin levels rise after death because of continuing extraction of oxyhemoglobin. Hence cherry red skin is an autopsy finding and uncommon in live patients. (16).

CHRONIC TOXICITY:

Ingestion: see Ingestion, ACUTE TOXICITY.

Inhalation: Chronic exposure to cigarette smoke can produce elevated COHb levels in the blood (17). The blood of cigarette smokers can contain between 2-10% COHb (18) and can sometimes be as high as 18% COHb (19). Individuals not exposed to smoking have an average of 1% COHB (19).

Dogs exposed to 100 ppm carbon monoxide 5.5 hours/day, 6 days/week for 11 weeks showed persistent EKG changes as early as 2 weeks into the study. At necropsy, there were signs of degeneration in the individual cardiac muscle fibers, hemorrhage and necrosis. Disturbance of gait and posture were correlated to histological changes in the cerebral cortex, and globus pallidus (20).

Eye Toxicity: Manifestations of severe visual disturbance can occur in cases of acute CO poisoning associated with a period of unconsciousness. The types of disturbances that occur may be placed into three categories: (a.) amaurosis or hemianopsia, (b.) constriction of the visual fields, and (c.) visual abnormalities associated with optic nerve disturbances (21). Retinal venous engorgement and peripupillary hemorrhage have also been reported. All patients diagnosed with CO poisoning and exposed to CO for over 12 hours manifested retinal hemorrhages (22).

Carbon monoxide at levels in tobacco smoke have been suspected to impair night-time vision and lead to early macular degeneration. In rats, chronic prenatal exposure to similar concentrations has been shown to affect visual evoked cortical potentials (21).

Skin Toxicity: see Skin Toxicity ACUTE TOXICITY

SENSITIZATION: No information on the sensitization potential of carbon monoxide was found in the open literature.

TARGET ORGAN EFFECTS: The tissues most affected by CO are those which are most sensitive to oxygen deprivation such as the brain and the heart. The overt lesion in these tissues is mostly hemorrhage. The severe headache associated with CO exposure is believed to be caused by cerebral edema and increased intracranial pressure resulting from excessive transudate leakage of fluids through the hypoxic capillaries. (7).

ABSORPTION-METABOLISM-EXCRETION: Absorption -- Carbon monoxide is readily absorbed from the lungs (7). Once absorbed, CO reacts with the reduced iron in the hemoglobin (Hb) of the blood to form carboxyhemoglobin (COHb). The affinity of hemoglobin for carbon monoxide is between 210 - 300 times greater than its affinity for oxygen and COHb is incapable of combining with oxygen . As a result, the delivery of oxygen to the tissues is reduced. Exposure to air containing 0.4% (4000 ppm) CO for 20-30 minutes results in the conversion of 70% of the hemoglobin in the blood to COHb (15). The presence of COHb also alters the dissociation of oxygen from oxyhemoglobin so that the remaining oxyhemoglobin is somewhat less efficient in transporting oxygen, thereby producing even more compromise in the delivery of oxygen to the tissues (23).

Although hypoxia has, for many years, been thought to be the sole mechanism of toxicity of CO, there is evidence to suggest that CO can also have direct effects. *In vitro* studies indicate that CO can inhibit specific cytochromes (a and a^3) as well as the P450 reductive reactions (24,25). The net effect then, is not only on oxygen transport but also on oxygen utilization which creates the condition of hypoxia.

Distribution - Although some CO is bound by muscle myoglobin, for the most part, CO is confined to the COHb in the blood. However, CO crosses the placenta readily thereby putting the developing fetus at risk.(see Reproductive Toxicity). The expected blood COHb levels for an average adult under condition of light work and an atmosphere of 35 ppm CO will be approximately 5% (see Table 3). An exposure to 200 ppm for 15 minutes at a heavy work load will also produce a COHb level of 5% (26). The factors that determine the final level of carboxyhemoglobin in the blood are: 1) The amount of inspired CO; 2) The minute alveolar ventilation at rest and during exercise; 3) endogenous supply of CO; 4) blood volume; 5) barometric pressure; and 6), the relative diffusion capability of the lungs. The rate of diffusion from the alveoli and the binding of CO to the blood Hb are steps that limit the rate of uptake into the blood (27).

There are also endogenous sources for CO. For example, carbon monoxide is produced from the metabolism of the alpha methane carbon atom in the protoporphyrin ring by hemoxygenase during hemoglobin catabolism. This results in a basal COHb level of 0.4 - 0 .96% (16). Pregnant women produce nearly twice as much endogenous carbon monoxide (28). Other metabolic mills can also produce carbon monoxide; for example, the metabolism of methylene chloride or the metabolism of dihalomethanes (16,24).

Excretion - Carbon monoxide is not a cumulative poison since COHb is fully dissociable and once exposure has ceased, the hemoglobin will revert to oxyhemoglobin. The biological half life of CO in the blood in sedentary adults is 2- 5 hours and the elimination becomes slower as the concentration decreases. Also, the lower the initial level of COHb, the slower the rate of excretion.

After a continuous exposure to CO for 49 hours, 50% of the CO was eliminated in 30 - 180 minutes and 90% was eliminated in 180-420 minutes (28). Thus, when air, free of carbon monoxide is inhaled, the carbon monoxide dissociates from the hemoglobin and is exhaled through the lungs (2). The administration of pure oxygen (100%) can decrease the half-life to ½ - 1 hour (16). Only a small amount of the CO is metabolized to carbon dioxide (7).

GENOTOXICITY: Genotoxicity attributed to carbon monoxide was not found in the open literature.

IMMUNOTOXICITY: Exposure to CO during day 0 - day 20 of pregnancy significantly decreased the ability of macrophages to ingest *Candida albicans* and decreased splenic macrophage oxygen release in 15 to 21 day old male rats. This finding indicates that gestational exposure to CO induces in the rat, reversible immunological changes characterized by splenic macrophage function. (29).

REPRODUCTIVE TOXICITY: The fetus and newborn infant are considered to be very susceptible to CO exposure for several reasons:

(1). Fetal hemoglobin has a greater affinity for CO than maternal hemoglobin (30).
(2) Due to differences in uptake and elimination of CO, the fetal circulation is likely to have COHb levels higher (up to 2.5 times) than seen in the maternal circulation (31,32).
(3) The half-life of COHb in fetal blood is 3 times longer than that of maternal blood (32);
(4) Since the fetus has a comparatively high rate of O_2 consumption, and a lower O_2 tension in the blood than adults, a compromised O_2 transport has the potential to produce a serious hypoxia (28).

Carbon monoxide gas readily crosses the placenta and CO exposure during pregnancy can be teratogenic (28).

Studies in laboratory animals of several species provide strong evidence that maternal CO exposures to 150- 200 ppm can lead to COHb levels of 15 - 25% and result in reduction in birth weight, cardiomegaly, delays in behavioral development and disruption of cognitive function (33-38). Some of these effects may be observed at concentration as low as 60-65 ppm or at COHb levels of approximately 6 - 11% (39,40).

Infants born to women who survived short term exposures to high concentrations of the gas while pregnant often display neurological squealae and there may be gross damage to the brain (6). The threshold time or CO content for fetal damage is not known, but normal infant outcome has been reported following an exposure to 24% CO over a number of hours prior to the 8th week of gestation (28). On the other hand, exposure to CO during the second and third trimester of gestation has resulted in stillbirths, either shortly after exposure or after a delay of several weeks (28).

Farrow et al. (41) reported a fetal death following accidental non lethal maternal carbon monoxide intoxication. The corrected COHb concentration was 61% at the time of death *in utero* while the maternal COHb concentration was only 7% after one hour of supplemental oxygen

Pregnancy outcome was reported in a prospective study of mothers poisoned by carbon monoxide. The sources of CO were malfunctioning furnaces, hot water heaters, car fumes and methylene chloride fumes. Babies exposed to mild or moderate levels of carbon monoxide exhibited normal physical and neurobehavioral development whereas 3 of the 5 cases judged to be a severely intoxicated resulted in 2 stillbirths and one cerebral palsy (42).

Pregnant rats continuously exposed to 150 ppm CO produce offspring with minor reductions in birth weight , The offspring show reduced growth rates, performed poorly on negative geotaxis tests (43-45) and demonstrated persistent memory deficits that became more pronounced in adulthood (34,35). The threshold for increased fetal mortality in CD-1 mice following a continuous exposure to

CO during pregnancy was reported to be 125 ppm (46). The percentage of successful pregnancies in rats was reduced to 69% (controls = 100%) at a 17 day continuous exposure level of 30 ppm carbon monoxide while exposure to 90 ppm reduced the embryo implantation rate to 38% (47). However, continuous exposure to 65 or 125 ppm CO from day 7 to 18 of pregnancy did not significantly affect the birth weight or the number of live implants in CD-1 mice but several neonatal reflexes were adversely affected in the high exposure group. The observed changes were dose related but not statistically significant in the 65 ppm exposed group (36). Some reproductive and other health effects associated with carbon monoxide exposure or COHb levels in the blood are presented in Table 4.

NEUROTOXICITY: CO exposure may cause neurological effects manifested by headache, dizziness, syncope, confusion, seizures, and coma. Visual field deficits (e.g. visual loss, dimness of vision) and retrobulbar neuritis have also been reported. Delayed effects following severe exposures can include subtle effects such as anorexia, apathy, lethargy, forgetfulness, personality changes, memory problems, and irritability. More severe effects can include neuropathies (sensory or motor), mental deterioration, disorientation, hypokinesia, mutism, confusion, severe memory loss, gait disturbances (ataxia, akin to multiple sclerosis), incontinence, speech disturbances, tremor, movement disorders and a Parkinsonian syndrome (16,51).

Carbon monoxide induced hypoxia in the cochlea and brain stem leads to central hearing loss and vestibular dysfunction (vertigo, nausea, vomiting) with the vestibular symptoms usually more prominent than the hearing loss (16).

Signs of brain or nerve injury may appear at any time within three weeks following an acute exposure (6). Characteristically, those patients manifesting delayed neuropathology are middle aged or older. Most of the neurological symptoms associated with CO exposure can resolve within a year but memory deficits and gait disturbances may remain (16,52).

In the cat, a COHb level of 7.5% caused an inhibition of the b-wave of the electroretinogram (53) and inhibited the spontaneous electrical activity of Purkinje cells in tissue culture (54) but these effects may be mediated by direct inhibition of cytochrome oxidase in these tissues (25).

CARCINOGENICITY: The carcinogenic potential of CO does not appear to have been adequately tested.

OTHER: Hematuria, albuminuria, renal failure, rhabdomyolysis (55), myoglobinuria and acute renal tubular necrosis have developed following acute CO poisoning. Several case of hemolytic anemia after CO poisoning have also been reported Thrombocytopenia purpura with respiratory dysfunction occurred in a patient who had 20% COHb level 12 hours post exposure, (16).

CO poisoning may precipitate myocardial injury or aggravate an underlying vascular disease (56). COHb levels greater than 20% can produce symptoms that mimic cardiac infarction such as chest pain, diaphoresis and angina, result in EKG changes associated with cardiac infarction and produce an isoenzyme pattern indicative of cardiac infarction. (57). Carbon monoxide at 1,500 or 2,400 ppm slowed both AV conduction and ventricular repolarization (58) and decreased blood pressure and peripheral resistance (59). Rats exposed to 500 ppm CO for up to 32 days showed increased ventricular weights (60). Carbon monoxide exposure that increases capillary permeability also appears to accelerate plaque formation in animals on atherogenic, high cholesterol diets but this action is believed to be due to the hypoxic state (24). In monkeys, 120 ppm CO exposure for 24 weeks produced a sustained COHb level of 12% and resulted in a polycythemia and elevated (35 - 50%) hematocrit (28). This effect is also likely to occur due to an induced hypoxia and may represent more of an adaptive response to chronic hypoxia (25).

Decreased exercise performance has consistently been shown at a blood level of about 5% COHb in young, healthy, nonsmoking individuals (61,62). Cigarette smoking has a similar effects in non athletic human subjects, indicating a reduced ability for sustained work (63). The lowest observed effect of exercise-induced angina occurred at 3-4% COHb in patients with coronary artery disease (64).

EPIDEMIOLOGY: A crew of Holland tunnel workers worked 2 hours at an average tunnel concentration of 760 ppm carbon monoxide, alternating with 2 hours out of the tunnel for 8 hour swing shifts. These workers demonstrated an average of 5% COHb with no one above 10%. The average daily exposure was 35 ppm CO. No symptoms of adverse heath effects were reported. (26). However, a retrospective study of 1212 tunnel officers exposed to CO that resulted in COHb levels of 5% or less were found to have significantly elevated risk of arteriosclerotic heart disease (19), but other epidemiological and animal studies indicate that CO is not atherogenic (65). A longitudinal study of 100 consecutive admissions of carbon monoxide poisoning found that 32% of the patients had obvious neuropsychiatric signs and symptoms (66,67).

ENVIRONMENTAL FATE: Natural sources such as atmospheric oxidation of methane, forest fires, terpene oxidation and carbon monoxide-producing microorganisms in the oceans account for 40 - 60% of the atmospheric carbon monoxide. Human activities account for the rest (7,25). Motor vehicle exhaust accounts for about 55 - 60% of the man-made emissions of carbon monoxide (68). Concentrations as high as 30% have been measured in automobile exhaust (6) although the range of 1 - 7% is more common (69,70). In remote area of the southern hemisphere, natural background levels of CO average 0.05 mg/m^3 (0.04 ppm; 4×10^{-5}%) -but in the northern hemisphere, background levels are 2-3 times higher with considerably greater concentrations in cities (25).

Natural gas associated with petroleum deposits does not normally contain CO but during processing by petroleum cracking (manufactured gas), CO may be produced so that the distributed gas (to households) may contain between 2 - 15% CO (6). An unusual source of CO is represented by the propane fueled re-surfacing machines (Zamboni) for indoor ice skating rinks with a number of CO overexposures reported for this source (6).

Carbon monoxide has also been identified as a common constituent of the head space in silos containing dry grain. Levels up to 1000 ppm ($\approx$ 1250 mg/m^3) have been reported over stored wheat, oats, paddy and field peas. The evolution rate from grain can be up to 9 ng per gram of grain per day (71).

Atmospheric removal of CO occurs primarily by reaction with hydroxyl ($OH^{\bullet}$) radicals to form carbon dioxide and hydrogen atoms. The hydrogen atoms, in turn react with oxygen to form hydroperoxyl radicals ($HO_2^{\bullet}$) which react with NO to form NO_2. The photolysis of NO_2 leads to the formation of ozone. Thus, CO can contribute to the formation of photochemical smog. (22). The atmospheric half-life of CO ranges between 2 to 6 months (25).

ENVIRONMENTAL TOXICITY: A small amount of carbon monoxide is produced normally by the body. This endogenous carbon monoxide is sufficient to maintain a carbon monoxide hemoglobin saturation level of 0.4 - 0.96% (9,67). In some individuals with blood disease such as hemolytic anemia, the endogenous carbon monoxide saturation may reach 6%. (69).

Occupational exposure to carbon monoxide is a concern for firefighters, traffic police, coal miners, coke oven workers, smelter workers, caisson workers, toll booth attendants and transportation mechanics (56). Large quantities of carbon monoxide are released by burning charcoal and can result in poisoning or death. As a result, hibachis or other small charcoal fires should never be used as a source of heat in sleeping quarters or enclosed spaces(69).

The major source of carbon monoxide for many people is tobacco smoking. The average concentration in the smoke reaching the lungs is about 400 ppm (69, 72). Cigarettes can yield an average of 67 mg of carbon monoxide per cigarette. In a 13.6 m^3 chamber with an air change rate of 3.55 changes/hour and a cigarette rate of one /15 minutes, the carbon monoxide concentration averaged 4.76 mg/m3 or 3.9 ppm (73). Smoking cigarettes can produce carboxyhemoglobin levels higher than exposure to carbon monoxide levels present in street air. Heavy smokers can generate carboxyhemoglobin levels as high as 15 - 17% (28).

REGULATORY STATUS: The recommended and enforceable occupational exposure standards for carbon monoxide are presented in Table 5.

Table 5. Recommended and enforceable occupational exposure values for Carbon Monoxide. .

Standard	Value
ACGIH	
TLV	25 ppm (29 mg/m^3)
BEI	3.5% carboxyhemoglobin
BEI	20 ppm in exhaled air
OSHA	
PEL	50 ppm (55 mg/m^3)
Ceiling	200 ppm (229 mg/m^3)
STEL	400 ppm (458 mg/m^3)
IDLH	1500 ppm (1320 mg/m^3)
NIOSH	
REL-TWA	35 ppm (40 mg/m^3)
ASHRAE	35 ppm (1 hr.) 9 ppm (8 hr.)

(Refs: 74-76)

The National Ambient Air Quality Standard (NAAQS) for carbon monoxide is 9 ppm as an 8-hour non-overlapping average (Table 6). This value is not to be exceeded more than once per year. The rounding convention in the standard [40 CFR, Part 50] specifies that values of 9.5 ppm or greater, are counted as exceeding the level of the standard. An area meets the carbon monoxide NAAQS if no more than one 8-hour value per year exceeds the threshold. High values that occur within 8 hours of the first one are exempted. This is known as using “non-overlapping averages”. To be in attainment, an area must meet the NAAQS for two consecutive years and carry out air quality monitoring during the entire time [Clean Air Act, Section 107(d)(4)(A) and Section186]. Air quality carbon monoxide value is estimated using EPA guidance for calculating design values (Laxton Memorandum, June 18, 1990).

The state of California has promulgated similar ambient air quality standards which are also presented in Table 6.

Carbon Monoxide is listed by the State of California as a chemical known to cause reproductive harm (Proposition 65).

Table 6. National and State of California Ambient Air Quality Standards for Carbon Monoxide

Averaging Time	California Standard	National Standard
8 hour	9 ppm	9 ppm
	10 mg/m^3	10 mg/m^3
1 hour	20 ppm	35 ppm
	23 mg/m^3	40 mg/m^3
Lake Tahoe Area	6 ppm	--
8 hour	7 mg/m^3	--

(Ref. 77,78)

Possible NOAEL: In laboratory animals, maternal exposure to carbon monoxide can result in reduced birth weight, cardiomegaly, delays in behavioral development and neurological deficits. Pregnant rats exposed continuously to 150 ppm CO produce offspring with minor reductions in birthweight, showed reduced growth rates, performed poorly on negative geotaxis tests (43,44) and demonstrated persistent memory deficits that became more pronounced in adulthood (34,35). In CD-1 mice. 125 ppm CO from day 7 to 18 of pregnancy produced an adverse effect on several neonatal reflexes (36). At 65 ppm CO, the observed changes were not significant (39,40). Thus, from animal studies, 125 ppm represents a likely LOAEL. and 65 ppm represents a likely NOAEL. However, in rats, exposure levels of 30 ppm CO, reportedly reduced successful pregnancy rate to 69% versus 100 % for unexposed animals (47), a difference which was considered to be statistically significant.

According to the ACGIH (26), ambient CO exposure to 25 - 35 ppm results in COHb blood levels of 3.5 - 5.0%. In humans, CO has been implicated in aggravating cardiovascular disease (62,63). Exercise-induced ischemic angina occurred in patients with coronary artery disease at carboxyhemoglobin levels of 3-4% (65). Decreased exercise performance has consistently been shown at COHb levels of 5% in healthy young men (61,62). Therefore, the level of 3-5% COHb (25-30 ppm ambient CO levels) may represent a possible NOAEL for CO exposures.

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Table 1. Typical Symptoms associated with COHb levels

COHb level	Symptoms
0-10%	no symptoms.
10-20%	mild headache and breathlessness.
20-30%	throbbing headache, irritibility, emotional instability, impaired judgment, defective memory and rapid fatigue.
30-40%	severe headache, weakness, nausea, vomiting, dizziness, dimness of vision, confusion.
40-50%	increasing confusion, severe ataxia, accelerated respirations, possible hallucinations.
50-60%	syncope, coma, convulsions, tachycardia with weak pulse.
60-70%	increasing depth of coma with incontinence.
70-80%	profound coma, thready pulse, death.
>80%	rapid death.

(ref. 6)

Table 2. Acute Toxicity Values to Carbon Monoxide for mammalian species.

Species	parameter - value	comments
Human	TClo - 545 ppm/10 min TClo - 650 ppm/45 min LClo - 4000 ppm/30 min LClo - 5000 ppm/5 min	headache methemoglobinemia
monkey	TClo - 200 ppm/24H/90D	hematocrit
mammal	LClo - 5000 ppm/5 min	details not provided
dog	LClo - 4000 ppm/46 min	
rabbit	TClo - 180 ppm/24H TClo - 182 ppm/3H/13W TClo - 50 ppm/24H/8W LClo - 4000 ppm	1-30D preg. Stillbirth cardiovascular hemorrhage decreased platelets
guinea pig	TClo - 182 ppm/5H/4W TClo - 182 ppm/5H/30W TClo - 200 ppm/24H/90D LC_{50} - 5718 ppm/4H	Hyperglycemia Arrhythmia, EKG changes hematocrit
rat	TClo - 0.8 ppm/24H/72D TClo - 150 ppm/24H TClo - 75 ppm/24H TClo - 1800 ppm/1H/14D TClo - 27 ppm/8H/10W TClo - 96 ppm/24H/90D TClo - 250 ppm/5H/20D - LC_{50} - 1807 ppm/4H	menstrual cycle, fertility, newborn 1-22 D preg. (dev. Abnorm.) 0-20 D preg immune/reticuloendo. sys. Cardiovascular effects spasticity hematocrit carboxy hemoglobin
mouse	TClo - 65 ppm/24 H TClo - 250 ppm/7H TClo - 125 ppm/24 H TClo - 8 pph/1H LC_{50} - 2444 ppm/4H	7-18 D preg. -newborn (behavioral) 6-15 D preg. post implant loss 7-18 D preg. - fetotoxic 8D preg - fetotoxic; CNS abnormalities

(Ref: 8)

Table 3. COHb Levels and associated ambient air levels for Humans and monkeys

Air concentration	Time of exposure	%COHb	Species	Reference
0 ppm	3 hr	0.96	human	Theodore, et al., (9)
35 ppm	light work	5.0	human	ACGIH, (26)
200 ppm	heavy work (15 min)	5.0	human	ACGIH. (26)
50 ppm	3 hr	2.98	human	Theodore, et al., (9)
125 ppm	3 hr	6.64	human	Theodore, et al., (9)
250 ppm	3 hr	12.4	human	Theodore, et al., (9)
100 ppm	8 hr	11-13	human	Stewart & Peterson (10)
50 ppm	105 days	3.7	monkey	Theodore, et al., (9)
400 ppm	7 days	30.1	monkey	Theodore, et al., (9)
50 ppm	105 days	8.4	human	Theodore, et al., (9)
400 ppm	7 days	41.0	human	Theodore, et al., (9)
170 ppm	1 hr	8.0	human	Theodore, et al., (9)

(ref:9,10)

Table 4. Reproductive and Health Effects associated with CO exposure and COHb levels in the blood in experimental animals

COHb level or air conc.	duration	interval	outcome	ref
24.5% (human)	several hours	<8 wks pregnant	low birth wgt	Haddad, (28)
5-10% 70 ppm (human)	2 hours	swing shifts	no effects	ACGIH, (26).
25% (human)	15 min	preexisting coronary artery disease	death	ACGIH, (26)
75% (human)	1 min	--	death	Ellenhorn and Barceloux, (16)
30,000 ppm	1min.	--	death	Humphries, (15)
100 ppm (dogs)	5.5h/d,6d/wk.	2 wks	EKG changes & necrosis	Hamilton & Hardy, (20)
150 ppm(rats)	cont.	--	low birth wgt neuro effect	Fechter & Annau (43)
180 ppm (rabbits)	cont.	--	prenatal death	Shepard, (44)
500 ppm (rats)	cont..	32 days	inc. ventr wgt	Clubb et al. (60)
180 ppm (rabbits)	4 hrs	--	intimal damage edema	Casarett & Duoll (24)
5900 ppm (rats)	5-8min 21 days	10 days	abortion abnormal growth	Zenz (48)
90 ppm (rabbits)	cont.	30 days	inc. fetomortality	Zenz (50)
180 ppm (rabbits)	cont.	30 days	inc. fetomortality dec. birthwgt	Zenz (50)
150 ppm (rats)	cont.	20 days	behavioral effects	DiGiovanni et al., (48)
75 ppm (rats)	cont.	20 days	no effect	DiGiovanni et al., (48)
500 ppm (rats)	cont.	30 days	cardiovascular effects	Penney et al., (33)
1000 ppm - 1200 ppm (rats)	2 hr	20 days	reduced birth wgt	Leichter (49)
75ppm (rats)	cont.	20 days	alteration of immune activity.	Giustino (29)

(Ref: 27)
cont. = continuous