940 Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for carbon monoxide

http://www.atsdr.cdc.gov/toxprofiles/tp201.pdf

Summary of Health Effects

Health effects associated with acute carbon monoxide poisoning have been extensively documented. In the last decade, growing evidence has revealed endogenously produced carbon monoxide (produced from catabolism of heme and other endogenous precursors) to be a cell signaling agent that contributes to the regulation of numerous physiological systems, including brain and muscle oxygen storage and utilization (myoglobin, neuroglobin), relaxation of vascular and extra-vascular smooth muscle, modulation of synaptic neurotransmission, anti-inflammation, anti-apoptosis, anti-proliferation, and anti-thrombosis (see Section 3.5.2, Mechanisms of Toxicity). Endogenously produced carbon monoxide is not associated with toxicity; carbon monoxide toxicity occurs following exp osure to exogenous carbon dioxide. Toxic effects of carbon monoxide are due to effects on cell metabolism through hypoxic and non-hypoxic modes of action. Both modes of action are thought to result from the ability of carbon monoxide to bind to heme and al   ter function and/or metabolism of heme proteins. Formation of carboxyhemoglobin (COHb) decreases the O_2 carrying capacity of blood and impairs release of O_2 from Hb for its utilization in tissues. Current toxicological and epidemiological research has focu   sed on examining health effects of low-level carbon monoxide exposures that do not result in overt carbon monoxide poisoning and attempting to understand the connections between carbon monoxide toxicity and carbon monoxide in vivo production and metabolism   . This research has revealed that the heart and cardiovascular system and the brain and developing nervous system are particularly sensitive to carbon monoxide. These studies have also shown   that people with ongoing cardiovascular and/or respiratory disease may be particularly vulnerable to carbon monoxide.

Modes of Action of Carbon Monoxide. Carbon monoxide exerts effects on cell metabolism through hypoxic and non-hypoxic modes of action. Both modes of action are thought to be largely (if not entirely) the result of the ability of carbon monoxide to bind to heme and alter function and/or metabolism of heme proteins. The binding affinity of carbon monoxide for hemoglobin is over

200 times greater than that of oxygen for hemoglobin. Formation of COHb decreases the O2 carrying capacity of blood and impairs the release of O2 from Hb for its utilization in tissues. Through similar mechanisms, carbon monoxide decreases O2 storage in muscle cells by binding to, and displacing O2 from, myoglobin. Although all tissu es are vulnerable to carbon monoxide-induced hypoxic injury, those having the highest O2 demand are particularly vulnerable, including the brain and heart.

Most of the non-hypoxic mechanisms of action of carbon monoxide have been attributed to binding of carbon monoxide to heme in proteins other than Hb. Notable targets of carbon monoxide include components of several important physiological regulatory systems, including brain and muscle oxygen storage and utilization (myoglobin, neuroglobin); nitric oxide cell signaling pathway (e.g., nitric oxide synthase, guanylyl cyclase); prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase); energy metabolism and mitochondrial respiration (cytochrome c oxidase, cytochrome c, NADPH oxidase); s teroid and drug metabolism (cytochrome P450); cellular redox balance and reactive oxygen species (ROS; catalase, peroxidases); and various transcription factors (e.g., neuronal PAS domain protein, NPAS2, implicated in regulation of circadian rhythm). Non-hypoxic modes of action are discussed in greater detail in Section 3.5.2.

Endogenous Carbon Monoxide. In addition to inhalation exposure to carbon monoxide in air, internal exposures to carbon monoxide occur as a result of production of carbon monoxide fro m endogenous precursors (e.g., heme degradation, auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids) and from oxidative metabolism of exogenous precursors (e.g., carbon tetrachloride, dichloromethane, and other dihalomethanes). The latter two metabolic sources of carbon monoxide result in a carbon monoxide body burden in the absence of exposure to exogenous carbon monoxide in air. Endogenous carbon monoxide production rate has been estimated to be approximately 0.42 mL carbon monoxide at standard temperature and pressure, dry (STPD)/hour or 0.006 mL carbon monoxide/hour-kg body weight. However, numerous physiological and disease factors affect the rate of endogenous production of carbon monoxide, i ncluding the menstrual cycle, pregnancy, diseases, and stimuli that increase catabolism of Hb or other heme proteins, including hemolysis, hematomas, hemolytic anemias, thalassemia, and Gilbert's syndrome.

Growing evidence has revealed endogenous carbon m onoxide to be a cell signaling agent that contributes to the regulation of numerous physiological systems, including brain and muscle oxygen storage and utilization (myoglobin, neuroglobin), relaxation of vascular and extra-vascular smooth muscle, modulati on of synaptic neurotransmission, anti-inflammation, anti-apoptosis, anti-proliferation, and anti-thrombosis. This has potentially important implications for the understanding of carbon monoxide toxicology and dose-response relationships for the following reasons: (1) carbon monoxide modulation of physiological processes may underlie some aspects of the toxicity of exogenous carbon monoxide;

(2) exogenous carbon monoxide may disrupt physiological regulation of those systems that are responsive to endogenous carbon monoxide (e.g., vascular resistance); and (3) exposures to exogenous carbon monoxide may affect carbon monoxide-mediated physiological responses at levels that approach those resulting from endogenous production. One implication of this is that the dose threshold for effects of exogenous carbon monoxide on carbon monoxide-modulated physiological systems may lie near or below ambient air carbon monoxide concentrations.

Toxicokinetics. Inhaled carbon monoxide is rapidly and extensively absorbed into blood and distributes throughout the body. The distribution of carbon monoxide in the body largely reflects the binding of carbon monoxide to heme proteins (e.g., Hb, myoglobin). Measurements of total carbon monoxide concentrations in tissues obtained from human autopsies showed the highest concentrations in blood, spleen, lung, kidney, and skeletal muscle, with detectable levels also in brain and adipose tissue. However, as noted above (see Modes of Action of Carbon Dioxide), due to the high O_2 demand of the brain relative to other tissues, the brain is most sensitive organ to the effects of carbon monoxide. Higher concentrations of carbon monoxide in blood, heart, skeletal muscle, and spleen reflect the abundance of the major carbon monoxide binding proteins in these tissues. In blood, carbon monoxide rapidly distributes into erythrocytes where it exists primarily as a complex with Hb (COHb). Carbon monoxide in muscle exists primarily as a complex with myoglobin (COMb). Carbon monoxide in the maternal system distributes to fetal tissues where it binds to fetal Hb and other heme proteins. Steady-state fetal blood COHb concentrations are approximately 10−15% higher than maternal blood (fetal/maternal ratio=1.1−1.15) and fetal blood COHb elimination kinetics are slower than maternal blood. Carbon monoxide binding to fetal Hb is analogously similar to maternal Hb.

Absorbed carbon monoxide is eliminated from the body by exhalation and oxidative metabolism. Oxidative metabolism of carbon monoxide has been estimated to be a relatively small fraction (<10%) of endogenous carbon monoxide elimination. Under most conditions, the dominant route of elimination of absorbed carbon monoxide is exhalation. The decline in blood %COHb following cessation of an inhalation exposure to carbon monoxide exhibits at least two kinetic phases. The fast phase is thought to reflect a combination of exhalation of carbon monoxide along with slower distribution of blood carbon monoxide to tissues that continues after cessation of exposure. The elimination half-time for the slow phase is approximately 100−300 minutes. The carbon monoxide elimination half-time increases with age, with the most pronounced increase occurring from age 2 to 20 years and is approximately 6% longer in males compared to females. Exercise decreases carbon monoxide elimination half-time, although exercise and the increase in respiration would lead to increased CO exposure, if CO is still present in inspired air.

The importance of COHb as a potential biomarker of carbon monoxide exposure and hypoxia, particularly at low levels of exposure, has led to the development of a physiologically-based mechanistic model of carbon

monoxide kinetics for predicting relationships between exposure and blood COHb levels. The model that h as received the greatest attention and use in risk assessment and in clinical medicine is the Coburn-Forster-Kane (CFK) model. This model can be used to predict steady-state blood COHb levels that correspond to a given continuous inhalation exposure to carbon monoxide in a typical adult. The CFK model has been used to support discussions of the health effects of carbon monoxide in this Toxicological Profile, by providing a means for interconverting carbon monoxide exposure levels expressed in units of ppm o r mg/m3 and corresponding equivalent steady-state COHb% values (i.e., the COHb% that would be achieved with continuous exposure to the reported air carbon monoxide concentration). Predicted steady-state blood COHb levels corresponding to a range of carbon monoxide exposure concentrations are presented in the introduction to Section 3.2 (Table 3-1). Several other toxicokinetics models are described in Section 3.4.5.

Acute Carbon Monoxide Poisoning. Carbon monoxide poisoning is one of leading causes of morbi dity and mortality due to poisoning in the United States. It has been estimated that carbon monoxide poisoning results in over 50,000 emergency room visits per year in the United States. The principal mechanism of many adverse effects of carbon monoxide ex posure is COHb-induced tissue hypoxia; thus, tissues with high oxygen requirements (e.g., brain, heart) are the most sensitive to carbon monoxide-induced hypoxia. However, other non-hypoxic mechanisms (e.g., binding of carbon monoxide to other heme protein s, such as myoglobin and cytochrome c oxidase) and alterations in biological and physiological functions of endogenous carbon monoxide, likely contribute to the adverse effects of acute carbon monoxide poisoning.

The extent of injury from acute carbon mon oxide exposure depends upon the concentration and duration of exposure and the underlying health status of the exposed individual. The most commonly reported signs and symptoms associated with acute carbon monoxide poisoning are due to effects on the central nervous system and the cardiovascular system; however, because carbon monoxide exposure has the potential to affect nearly all tissues, the clinical presentation of acute carbon monoxide poisoning includes a wide range of symptoms. The severity of carbo n monoxide poisoning is typically categorized as mild, moderate, or severe, based on clinical presentation. Signs and symptoms of mild carbon monoxide poisoning include headache, nausea, vomiting, dizziness, blurred vision, and occasionally cherry red lips and skin; headache and dizziness are the most commonly reported symptoms. Because these symptoms mimic flu-like viral illnesses, mild carbon monoxide poisoning can easily be misdiagnosed. Symptoms associated with moderate carbon monoxide poisoning may inc lude confusion, syncope, chest pain, dyspnea, weakness, tachycardia, tachypnea, and rhabdomyolysis. Effects of severe poisoning may be life-threatening, including cardiac arrhythmias, myocardial ischemia, cardiac arrest, hypotension, respiratory arrest, noncardiogenic pulmonary edema, seizures, and coma. In addition to the immediate-onset effects of exposure, delayed-onset development of neuropsychiatric impairment typically occurs from several days to approximately 3–4 weeks of exposure, with symptoms incl uding inappropriate

euphoria, impaired judgment, poor concentration, memory loss, cognitive and personality changes, psychosis, and Parkinsonism Symptoms of acute carbon monoxide poisoning in children are the same as those in adults. Acute carbon monoxide poisoning during pregnancy has been associated with spontaneous abortion and fetal death; pregnancy outcome is likely to be dependent upon the severity of maternal poisoning and fetal age.

The relationship between the severity of clinical signs and sympto ms of acute carbon monoxide poisoning and COHb levels is not well correlated. The poor correlation may be due to the length of time elapsed between cessation of exposure and measurement of COHb levels or to effects of supplemental oxygen treatment prior to   COHb measurement. Generally, in healthy individuals, mild carbon monoxide poisoning that requires medical intervention are associated with COHb levels >20%. Fatalities due to carbon monoxide poisoning have been reported for a wide range of COHb levels (3   –70%). Levels of COHb >50% are frequently fatal.

Primary Targets of Low-level Carbon Monoxide Exposure   . The primary targets of low-level exposures to carbon monoxide (i.e., those that result in blood COHb levels <20%) appear to include the heart and cardio   vascular system, the central nervous system, and the fetus and neonate. Adverse effects in the respiratory tract have been observed in human clinical studies and in animal studies at higher exposures than those associated with effects on the cardiovascular and central nervous systems and on development. A large body of epidemiologic studies has also provided evidence that ambient levels of carbon monoxide in air may contribute to respiratory morbidity and aggravation of ongoing respiratory disease (e.g., as   thma; see Table 3-3). Epidemiologic studies have also examined possible associations between ambient air carbon monoxide concentrations and hematologic biomarkers of coagulation and inflammation. Although some studies have found significant associations, collectively, findings from these studies are inconclusive.

Cardiovascular System . Cardiovascular effects of inhalation exposures to carbon monoxide have been evaluated in controlled human clinical studies, epidemiology studies, and various animal models (monkeys, dogs, rats, and rabbits). In general, these studies provide convincing evidence for adverse cardiovascular effects in association with carbon monoxide exposures that result in blood COHb levels   2.4%, with effects occurring at the lowest levels in subjec ts with compromised cardiovascular function (e.g., coronary artery disease).

Results of controlled clinical studies in patients with coronary artery disease show that acute-duration exposure to carbon monoxide at levels producing blood COHb levels between   2.4 and 5.9% exacerbates underlying cardiovascular disease, including enhanced myocardial ischemia and increased cardiac arrhythmias. In patients with exertional angina, carbon monoxide exposure exacerbated exercise-induced myocardial ischemia, including decreased time-to-onset of angina symptoms, increased duration of angina symptoms, decreased time-to-onset of ST-segment depression (electrocardiogram [EKG or ECG] change indicative of myocardial ischemia),

and decreased left ventricular ejection fraction. At the lowest blood COHb level evaluated in patients (i.e., COHb 2.4%), time-to-onset of angina symptoms and ST-segment depression were significantly decreased by 4.2 and 5.1%, respectively.

Epidemiological studies of exposure to carbon monoxide and cardiovascular outcomes have yielded mixed results. In general, the weight of evidence suggests that risks of certain specific outcomes (hospitalizations and emergency room visits related to congestive heart failure, ischemic heart disease, myocardial infarction, and stroke) are associated with increasing ambient carbon monoxide concentrations. The interpretation of these associations is complicated by the possibility that ambient air carbon monoxide levels may be a surrogate measure for air pollution in general. However, the corroborated observations of associations between carbon monoxide exposure and outcomes related to ischemic heart disease is particularly provocative in the context of results of human clinical studies in which carbon monoxide-induced hypoxia exacerbated ischemia symptoms in patients with coronary artery disease. Mean ambient air carbon monoxide concentrations reported in studies that have found carbon monoxide-associated adverse cardiovascular outcomes ranged from 0.5 to 10 ppm, with maximum values ranging from 2 to 50 ppm. These values correspond to approximate steady-state blood COHb levels of <2% for the mean and <10% for the maximum.

Studies in animals have investigated adverse cardiovascular effects of carbon monoxide exposure over a much wider range of exposure conditions (e.g., exposure concentration and duration) and have evaluated additional outcome measures that are not possible to assess in humans. These studies provide further evidence of adverse cardiovascular effects of carbon monoxide exposure, including compensatory alterations in hemodynamics, cardiac hypertrophy, cardiac arrhythmias, and possibly atherosclerosis.
Based on studies described above, a blood COHb concentration of 2.4% is identified as the lowest observed-adverse-effect level (LOAEL) for adverse cardiovascular outcomes in coronary artery disease patients. A no-observed-adverse-effect level (NOAEL) for this effect was not identified. The LOAEL for COHb can be converted to an equivalent human exposure concentration (for continuous exposure) that would yield the same steady-state blood COHb concentration (2.4%) by implementing the CFK model. The human equivalent exposure concentration is approximately 14 ppm.

Developmental Effects. Epidemiological studies have examined possible associations between exposure to ambient air carbon monoxide concentrations and various developmental outcomes, including pre-term birth, birth weight, congenital anomalies, neurodevelopment, and neonatal and infant death. Results of these studies have been mixed and collectively do not provide strong evidence for developmental effects in association with exposures to ambient levels of carbon monoxide. In general, these studies examined relatively low air carbon monoxide concentrations, typical of ambient levels (e.g., mean concentrations ranging from 0.5 to 3 ppm, with highest reported values 10 ppm; see Table 3-8). These studies typically

relied on average ambient carbon monoxide concentrations (based on regional air monitoring) for estimating   exposures and do not necessarily represent exposures that occurred to individuals during any particular period of gestation.

Numerous studies on developmental effects of gestational and early postnatal exposure to carbon monoxide have been conducted in an   imals. In general, most studies evaluated effects of relatively low carbon monoxide concentrations (i.e.,   300 ppm), with exposure concentrations selected to produce maternal COHb levels typically associated with smoking (5–10%); however, studies did not c onsistently report maternal or fetal COHb levels. Studies in animals have examined effects of carbon monoxide exposure on numerous developmental outcomes, including several outcomes that have not been assessed in epidemiological studies (e.g., auditory and immune system development). Results of animal studies show adverse developmental effects of gestational and early postnatal carbon monoxide exposure, including decreased fetal weight, adverse central nervous system development, altered peripheral nervous   system development, cardiac effects, altered sexual behavior, immunological effects, and hematological effects. In addition, some studies showed that developmental effects persisted beyond the postnatal period, although persistence of effects was not exami   ned in all studies. The lowest LOAEL values for developmental effects were obtained in studies evaluating effects of carbon monoxide on the developing auditory system (i.e., LOAEL 12–25 ppm); however, since other developmental outcomes were not assessed at this range of low carbon monoxide concentrations, it is not possible to determine if the developing auditory system is more sensitive to carbon monoxide exposure than other systems. Gestational and/or early postnatal exposure of rats to 25 ppm carbon mono   xide produced morphological changes in the developing auditory system, including swelling, cytoplasmic vacuolization, and atrophy of nerve terminals innervating inner hair cells; "distorted myelin" with vacuolization in the 8th cranial nerve at the level o f the internal auditory canal; decreased immunoreactivity of the enzymes cytochrome oxidase, NADH-TR, and calcium-mediated myosin ATPase; and decreased immunostaining of neurofilament and myelin basic protein in the organ of corti. Exposure of rat pups dur   ing the early postnatal period decreased action potential amplitude of the 8th cranial nerve at   12 ppm carbon monoxide and decreased otoacoustic emissions at   50 ppm carbon monoxide, with effects on action potential amplitude of the 8th nerve persisting through age 73 days.

Based on studies described above, a maternal exposure concentration of 12 ppm is identified as a LOAEL for adverse neurodevelopmental outcomes in rats. This LOAEL can be converted to an equivalent blood COHb level in the rat by impleme ntation of the CFK model, as adapted for the rat. The time-averaged blood COHb level predicted for the 16-day exposure (22 hours/day) is 1.8%. The equivalent human exposure concentration (for continuous exposure) that would yield the same steady-state bloo d COHb concentration (1.82%) is approximately 10 ppm.

Central Nervous System. As previously noted, acute exposure to high levels of carbon monoxide produces symptoms of central nervous system toxicity, including headache, dizziness, drowsiness, weakness, nausea, vomiting, confusion, disorientation, irritability, visual disturbances, convulsions, and coma. Lesions of the basal ganglia (primarily of the globus pallidus) and white matter have also been observed in magnetic resonance imaging (MRI) and computed tomography (CT) scans in association with acute carbon monoxide poisoning. Motor impairments consistent with damage to basal ganglia have been observed following carbon monoxide poisoning. Following acute-onset effects, delayed development of neuropsychia tric impairment may occur from several days to 3 –4 weeks of exposure, with symptoms in cluding inappropriate euphoria, impaired judgment, poor concentration, memory loss, cognitive and personality changes, psychosis, and Parkinsonism. Delayed neuropsychiatric impairment has been estimated to occur in up to 68% of patients with acute carbon monoxide poisoning. There is a poor correlation between initial symptom severity, and the likelihood of developing of delayed neuropsychiatric impairment. Exposures to car bon monoxide in utero have also been associated with decrements in neurodevelopment, as assessed later in childhood with neuropsychological tests.

Based on an extensive database of acute carbon monoxide poisoning, it is generally accepted that central nervous system symptoms are associated with acute exposures that result in blood COHb leve ls 20%. However, despite extensive clinical experience, general consensus on the dose-response relationship for carbon monoxide-induced nervous system effects at blood COHb levels between 5 and 20% has not been achieved.
Based on studies described above, a blood COHb concentration of 20% is identified as a LOAEL for adverse neurological outcomes, although the LOAEL range may extend below this level to 5%. These levels, 5 and 20%, can be converted to equivalent human exposure concentrations (for continuous exposure) that would yield the same steady-state blood COHb concentration by implementing the CFK model. The human equivalent exposure concentrations are approximately 32 ppm (COHb=5%) and 160 ppm (COHb=20%).

Respiratory Effects. Although cardiopulmonary arrest is an end point of fatal carbon monoxide poisoning, results of controlled clinical studies in healthy subjects indicate that the respiratory tract does not appear to be a primary target organ for carbon monoxide toxicity. Brief exposure to carbon mo noxide at levels >1,000 ppm may decrease ventilatory performance, although conflicting results have been reported. Epidemiological studies have examined possible associations between ambient air carbon monoxide concentrations and mortality. These studies h ave examined relatively low carbon monoxide concentrations (from a toxicological perspective) that are typical of ambient conditions of the study period (mean concentrations ranging from 0.3 to 10 ppm with the highest values 30 ppm; see Table 3-3). Collec tively, these studies have yielded mixed results, with some studies finding significant associations between increasing ambient air carbon monoxide concentrations and respiratory outcomes (e.g., exacerbation of asthma symptoms, hospitalizations and emergency room visits related to asthma) and few studies

finding associations that persist after accounting for exposures to other air pollutants that also have been shown to contribute to respiratory disease risk (e.g., NO2, O3, particulate matter [PM], and SO2). The lack of strong evidence for associations between ambient air carbon monoxide concentrations at <30 ppm and pulmonary function is also consistent with the results of human clinical studies. Studies conducted in animals provide supporting evidence that the respiratory tract does not appear to be a primary target organ for carbon monoxide. Most of these studies evaluated carbon monoxide exposures that produced much higher COHb concentrations (i.e., COHb >50%) than those evaluated in controlled clinical s tudies in humans. In the studies that found effects on lung function (e.g., decreased compliance and increased airway resistance), animals had been exposed to carbon monoxide concentrations in the range of 8,000–28,400 ppm.

Hematological Effects . Hematolo gical effects of carbon monoxide include compensatory responses to tissue hypoxia resulting from binding of carbon monoxide to Hb (e.g., increased blood volume, Hb, hematocrit, and erythrocyte count and volume). Possible associations between ambient air carbon monoxide concentrations and biomarkers of coagulation and inflammation have been examined in epidemiological studies. Biomarkers examined have included inflammation markers, C-reactive protein (CRP), serum amyloid A (SAA), and white blood cell (WBC) c ount; cell adhesion markers, E-selectin, von Willebrand factor, antigen (vWF), ICAM-1; and coagulation markers, fibrinogen, factor VII (FVII), prothrombin fragment 1+2, prothrombin time (PT), and activated partial thromboplastin time (APTT).

Although some studies found significant associations between environmental carbon monoxide exposures and alteration in plasma proteins, these studies do not distinguish between possible direct effects of carbon monoxide and/or other air pollutants directly on coagulat ion and immune systems from indirect effects that result in changes in blood biomarkers. Furthermore, findings across studies are inconsistent. Environmental carbon monoxide exposures were shown to correlate with elevated C reactive protein in one trial, b ut not another by the same group. Plasma fibrinogen was increased in one study, decreased in one study, and unchanged in two studies. Other studies reported an elevation in soluble intercellular adhesion molecule-1, along with decreases in coagulation fact or VII, serum albumin, and prothrombin time. Therefore, no conclusions can be drawn at this time on whether low-level environmental exposures may alter plasma inflammatory or coagulation markers. Nevertheless, direct effects are plausible, given mechanistic studies that have revealed evidence that endogenous carbon monoxide may participate in the regulation of thrombosis and immune function (see Section 3.5.2, Mechanisms of Toxicity).