

Annex B. Dosimetry Studies

Table B-1. Recent studies related to CO dosimetry and pharmacokinetics.

Reference	Purpose	Findings
Aberg et al. (2009, 194082)	To investigate CO concentrations in blood donors in Sweden.	The mean CO concentration in blood donors was 84.5 µmol/L. Concentrations over 130 µmol/L were found in 6% of blood, and the highest concentration was 561 µmol/L. By using a calculation, 23% of banked blood bags could exceed 1.5% COHb, with a highest fraction of 7.2% COHb.
Abram et al. (2007, 193859)	To present the Quantitative Circulatory Physiology (QCP) model as a teaching module in the practice of medicine.	QCP is a dynamic mathematical model based on published models and parameters of biological interactions.
Alcantara et al. (2007, 193867)	To use a quantum mechanics/molecular mechanics approach to understand the cooperativity of Hb ligand binding and differences in energy between T and R Hb functional states.	The ligand binding energies between R and T states differ due to strain induced in the heme and its ligands and in protein contacts in the α and β chains.
Adir et al. (1999, 001026)	To determine if low concentrations of CO would affect exercise performance and myocardial perfusion in young healthy men.	Men with COHb levels between 4 and 6% had decreased exercise performance measured by decreased mean duration of exercise (1.52 min) and maximal effort described by metabolic equivalent units (2.04). No changes were seen in lactate/pyruvate ratio, arrhythmias, or myocardial perfusion.
Anderson et al. (2000, 011836)	To investigate if CO could be endogenously produced in the nose and paranasal sinuses.	Both nose and paranasal sinuses contained HO-like immunoreactivity, mostly in the respiratory epithelium, indicating local CO production in the upper respiratory airways.
Arora et al. (2001, 186713)	To evaluate the effect of multiple transfusion recipient thalassemics on pulmonary function.	D _L CO was decreased in all the patients with restrictive lung disease and fall in D _L CO showed a good correlation with the severity of restrictive disease. Thalassemics had a decrease in lung volume and a proportional decrease in flow rate.
Benignus et al. (2006, 151344)	To adapt and use a human model for toluene uptake and elimination including a brain compartment.	The QCP 2004 model was used to construct simulations of scenarios of toxicant exposure and human activities. QCP accurately predicted toluene blood concentrations from inhaled exposure.
Bos et al. (2006, 194084)	To use a PBPK model to set AEGL for methylene chloride.	This model adequately predicted COHb levels formed by various methylene chloride concentrations, specifically in nonconjugators lacking the GSTT-1 enzyme, and proposed AEGL values.
Bruce and Bruce (2003, 193975)	To create a mathematical model to predict uptake and distribution of CO in both vascular and tissue compartments during constant or variable inhalation levels of CO.	This model contains 5 compartments: lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue. It was constructed to include tissue compartment flux and difference between venous and arterial COHb for short exposures which is not possible with the CFK model.
Bruce and Bruce (2006, 193980)	To use their mathematical multicompartment model along with experimental data to predict the factors that influence the washout rates of CO, along with predicting the rates of CO uptake, distribution in vascular and extravascular (muscle and nonmuscle tissue) compartments, and washout over a range of exposure and conditions.	Rates of CO washout follow a biphasic elimination where washout was faster immediately post exposure. The difference in rates is likely due to slow equilibration between vascular and extravascular compartments. Important factors contributing to washout kinetics include: peak COHb level, exposure duration and concentration, time after exposure samples were obtained, and individual variability.
Bruce and Bruce (2008, 193977)	To develop a mathematical model able to integrate a large body of indirect experimental findings on the uptake and distribution of CO by accounting for arteriole to venule shunting via intratissue pathways and diffusion of blood gases into tissues from pre-capillary vessels like arterioles.	The former model of Bruce and Bruce (2006, 193980) was altered by adding a mass balance equation for O ₂ so pO ₂ is directly calculated in the compartments, and the muscle compartment is divided into two sub-compartments of muscle and nonmuscle tissue. CO uptake from blood by muscle is much slower than O ₂ , thus COHb% will fall rapidly while COMb% could remain high.

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Reference	Purpose	Findings
Carraway et al. (2000, 021096)	To test the hypothesis that HO-1 gene expression and protein are upregulated in the lungs of rats during chronic hypoxia.	Rats were exposed to HH (17,000 ft) for 1-21 days. COHb increased after 1 day and progressively after 14 days. HO-1 protein and activity were upregulated during early chronic hypoxia. This HO-1 was localized to inflammatory cells and then to newly muscularized arterioles.
Castillo et al. (2006, 193234)	To describe a new method for measurement of CO D_LCO and V_A in sleeping infants (6-22 mo old), using a single 4-s breath-hold technique.	V_{A30} and D_LCO increased with increasing body length, and the method could be used as a measurement of lung development and growth.
Chakraborty et al. (2004, 193759)	To present an analytical expression for diffusing capacity of CO, NO, CO ₂ , and O ₂ to the red blood cell in terms of optimum size and shape of the RBC, thickness of the unstirred plasma layer surrounding the RBC, diffusivities and solubilities of the gas in RBC and boundary layer, hematocrit, and the slope of the dissociation curve.	Results indicate the discoidal shape of the RBC is optimal for O ₂ uptake and reaction velocity is limited by mass transfer resistance in surrounding stagnant plasma layer. The paper overviews rate constants and reaction kinetics for CO binding to Hb. CO diffusing capacity is shown to be reaction-rate limited at low pCO under normoxic and hyperoxic conditions, but diffusion-rate limited under hypoxic and high pCO conditions.
Cronenberger et al. (2008, 194085)	To develop a population-based model to describe and predict the pharmacokinetics of COHb in adult smokers.	This two-compartment model included zero-order input and first-order elimination and required a compartment for extravascular binding of CO to accurately predict COHb formation during multiple short and rapid inhalations, followed by a period of no exposure, as occurs in smoking. Smokers' COHb ranged from 0.8 to 11.1%.
Cronje et al. (2004, 180440)	To analyze CO uptake and elimination in the brain, muscle, heart, and blood of rats, with the intent of testing the Warburg hypothesis that CO partitioning is directly proportional to the CO/O ₂ ratio.	Results indicate that tissue and blood CO concentration dissociate during CO inhalation, but CO concentration does not follow blood CO concentration or 1/pO ₂ as in the Warburg theory during intake or elimination. Tissue CO concentration increases later during the resolution period and varies significantly among animals and tissues. The deviation from the predicted values in the brain is likely due to the release of heme and increase in NADPH stimulating endogenous CO production by HO.
De las Heras et al. (2003, 194087)	To assess production of CO (venous COHb measured by CO-oximeter and exhaled CO) in patients with cirrhosis with and without spontaneous bacterial peritonitis.	Patients with SBP had higher CO production than noninfected cirrhotic patients and both groups of patients had higher CO production compared to healthy controls. CO production decreased slowly after resolution of the disease.
Dutton et al. (2001, 021307)	To monitor CO, NO ₂ , and PAH emissions during the operation of unvented natural gas fireplaces in two residences in Boulder, CO, at various times between 1997 and 2000.	Results showed significant accumulation of CO, NO ₂ , and PAH indoors when the fireplaces were used. CO concentrations could exceed 100 ppm. NO ₂ concentrations averaged 0.36 ppm over 4 h. PAH 4-h time avg reached 35 ng/m ³ .
Ehlers et al. (2009, 194089)	To determine the level of COHb found in banked blood in the Albany, NY region.	The avg COHb level was 0.78%. The highest recorded COHb level was 12%, and 10.3% of packed red blood cell units had levels of 1.5% COHb or higher.
Gosselin et al. (2009, 190946)	To develop a variant of the CFK model that links COHb levels in humans to ambient CO levels under various environmental or occupational exposure conditions.	The model adds alveoli-blood and blood-tissue CO exchanges and mass conservation of CO at all times to the CFK equation. The model better predicted COHb formation over a wide range of CO levels and scenarios with linear regression analysis of predicted vs observed values generating a slope of 0.996 (95% CI: 0.986-1.001) compared to 0.917 (95% CI: 0.906-0.927) using the CFK model
Hampson and Weaver (2007, 190272)	To present a case study of a man with drug-induced hemolytic anemia and hepatic failure.	The man had elevated endogenous CO production resulting in levels of COHb as high as 9.7%.
Hart et al. (2006, 194092)	To investigate the relationship between COHb and smoking habit and mortality.	COHb was related to self-reported smoking in a dose-dependent manner. COHb was positively associated with all causes of mortality analyzed including CHD, COPD, stroke, and lung cancer. Mean COHb levels ranged from 1.59% in never-smokers to 6.02% in the most often smoking group.
Hsia (2002, 193857)	To review the current concepts and practical relevance of the diffusing capacity/cardiac output interaction, in hopes of aiding in the interpretation of diffusing capacity, membrane diffusing capacity, and capillary blood volume.	This review helped to understand the determinants of changes in diffusing capacity, including hematocrit, erythrocyte distribution, blood volume, lung volume, and cardiac output.
Johnson et al. (2006, 193874)	To test that heme-derived CO formation is increased and contributes to hypertension and arteriolar endothelial dysfunction in obese Zucker rats.	Obese Zucker rats showed increased respiratory CO excretion that was lowered by HO inhibition. Skeletal muscle arterioles of obese rats had attenuated ACh and flow responses that were abolished by HO inhibition (HO inhibition enhanced dilation).
Lamberto et al. (2004, 193845)	To evaluate which component, alveolar membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc), is responsible for decreased resting D_LCO in sarcoidosis patients and which component is the best predictor of gas exchange abnormalities.	Patients with pulmonary sarcoidosis had decreased lung volumes, a loss in D_LCO , and gas exchange abnormalities during exercise, including decreased P_aO_2 and increased alveolar-arterial oxygen pressure difference. Dm accounted for the majority of the decrease in D_LCO and was predictive for gas exchange abnormalities.

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Levesque et al. (2000, 011886)	To describe the results of air quality monitoring in an indoor ice skating rink during Monster Truck and car demolition exhibitions.	Maximum time-weighted avg levels of CO were 100 ppm, with several peaks exceeding 200 ppm (max: 1,600 ppm).
Lim et al. (2000, 126969)	To investigate the expression of HO-1 and HO-2 in bronchial biopsies obtained from patients with mild asthma compared with that of subjects without asthma.	HO-1 and HO-2 expression is widely distributed equally in healthy subjects and subjects with asthma and is not modulated by inhaled corticosteroid therapy.
Mahoney et al. (1993, 013859)	To compare CO-oximeter measurements of COHb against a gas chromatography reference method.	In general, the 5 CO-oximeters that were tested underestimated COHb concentrations for COHb >2.5% and overestimated COHb concentration for COHb ≤ 2.5%, when compared to reference gas chromatography method.
Marks et al. (2002, 030616)	To review the analytical methods for measurement of endogenous formation of CO in a variety of tissues.	A variety of methods have been used to measure endogenous CO. The rate of formation varies over a narrow range, from 0.029 nmol/mg protein/h to 0.28 nmol/mg protein/h depending on tissue. Brain and liver regions tend to have the highest rates of CO formation, likely due to high levels of HO activity in these tissues.
Marvisi et al. (2007, 186702)	To evaluate D _L CO impairment and microalbuminuria in patients with active ulcerative colitis (UC) and to assess whether these tests correlate with intestinal inflammation.	Reduced D _L CO was present in 67% of patients. Microalbuminuria was present in 63% of patients with ulcerative colitis.
Merx et al. (2001, 002006)	To investigate the effect of CO inactivation of Mb in wild-type and myo ^{-/-} mice on hemodynamics and oxygen dynamics.	Fully oxygenated Mb treated with 20% CO had no change in left ventricular developed pressure or coronary venous pO ₂ . Partially O ₂ -saturated Mb (87% O ₂ Mb) exposed to 20% CO had significantly decreased LVDP (12%) and PvO ₂ (30%) in wild-type but not myo ^{-/-} hearts.
Monma et al. (1999, 180426)	To study whether exhaled CO levels were increased in seasonal allergic rhinitis.	Exhaled CO concentrations were higher in allergic rhinitis patients during cedar pollen season (3.6 ppm; SD 0.3 ppm) than out (1.2 ppm; SD 0.1 ppm).
Morimatsu et al. (2006, 194097)	To examine exhaled CO, arterial COHb, and bilirubin IXa levels in critically ill patients.	Exhaled CO concentrations were significantly higher in critically ill patients compared to controls. There was a significant correlation between exhaled CO and COHb or bilirubin. There was no correlation between exhaled CO and disease severity or degree of inflammation. There was higher exhaled CO in survivors compared to nonsurvivors.
Muchova et al. (2007, 194098)	To determine if long-term use of statins affects HO activity and blood and organ CO and bilirubin in FvB mice (6-8 wk).	Rosuvastatin and atorvastatin treatment increased COHb, plasma bilirubin, and heart tissue CO content. Both statins caused an increase in HO activity in heart tissue, whereas no changes were seen in brain or lung. Liver HO activity was inconsistent over time and between statins. Both statins decreased the heart antioxidant capacity, and changes in HO activity and antioxidant capacity can be reversed by HO inhibitor treatment.
Neto et al. (2008, 194672)	To develop a model of the respiratory system to analyze CO transport in the human body submitted to several physical activity levels.	The model contains 6 compartments including: alveolar, pulmonary capillaries, arterial, venous, tissue capillary, and tissues (muscular and nonmuscular). The highest and lowest COHb levels were simulated in the walking individual, suggesting that greater variability in COHb occurs in higher physical activity levels.
Pelham et al. (2002, 025716)	To review the literature on exposure and effects of mainly CO and NO ₂ in enclosed ice rinks.	CO levels as high as 300 ppm were recorded after episodes of malfunctioning ice resurfacing equipment or inadequate ventilation.
Paredi et al. (1999, 194102)	To investigate the level of exhaled CO produced by diabetic patients.	Diabetic patients (types 1 and 2) had higher levels of exhaled CO than healthy subjects. Exhaled CO levels correlated with the incidence of glycemia and the duration of diabetes.
Paredi et al. (1999, 118798)	To investigate whether cystic fibrosis patients have higher exhaled levels of CO and if this is reduced by corticosteroid therapy.	Cystic fibrosis patients had higher exhaled CO concentrations compared to healthy controls. Patients receiving corticosteroid therapy had lower exhaled CO concentrations.
Pesola et al. (2004, 193842)	To determine if healthy African Americans may be misdiagnosed as having respiratory deficient due to comparison using Caucasian-derived prediction equation estimates of D _L CO.	The lung volume of African-American individuals is 10-15% lower than Caucasians. The measured D _L CO was consistently significantly lower in African-Americans than what would be predicted. Thus, the authors suggest a race correction reduction of the Miller PEE for diffusion of 12%.
Pesola et al. (2006, 193855)	To determine if healthy Asians may be misdiagnosed as having respiratory deficient due to comparison using Caucasian-derived prediction equation estimates of D _L CO.	The lung volume of Asian individuals is 10-15% lower than Caucasians. Thus a Chinese-derived prediction for D _L CO should be used.

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Prommer and Schmidt (2007, 180421)	To determine the error in total Hb mass measurements using the optimized CO-rebreathing method due to loss of CO to Mb	Optimal blood mixing (when venous and arterial blood COHb% are equivalent) was determined to be after 6 min. A small volume of administered CO leaves the vascular space (0.32% per min). A 2.3% increase in total Hb mass would be found if CO diffusion was not included.
Proudman et al. (2007, 186705)	To review the signs of pulmonary arterial hypertension, including a drop in D _L CO in patients with systemic sclerosis.	
Richardson et al. (2002, 037513)	To combine invasive vascular measures of arterial and venous blood and muscle blood flow with noninvasive magnetic spectroscopy of deoxy-myoglobin and high energy phosphates to determine the effects of mild CO poisoning (20% COHb) in humans during muscular work.	Five humans were analyzed under normoxia, hypoxia, normoxia + CO (20% COHb), and 100% O ₂ + CO. Maximum works rates and maximal oxygen uptake were reduced in H, CO _{norm} , and CO _{hyper} . CO and H caused elevated blood flow. Net muscle CO uptake from blood was less during 20% COHb trials than during normoxia and hypoxia (1-2%) trials.
Sakamaki et al. (2002, 186706)	To evaluate the association of patients with aortic aneurysm to the prevalence obstructive airway disease.	Patients with AA had lower FEV ₁ and D _L CO than controls. Presence of AA and male gender were associated with a higher risk of airway obstruction.
Scharte et al. (2000, 194112)	To investigate whether exhaled CO concentrations are increased in critically ill patients.	Critically ill patients had higher exhaled CO concentrations and higher total CO production rates compared to healthy controls. No correlation was found between exhaled CO concentration and venous or arterial COHb.
Scharte et al. (2006, 194115)	To investigate the relationship between the severity of illness and endogenous CO production in critically ill patients.	CO production rates weakly correlated with the multiple organ dysfunction score (R=0.27). Cardiac disease patients and patients undergoing dialysis produced higher amounts of CO compared to critically ill control patients.
Schachter et al. (2003, 186707)	To evaluate the association between severe gastroesophageal reflux and lung function.	Patients with severe gastroesophageal reflux had reduced D _L CO, remaining significant after adjusting for age, gender, BMI, and smoking.
Shimazu et al. (2000, 016420)	To study the effects of short-term (min) or long-term (several h) CO exposure on COHb elimination and developing a mathematical model to simulate this event.	COHb exhibited an initial rapid decrease followed by a slower phase which is compatible with a 2-compartment model and biphasic elimination. Both exposures fit the 2-compartment, single-central-outlet mathematical model.
Shimazu (2001, 016331)	To discuss the findings of Weaver et al. (2000, 016421) on COHb t _{1/2} .	The authors discuss that CO elimination is biphasic and is heavily affected by duration of exposure which was not taken into account in the Weaver et al. (2000, 016421) paper.
Sylvester et al. (2005, 191954)	To assess the usage of end tidal CO levels in children with sickle cell disease for measurement of hemolysis.	Children with sickle cell disease had higher exhaled CO levels (4.9 ppm; SD 1.7 ppm) compared to healthy controls (1.3 ppm; SD 0.4 ppm). A positive correlation existed between end-tidal CO levels and COHb and bilirubin.
Takeuchi et al. (2000, 005675)	To examine the relationship between min ventilation and rate of COHb reduction during breathing 100% O ₂ and during normocapnic hyperoxic hyperpnea.	Patients were exposed to 400-1,000 ppm CO, resulting in 10-12% COHb. The half-time of COHb reduction was 78 ± 24 min during 100% O ₂ treatment and 31 ± 6 min during normocapnic hyperpnea with O ₂ treatment.
Tarquini et al. (2009, 194117)	To measure plasma CO levels in patients with liver cirrhosis and portal hypertension.	Plasma CO was higher in ascetic patients than nonascitic patients and both were higher than healthy controls. HO activity was higher in cirrhotic patients than healthy subjects and highest in patients with ascites.
Terzano et al. (2009, 108046)	To investigate the effect of postural changes on gas exchange in patients with COPD and healthy subjects.	D _L CO increased in healthy individuals from upright to supine position and upright to prone position. D _L CO did not significantly change in COPD patients from upright to prone position. This is explained by homogeneous perfusion in healthy individuals and increased rigidity of lung capillaries due to COPD.
Tran et al. (2007, 194120)	To assess the correlation of COHb to severity of liver disease.	No correlation was found with the Model for End Stage Liver Disease score, Child Turcotte Pugh score, or other biochemical or clinical measures of disease severity, such as spleen size, bilirubin, disease duration, or AST/ALT. The mean COHb was 2.1%.
Vreman et al. (2005, 193786)	To develop a sensitive and reproducible method of CO quantification in rodent (mouse and rat) tissue pre- and postexposure in hopes of understanding endogenous CO production.	Tissues were sonicated mixed with sulfosalicylic acid for 30 min at 0°C and then liberated CO was analyzed by gas chromatograph. Blood contained the highest CO concentration. Lowest concentrations were found in brain, testes, intestine, and lung (endogenously).
Vreman et al. (2006, 098272)	To test a method of CO quantification in frozen postmortem human tissues from 3 determined categories of fatalities: trauma with no suspected CO exposure (controls), fire-related, and CO asphyxiation.	CO levels were analyzed in adipose, brain, muscle, heart, kidney, lung, spleen, and blood (ordered from approximate low to high tissue concentration). It was suggested that blood, muscle, brain, lung, and kidney are suitable for diagnosing death due to lethal CO exposure due to regression analysis against COHb values.

Reference	Purpose	Findings
Weaver et al. (2000, 016421)	To determine if COHb half-life is influenced by CO poisoning vs experimental CO exposure, loss of consciousness, concurrent tobacco smoking, or P _a O ₂ .	COHb t _{1/2} determined was 74 ± 25 min with a range from 26 to 148 min by a single exponential decrease function. This is shorter than most clinical studies and was inversely proportionate to P _a O ₂ , however, not influenced by age, gender, smoke inhalation, loss of consciousness, tobacco smoking, or method of O ₂ treatment.
Whincup et al. (2006, 195129)	To report COHb levels from a population-based study in men aged 60-79 yr during the 20-yr follow-up of the British Regional Heart Study cohort.	Mean COHb: 0.46%; Median COHb: 0.5% 9.2% of men had COHb levels of 2.5% or greater (93% were smokers) 0.1% of men had COHb levels of 7.5% or greater Smoking is the highest influence on COHb levels; however, other factors independently related were season, region, gas cooking and central heating, and active smoking
Widdop (2002, 030493)	To review carbon monoxide analysis methods, including CO-oximeters and gas chromatography.	
Wu and Wang (2005, 180411)	To review the endogenous production of CO through HO, as well as discuss physiological roles for CO both toxic and therapeutic.	CO is produced endogenously by HO-1 and -2 and acts as a gasotransmitter, inducing cell signaling cascades. The review discusses possible roles for CO in the various organ systems and the potential pharmacological and therapeutic applications for CO.
Yamaya et al. (1998, 047525)	To determine whether upper respiratory tract infections increase exhaled CO concentrations.	Exhaled CO increased in patients at the time of upper respiratory tract infection symptoms but decreased to nonsmoking healthy control levels during recovery.
Yamaya et al. (2001, 180130)	To determine whether the level of CO is related to the severity of asthma.	Severe asthmatics exhaled more CO than nonsmoking controls. Exhaled CO concentrations in unstable severe asthmatics were higher than in stable severe asthmatics. Mild and moderate asthmatics did not differ from controls. Exhaled CO was correlated with FEV ₁ in all asthmatics.
Yasuda et al. (2002, 035206)	To determine whether arterial COHb is increased in patients with inflammatory pulmonary diseases.	Arterial COHb concentrations are increased in patients with inflammatory pulmonary diseases, including exacerbated bronchial asthma (1.05%), pneumonia (1.08%), and idiopathic pulmonary fibrosis (1.03%) over controls (0.6%).
Yasuda et al. (2004, 191955)	To determine if COHb levels in the venous blood and arteriovenous COHb (a-vCOHb) differences are increased in patients with inflammatory pulmonary diseases compared to patients with extrapulmonary inflammation and control subjects.	Patients with inflammatory pulmonary diseases, including bronchial asthma and pneumonia, had a large a-vCOHb difference. Both arterial and venous blood COHb increased in patients with inflammatory pulmonary disease, such as bronchial asthma, pneumonia, pyelonephritis and active rheumatoid arthritis.
Yasuda et al. (2005, 102183)	To study the relationship between COHb and disease severity in patients with COPD.	COHb concentrations increased in patients with COPD at a stable condition over controls and patients with COPD with exacerbations were further increased.
Yerushalmi et al. (2009, 186711)	To evaluate the association of dose-dense chemotherapy in breast cancer patients with pulmonary dysfunction.	Patients receiving dose-dense chemotherapy for breast cancer had a significant reduction in D _L CO.
Zegdi et al. (2002, 037461)	To compare endogenous CO production in mechanically ventilated critically ill adult patients with and without severe sepsis.	CO production was higher in septic patients during the first 3 days of treatment compared to controls. Survivors of sepsis had a significantly higher CO production compared to nonsurvivors.

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