

Annex E. Toxicological Studies

Table E-1. Human and animal studies.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Acevedo and Ahmed (1998, 016003)	Human pregnant myometrium			HO-1 and HO-2 (mRNA and protein) were upregulated in pregnant myometrium when compared to nonpregnant myometrium. The HO activator hemin inhibited spontaneous and oxytocin-induced contractility of the myometrium. Progesterone induced HO-1 and HO-2 mRNA expression.
Achouha et al. (2008, 179918)	Human arteries	Until equilibrium	Approximately 30 µM	CO induced endothelium- and NO-independent relaxation of precontracted human ITA and RA graft by partially stimulating cGMP production. The mechanism and extent of relaxation depended upon the tissue.
Ahmed et al. (2000, 193863)	Human placenta			Placental HO-1 was significantly higher at term. HO-1 significantly attenuated TNF α -dependent cellular damage in placental explants. HO-1 was significantly attenuated in pre-eclampsia pregnancies vs non-pre-eclamptic pregnancies. Placental arteries exposed to the HO activator hemin demonstrated reduced vascular tension (i.e., placental blood vessel relaxation).
Ahmed et al. (2005, 193865)	Human placental cotyledons			The source of CO in term human placental chorionic villi was found to be the catalysis of heme by HO and not endogenous lipid peroxidation.
Alexander et al. (2007, 193869)	Rat Sprague Dawley Adult female			Modulation of the HO/CO system in the anterior pituitary of the female rat led to altered secretion of gonadotropins and prolactin.
Alexandrescu et al. (2002, 192373)	Rat Sprague Dawley Female			The role of the HO/CO system in estrous cyclicity, pregnancy and lactation was evaluated using HO inhibitors and substrates. The HO inhibitor CrMP decreased time in estrous. Administering HO-inhibitors to pregnant rodents induced total litter loss. CrMP induced decreased litter weight gain during lactation, which the authors attribute to maternal milk production or ejection problems as cross-fostered pups regained weight lost during nursing on CrMP dams.
Alexandrescu and Lawson ((2003, 193871)	Rat Sprague Dawley Adult female			Modulation of the HO/CO system in the anterior pituitary of the female rat led to altered secretion of gonadotropins and prolactin.
Alexandrescu and Lawson (2003, 193876)	Rat Sprague Dawley Adult female ovary			HO-1 and HO-2 were localized in the ovaries in rats, and treatment of rat ovaries in vitro with CrMP, an inhibitor of HO, or with hemin, a substrate for HO induced steroidogenic changes in the ovaries.
Alonso et al. (2003, 193882)	Human muscle tissue mitochondria	5 min	50-500 ppm	CO significantly reduced muscle mitochondrial cytochrome c oxidase activity by 20%, 42%, and 55% after treatment with 50, 100, and 500 ppm CO respectively but did not change the activity of 3 other electron transport proteins.
Andersen et al. (2006, 180449)	Rat Long Evans Male Mouse C57BL/6J Male Cerebral vessels		1-100 µM	CO did not dilate rat or mouse cerebral arteries until 100 µM, which is not a physiological concentration. Also, the HO inhibitors constricted vessels in a nonspecific manner.

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	Species / Model	Exposure Duration	CO Concentration	Findings
Antonelli et al. (2006, 194960)	Rat Wistar	GD5-GD20	75 ppm	Pups exposed to CO in utero had significant impairment of cortical neuronal glutamatergic transmission at PND1 in both neurons at rest and in neurons stimulated with depolarization.
Appleton and Marks (2002, 193935)	Human placenta			Endogenous CO production by HO in the human placenta was regulated by O ₂ availability. Placental HO activity was directly dependent on O ₂ availability; this does not vary between pre-eclamptic and normotensive placentas.
Ashfaq et al. (2003, 194002)	Human placenta			Placentas were collected from smokers and nonsmokers who gave birth to male infants. Premature aging and a statistically significant increase in apoptotic cells were seen in placentas from smokers vs nonsmokers.
Astrup et al. (1972, 011121)	Rabbit (strain not identified)	Continuous CO exposure over gestation	90 or 180 ppm	Skeletal abnormalities: Three pups (from n = 123) in the 180 ppm CO group had deformities in their extremities at birth, whereas no control and no 90 ppm CO-exposed animals manifested with this malformation.
Bainbridge et al. (2002, 043161)	Human placenta		72–3369 nM	Isolated human placenta exposed to solutions containing CO demonstrated a concentration-dependent decrease in perfusion pressure further demonstrating the role of CO in maintaining basal vasculature tone.
Bainbridge et al. (2006, 193949)	Human placenta	6 h	Starting concentrations of CO: 3.9 µM CO in cell culture media (control) and CO-exposed groups: 116 µM, 145 µM, 181 µM. After 3 h, the CO in the culture media was 3.7 µM (control), and CO-exposed cells 10.2, 12, and 15.9 µM.	C-section placentas were collected from healthy term pregnancies. Villous explants of placentas were cultured under hypoxia followed by reoxygenation (H/R). H/R- and CO-exposed placental tissue had decreased apoptosis and decreased PARP (a protein marker of apoptosis) vs control H/R-exposed cells. Secondary necrosis of the placental tissue post H/R was inhibited by CO treatment.
Bainbridge and Smith (2005, 193946)	Human placenta			The role of HO in the placenta and during pregnancy is reviewed in this article. The conflicting data on the activity, localization and expression of HO in the placentas of pre-eclamptic women are presented.
Bamberger et al. (2001, 016271)	Human placenta			Expression and tissue localization of soluble guanylyl cyclase in human placenta using antibody localization were characterized. These tools can be used in future studies to elucidate the NO/CO/cGMP pathway.
Barber et al. (1999, 193953)	Human myometrium			HO and NOS did not maintain human uterine quiescence during pregnancy.
Barber et al. (2001, 193891)	Human placenta			Women who had pregnancies with fetal growth restrictions (FGR) produced term placenta with significant decreases in HO-2 vs healthy pregnancies.
Baum et al. (2000, 016435)	Human			End-tidal CO measurements in women with pregnancy-induced hypertension and pre-eclampsia were significantly lower than in normotensive pregnant women.
Benagiano et al. (2005, 180445)	Rat Wistar Female	GD0-GD20	75 ppm	CO caused a significant reduction in glutamic acid decarboxylase and GABA immunoreactivities in the cerebellar cortex of adult rats prenatally exposed to CO (number of positive neuronal bodies and axon terminals and the area they covered). No difference was found in the microscopic structure of the cerebellar cortex or distribution patterns of GAD or GABA.
Benagiano (2007, 193892)	Rat Wistar Female	GD5-GD20	75 ppm	Prenatal CO reduced GAD and GABA immunoreactivities. There were no structural alterations of the cerebellar cortex.
Bergeron et al. (1998, 193967)	Rat Brain			To address the developmental changes of HO staining in the brain, immunohistochemical staining for HO-1 was performed on the developing rat brain at PND7, PND14, and PND21. HO-1 staining was most intense at PND7, and by PND21 reached its adult pattern of staining localizing to the hippocampus, thalamic and hypothalamic nuclei, with virtually no staining of endothelium, white matter and cortex. HO-2 is the dominant HO isoform in the brain.

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Bing et al. (1995, 079418)	Rodent			Spatial learning in the Morris water maze was enhanced in rodents exposed to the HO inhibitor tin protoporphyrin (Sn-PP).
Burmester et al. (2000, 099998)	Human Mouse			Nb had a high oxygen affinity similar to Mb, and thus may increase the availability of O ₂ to brain tissue.
Bye et al. (2008, 193777)	Rat Wistar Female	100 h/wk for 18 mo	200 ppm	CO-exposed (11-14.7% COHb) rats experienced a 24% decrease in aerobic capacity evidenced by VO ₂ max deficits. Left ventricular cardiomyocytes were longer and wider, had increased expression of growth-related proteins, and had impaired contraction-relaxation cycles. CO increased cGMP and impaired cardiomyocyte Ca ²⁺ handling. No change in BP was observed.
Cagiano et al. (1998, 087170)	Rat Wistar Female	GD0-GD20	75 or 150 ppm	At 5 mo of age, CO-exposed male offspring showed decrements in sexual behavior, including an increase in mount-to-intromission latency, a decrease in mount-to-intromission frequency, and a decrease in ejaculation frequency. Basal extracellular dopamine concentration in the nucleus accumbens was unchanged after CO-exposure. However, when stimulated with amphetamine administration, control rats had increased release of dopamine that is absent in CO-exposed rats.
Carmines and Rajendran (2008, 188440)	Rat Sprague Dawley	GD6-GD19 of gestation for 2 h/day	600 ppm	Significant decreases in birth weight were reported after CO exposure. Maternal body weight was unchanged during gestation, but corrected terminal body weight (body weight minus uterine weight) was significantly elevated in CO-exposed dams at term.
Carratu et al. (1993, 013812)	Rat Wistar Male pups	GD0-GD20	75 or 150 ppm	Prenatal CO exposure slowed the inactivation kinetics of transient sodium current in the sciatic nerve fibers of 40-day-old male rats. The maximum number of activatable Na channels at normal resting potential was increased in CO exposed rats, and the voltage-current relationship showed a negative shift of sodium equilibrium potential.
Carratu et al. (1995, 079427)	Rat Wistar		150 ppm	Sphingolipid homeostasis was disrupted in male offspring of prenatally exposed rats, without a disruption in motor function.
Carratu et al. (2000, 015935)	Rat Wistar	GD0-GD20	150 ppm	Maternal COHb (mean % ± SEM) was 1.9 ± 0.04 and 16.02 ± 0.98 in control and 150 ppm CO-exposed animals, respectively. Prenatal CO exposure had no effect on brain sphinganine (SA) or sphingosine (SO) levels in male offspring at 90 days of age. However, the sciatic nerve had significant increases in SO after CO exposure, and no changes in SA at 90 days of age. Motor activity, which could be affected by changes in myelination, showed no differences between CO and control animals at 90 days of age.
Carratu et al. (2000, 015839)	Rat Wistar	GD0-GD20	75 or 100 ppm	The myelin sheath thickness of the nerve fibers was significantly decreased in CO-exposed animals (75 and 150 ppm). Axon diameter was not affected by CO exposure. Even though CO affected myelination, it did not significantly affect motor activity of CO-exposed rats at 40 and 90 days.
Carraway et al. (2002, 026018)	Rat model of hypoxic pulmonary vascular remodeling (Strain of rat not stated)	3 wk	Hypobaric hypoxia ± 50 ppm	CO promoted remodeling and increased pulmonary vascular resistance in response to HH. The number of small muscular vessels was increased compared with HH alone. Changes in cell proliferation, apoptosis, actin and HO-1 gene and protein expression correlated with structural changes. COHb levels were <0.5% in controls, 1.5-2.8% in the HH treatment group, and 3.5-3.9% in the HH + CO treatment group.
Cella et al. (2006, 193240)	Rat Sprague Dawley			HO-1 production and HO concentration were shown to be regulated by estrogen in the rat uterus.
Chen (2001, 193985)	Rat Long Evans Male 2 mo	3.5 h	1201 ± 18 ppm	CO potentiates-noise induced hearing loss. The NMDA inhibitor (+)-MK-801 did not block the potentiation of the NIHL by CO.
Cheng et al. (2009, 193775)	Human atherectomy biopsy (clinical carotid artery disease) Mouse model of vulnerable plaque ApoE-/- mouse			HO-1 expression correlated with features of vulnerable human atheromatous plaque. HO-1 expression was upregulated in vulnerable lesions in the mouse model. Induction of HO-1 in the mouse impeded lesion progression into vulnerable plaques. Inhibition of HO-1 augmented plaque vulnerability. Overexpression of HO-1 resulted in plaque stabilization. It was concluded that HO-1 induction was atheroprotective.

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Chung et al. (2006, 193987)	Rat Sprague Dawley Male		3-6%	CO inactivation of Mb did not induce any change in the respiration rate, contractile function or high-energy phosphate levels in perfused rat hearts.
Cronje et al. (2004, 180440)	Rat Sprague Dawley Male 240-325 g	45 min	2,500 ppm	<p>Results indicate that tissue and blood (CO) (66-72% COHb) dissociate during CO inhalation, but tissue (CO) does not follow blood (CO) or $1/pO_2$ as in the Warburg theory during intake or elimination. Tissue (CO) 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. Immediately following exposure, tissue CO concentrations were found to be:</p> <p>Blood: 27,500 (800) pmol/mg Heart: 800 (300) pmol/mg Muscle: 90 (80) pmol/mg Brain: 60 (40) pmol/mg</p> <p>These values are estimates taken from a graph, with control levels in parentheses</p> <p>A later report stated that these tissue CO values were too high due to a computational error (Piantadosi et al., 2006, 180424)</p>
Cudmore et al. (2007, 193991)	Human placenta Human (HUVEC) Mouse (HO-1 deficient mouse on 129/SV × C57BL/6 background) Pig (Porcine aortic endothelial cells)			HUVEC cells, porcine aortic endothelial cells, HO-1 null mice and placental villous explants (normotensive and pre-eclamptic pregnancies) were used in this study. The HO-1/CO system inhibited sFlt-1 and sEng release, two factors upregulated in pre-eclampsia.
D'Amico et al. (2006, 193992)	Human embryonic kidney (HEK293) cells	0-30 min	20 μ M	Exogenous CO inhibited respiration in HEK293 cells under ambient O_2 concentration (21%). Inhibition was enhanced under hypoxic conditions. Increased endogenous CO resulting from HO-1 overexpression inhibited respiration by 12% and cytochrome c oxidase activity by 23%. This effect was enhanced under hypoxic conditions.
Dani et al. (2007, 193994)	Human (neonatal blood)			CO was lower at birth and 48-72 h postpartum in infants born by elective C-section and higher in vaginally born infants.
De Luca et al. (1996, 080911)	Rat Wistar Female Male pups	GD0-GD20	75 or 150 ppm	Prenatal CO (150 ppm) delayed development of the ion channels responsible for passive and active membrane electrical properties of skeletal muscle. CO-induced lower values of resting chloride conductance was reversed at PND80. CO-induced delayed developmental reduction of resting potassium conductance was reversed at PND60.
De Salvia et al. (1995, 079441)	Rat Wistar	GD0-GD20	75 or 150 ppm	Animals exposed to the higher dose of CO (150 ppm) in utero had significantly impaired acquisition (at 3 and 18 mo) and reacquisition (at 18 mo) of conditioned avoidance behavior.
Denschlag et al. (2004, 193894)	Human			Genetic polymorphisms in human HO-1 are linked to idiopathic recurrent miscarriages.
Dewilde et al. (2001, 019318)				Nb exists as a reversibly hexacoordinated Hb type with a His-Fe ²⁺ -His binding scheme. Dissociation of the internal ligand by O_2 or CO is the rate limiting step.
Di Giovanni et al. (1993, 013822)	Rat Wistar Female	GD0-GD20	75 and 150 ppm	CO (150 ppm) reduced the minimum frequency of ultrasonic calls as well as decreased responsiveness to a challenge dose of diazepam. There was no change in locomotion; however CO impaired learning in a two-way active avoidance task.
Dubois et al. (2002, 193911)	Rat Wistar Adult female 250 g	3 wk	530 ppm	Intrapulmonary resistance artery smooth muscle cells were isolated from control and exposed rats. Electrophysiological recordings provided evidence of increased Ca ²⁺ -activated K ⁺ current consequent to chronic CO exposure. The authors speculated that this could in part explain the vasodilatory effect of CO in the pulmonary circulation.

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Dubois et al. (2005, 180435)	Rat Wistar Male	21 days	50 ppm	CO attenuated PAHT by activating BK _{ca} channels in PA myocytes and reduced hemodynamic changes of PAHT.
Dubois et al. (2003, 180439)	Rat Wistar Male	21 days	50 ppm	CO induced relaxation of pulmonary artery rings in normoxic, hypoxic, and hypoxic-CO rats, and it was not endothelium dependent. Chronic hypoxia decreased acute CO sensitivity, while CO-hypoxia increased it. K ⁺ channel blocker reduced this effect while sGC blocker did not.
Durante et al. (2006, 193778)				Reviews the role of CO in cardiovascular function.
Favory et al. (2006, 184462)	Rat 250-300 g (Strain not stated)	90 min	250 ppm	CO inhibited myocardial permeabilized fiber respiration (complex IV), increased coronary perfusion pressure and left ventricular developed pressure (LVDP) first derivative and decreased the cGMP/cAMP ratio in the heart. These changes were maintained over 24-48 h of recovery in air. Cardiac function and vasodilatory responses were evaluated at 3-h recovery in air. β -adrenergic blockade had no effect on coronary perfusion pressure or LVDP first derivative. Total inhibition of vasodilator response to acetylcholine and partial inhibition of vasodilator response to nitroprusside were observed. An increase in myofilament calcium sensitivity was also observed. Thus CO promotes abnormalities in mitochondrial respiration, coronary vascular relaxation and myocardial contractility. The authors speculated that CO may have a detrimental effect on heart O ₂ supply-to-utilization which could potentially lead to myocardial hypoxia because of the increased O ₂ demand resulting from increased contractility, the inhibited mitochondrial respiration and the reduced coronary blood-flow reserve resulting from the decreased vasodilatory capacity. COHb was found to be 11% immediately after exposure. COHb levels gradually returned to baseline (1.5%) over the next 96 h.
Fechter and Annau (1977, 010688)	Rat Long Evans	Continuous CO exposure throughout pregnancy	150 ppm CO	The authors found a 5% significantly decreased birth weights at PND1 in gestationally CO-exposed pups vs control animals with weight decrements persisting to weaning; lactational cross fostering did not ameliorate the CO-dependent reduced growth rates. Dams exposed to CO during gestation had COHb over gestation of 15% with control dams having less than 1%. Decreased birth weight and pre-weaning weight were seen in CO-exposed pups despite a lack of weight decrement in CO-exposed dams vs air-exposed control dams.
Fechter et al. (1980, 011294)	Rat Long Evans	Continuous CO exposure throughout pregnancy	150 ppm	CO-exposed animals had cardiomegaly at birth (wet heart weight) that dissipated by PND4.
Fechter and Annau (1980, 011295)	Rat Long Evans	Continuous CO exposure throughout pregnancy	150 ppm	CO-exposed animals had decreased birth weight, impaired righting reflexes, impaired negative geotaxis, and delayed homing behavior.
Fechter et al. (1987, 012194)	Rat Long-Evans Male		1-4 mL/100 g BW (ip)	High-dose CO led to dose-dependent, reversible loss of the compound action potential sensitivity for high frequency tone bursts. Also, CO produced a dose-dependent elevation in the cochlear blood flow.
Fechter et al. (1987, 012259)	Rat Long Evans Male	Continuous CO exposure throughout pregnancy or from GD0 to PND10	75, 150, or 300 ppm	The neostriatum of each PND21 rat brains was collected and showed disrupted development following CO exposure (GD0-PND10 group, 300 ppm CO). Dopamine levels were also significantly elevated in CO-exposed animals (GD0-PND10, 150 and 300 ppm CO).
Fechter et al. (1997, 081322)	Guinea pigs		35 ml/kg gas (ip) 40% COHb	CO impairs high-frequency auditory sensitivity, shown by increased compound action potential threshold at higher test frequencies. Free radical inhibitors blocked this response.
Fechter et al. (1986, 012030)				Reviews the effects of carbon monoxide on brain development.

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Garofolo et al. (2002, 193930)	Human infants Rat	Rat: PND2-PND5		Human infants who die from SIDS showed decreased brainstem muscarinic receptor binding vs infants dying from other causes. β -adrenergic modulation of muscarinic receptors in developing heart was observed. Rodent β -adrenergic agonists at PND2-PND5 induced muscarinic receptor decrement in adenylyl cyclase.
Gautier et al. (2007, 096471)	Rat Wistar Adult male Model of right ventricular hypertrophy secondary to chronic hypoxia	3 wk of HH \pm CO in final wk Or 1 wk of CO	50 ppm	CO altered the right ventricular adaptive response to pulmonary hypertension which occurs secondarily to chronic hypoxia. Right ventricular end-systolic pressure (RVESP) and right ventricular shortening fraction (RVSF) were smaller in rats treated with CO+HH compared with rats treated with HH alone. CO alone had no effect on these measures. Hypobaric hypoxia had no effect on left ventricular function while CO+ HH led to an increased left ventricular shortening fraction (LVSF). CO alone led to a decrease in LVSF and the mitral E-to-A ratio, indicative of an LV-filling impairment. Hypobaric hypoxia decreased the relative RV perfusion and increased the relative LV perfusion. These effects were prevented with concomitant exposure to CO, although exposure to CO alone had no effects on myocardial perfusion. Morphologic and histologic analysis demonstrated RV hypertrophy in both the HH group and the CO+HH group and fibrotic lesions in the CO+HH group. The authors concluded that the 1-wk exposure to 50 ppm CO had a deleterious effect on RV myocardial perfusion adaptation to chronic hypoxia and pressure overload. Although the reduced RV pressure overload was beneficial, it was counterbalanced by impaired RV perfusion and redistribution of perfusion toward the LV.
Gaworski et al. (2004, 193933)	Rat Sprague Dawley	2 h/day, 7 days/wk by nose-only inhalation Males: 4 wk prior to and during mating; and Females: 2 wk prior to mating; during mating; and through weaning to PND21	Cigarette smoke: 150, 300, or 600 mg/m ³ Total Particulate Matter (TPM)	Maternal exposure to high concentrations of cigarette smoke during gestation and lactation reduced pup birth weight and retarded neonatal pup growth. Developmental and neurobehavioral testing of neonates did not show any behavioral effects following parental smoke exposure.
Ghio et al. (2008, 096321)	Rat Sprague Dawley Adult male	24 h	50 ppm	Mild neutrophil accumulation was observed in BALF, accompanied by increases in BALF MIP-2, protein and LDH. Iron status was altered since CO exposure led to an increase in BALF iron and ferritin, a decrease in lung non-heme iron and an increase in liver non-heme iron.
	Human bronchial epithelial cells (BEAS-2B)	2-24 h	10-100 ppm	CO exposure for 24 h led to a dose-dependent decrease in cellular non-heme iron, with the effect at 10 ppm statistically significant and the effect at 50 ppm maximal. This effect was reversible since removing the cells after 2 h of CO and incubating them in air restored non-heme iron concentrations at 24 h. A dose-dependent decrease in cellular ferritin was observed following exposure for 24 h to 50-500 ppm CO. In addition, exposure to 50 ppm CO for 20 h blocked iron uptake by cells, while exposure to 50 ppm CO for 2 h increased iron release from cells. Increased protein expression of the iron transporter DMT-1 was also noted after 24 h exposure to 50 ppm CO. Oxidative stress, mediator release and cell proliferation were also decreased by exposure to 50 ppm for 24 h. This effect was also reversible upon removal to air. Effects of CO on cell proliferation indices were mimicked by with the iron-depleting agent deferoxamine. The authors concluded that CO exposure altered lung iron homeostasis possibly by initially causing heme release from proteins.
Giustino et al. (1999, 011538)	Rat Wistar Male and pregnant female	GD0-GD20	75 or 150 ppm	This study showed that CO- exposed (75 and 150 ppm) male animals at 40 days of age had a significantly decreased time of exploration of novel objects. The 150 ppm CO group showed a lack of habituation after the second exposure to a previously viewed object. Blood COHb concentrations (mean \pm SEM) on GD20 were reported (0 ppm: 1.6 \pm 0.1; CO 75 ppm: 7.36 \pm 0.2; CO 150 ppm: 16.1 \pm 0.9).

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Giustino et al. (1993, 013833)	Rat Wistar	GD0-GD20	75 or 150 ppm	CO exposure in utero led to a reversible and dose-dependent loss of function of splenic macrophages, with decreased killing ability, decreased phagocytosis, and decreased ROS production during the macrophage respiratory burst.
Giustino et al. (1994, 076343)	Rat Wistar Male pups	GD0-GD20	75 or 150 ppm	CO (150 ppm) decreased the number of leukocyte common antigen (LCA+) cells at PND21. This was reversed by PND540. CO (75 ppm), and other measures of immunological changes showed trends toward reduction (macrophages, T cells, B cells, and MHC II cells).
Glabe et al. (1998, 086704)	Rat Sprague Dawley Male, Myocardium		pCO = 0-107 Torr	Increased pCO and increased COMb saturation did not alter high-energy phosphate signals (ATP, phosphocreatine, P _i). MVO ₂ began to decline at 87.6% COMb and is likely not due to cytochrome c oxidase inhibition.
Grover et al. (2000, 010465)	Fetal lamb (mixed breed)	10 min	500 ppm	Fetal methoxyhemoglobin (COHb%) ranged from 3.8 ± 0.2 to 8.1 ± 2.0 at 0 and 500 ppm CO, respectively. Inhaled 0-500 ppm CO administered to near-term fetal lambs did not induce pulmonary vasodilation (main pulmonary artery, left pulmonary artery, aorta and left atrium), and the HO inhibitor zinc protoporphyrin IX failed to affect baseline vascular tone.
Hara et al. (2002, 037497)	Rat Sprague Dawley Male	40 min	1,000-3,000 ppm	CO exposure increased extracellular dopamine levels and decreased its major metabolites in a Na ⁺ -dependent pathway. CO withdrawal and reoxygenation caused levels to return to control or overshoot, which may suggest an increase in oxidative metabolism of CO, mediated by MAO-A.
Harada et al. (2004, 193920)	Pig Granulosa cells			In this porcine model, HO was able to augment granulosa cell apoptosis allowing for proper follicular maturation.
Hendler and Baum (2004, 193925)	Human			End-tidal breath CO measurements in pregnant women with contractions (term and pre-term) were lower than those measurements in noncontracting women.
Hofmann and Brittain (1998, 052019)	Human			Partitioning of O ₂ and CO in the human embryonic Hb is discussed.
Iheagwara et al. (2007, 193861)	Mouse C57BL/6 Male	3 h	1,000 ppm	CO significantly reduced cytochrome c oxidase activity and V _{max} but not K _m in myocardial mitochondria. Cytochrome c oxidase protein levels and heme content were significantly decreased. The average COHb level was 61%, but no tissue hypoxia was observed in the heart.
Imai et al. (2001, 193864)	HO-1 transgenic mice which specifically over-express HO-1 in smooth muscle			Transgenic mice had a significant increase in arterial pressure and impaired nitrovasodilatory aortic responses. The mice had enhanced NO production and impaired sGC activity. The authors speculated that the effect of HO-1 overexpression was to suppress vasodilatory responses to NO in vascular smooth muscle.
Ischiropoulos et al. (1996, 079491)	Rat Wistar Male 200-290 g	60 min 40-60 min	1,000-3,000 ppm 1,000 ppm	CO poisoning resulted in free NO in brains as measured by electron paramagnetic resonance spectroscopy and in a 10-fold increase in nitrotyrosine as measured by immunohistochemical staining. These responses were blocked by pretreatment with a NOS inhibitor but not by neutrophil depletion. Brain nitrotyrosine formation was blocked by platelet depletion following 40-min but not 60-min exposure to 1,000 ppm CO. Following CO poisoning, myeloperoxidase activity, a measure of leukocyte sequestration, was increased in brain microvessels. This response was blocked by NOS inhibition but not by platelet depletion. Similar effects were noted for xanthine oxidase activation. The authors concluded that perivascular reactions mediated by peroxynitrite are key to CO poisoning effects in brain.
Johnson and Johnson (2003, 053611)	Rat Sprague Dawley Male 250-300 g		0-100 μM	CO produced a concentration-dependent, endothelium-dependent vasoconstriction in isolated gracilis muscle arterioles, evident at 1 μM CO. Pretreatment with a NOS substrate prevented this response, while pretreatment with a NOS inhibitor converted this response to a vasodilation. The authors concluded that exogenous CO was acting through NOS inhibition.

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Johnson et al. (2003, 193868)	Rat Dahl/Rapp salt-resistant and salt-sensitive model Male			High-salt diet increased COHb, BP, and aortic HO-1 protein levels in salt-sensitive Dahl rats. Enhanced immunostaining was observed for HO-1 but not HO-2 in isolated gracilis muscle arterioles. Compared with the low-salt diet, the high-salt diet resulted in a smaller vasoconstrictor response when NOS was inhibited. Vasoconstriction was exacerbated in arterioles from both low-salt- and high-salt-treated rats using both NOS and HO inhibitors. Acetylcholine-induced vasodilation was diminished in the high-salt diet group compared with the low-salt diet group. This effect was not seen using the HO inhibitor. The high-salt diet did not alter endothelium-independent vasodilation. The authors concluded that HO-derived CO caused dysfunction of the NO system in salt-sensitive rats treated with a high-salt diet.
Johnson et al. (2004, 193870)	Rat Sprague Dawley Male Deoxycorticosterone acetate (DOCA)-salt hypertension model Rats WKY Rats Spontaneously hypertensive (SHR)			Salt-sensitive DOCA rats, but not SHR, had elevated aortic HO-1 expression and blood COHb levels. Both had elevated mean arterial BP compared with controls. Acetylcholine-mediated vasodilation of isolated gracilis muscle arterioles was attenuated in DOCA rats but not SHR. Pretreatment with an HO inhibitor restored the response in DOCA rats. The authors concluded that HO-1-derived CO contributes to endothelial dysfunction in DOCA but not SHR.
Johnson et al. (2006, 193874)	Rat Zucker Lean and obese Male		100 µM CO	The obese rats had increased CO expiration and mean arterial pressure, which was decreased by pretreatment with a HO inhibitor. No difference was observed in HO-1 protein between lean and obese rats. Acetylcholine- and flow-mediated vasodilation of isolated gracilis muscle arterioles was attenuated in obese but not lean rats. Pretreatment with a HO inhibitor restored the response in obese rats. Exogenous CO prevented the restoration of flow-induced dilation by the HO inhibitor. The authors concluded that HO-derived CO contributes to endothelial dysfunction in this model of metabolic syndrome.
Katoue et al. (2005, 193896)	Rat Wistar			HO activity in the aorta is significantly increased during pregnancy, but aortic AVP-dependent vasoconstriction appears to be HO/CO independent.
Katoue et al. (2006, 193954)	Rat Wistar			Pregnancy-induced modulation of calcium mobilization and downregulation of Rho-kinase expression contributed to attenuated vasopressin-induced contraction of the rat aorta.
Khan et al. (2006, 193955)	Nb overexpressing BDNF × CD1 mice			Cerebral and myocardial infarcts were decreased in neuroglobin overexpressing mice, decreasing ischemic injury.
Kim et al. (2005, 193959)	Primary rat pulmonary artery smooth muscle cells Rat Inbred LEW Sprague Dawley 200-250 g	24 h or pretreatment for 1-2 h followed by 24 h post-treatment	250 ppm	Exposure of cells in culture to 250 ppm CO for 24 h inhibited serum-stimulated cell proliferation, increased expression of p21Waf1/Cip1, and decreased expression of cyclin A. CO also inhibited PDGF-stimulated cell proliferation and reversed the inhibitory effect of PDGF on caveolin-1 expression. Genetic silencing of caveolin-1 using siRNA, prevented the antiproliferative effect of CO. Endogenous CO, derived from HO-1 in an overexpression system, was found to upregulate caveolin-1 expression. Effects of CO on caveolin-1 were found to be mediated by p38 MAPK and cGMP. Experiments in fibroblasts deficient in p38 confirmed a role for p38 in CO-mediated inhibition of cellular proliferation via effects on p21Waf1/Cip1, cyclin A and caveolin-1. Experiments in fibroblasts deficient in caveolin-1 confirmed the role of caveolin-1 in the anti-proliferative effects of CO. In a model of neointimal injuries induced by balloon injuries in intact animals, exposure to CO inhibited neointimal formation and increased caveolin-1 expression in the intima and media.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Kim et al. (2008, 193961)	Primary rat hepatocytes Primary mouse hepatocytes Respiration-deficient human Hep3B cells	10-60 min	250 ppm	Exposure of cells in culture to 250 CO for 1 h twice a day prevented spontaneous hepatocyte death over 6 days in culture. CO also decreased caspase-3 activity. Cell death was determined to be partly due to apoptosis. CO also increased ROS as measured by dichlorofluorescein fluorescence in rat hepatocytes, mouse hepatocytes, and Hep3B cells but not in respiration-deficient Hep3B cells, indicating that ROS were mitochondrial in origin. An increase in mitochondrial oxidized glutathione was noted in rat hepatocytes treated with CO for 30 min. Increased Akt phosphorylation occurred following 10-30 min CO and was diminished by treatment with antioxidants. CO was found to activate NFκB through a PI3K and oxidant-dependent pathway. CO mediated spontaneous cell death was found to be dependent on ROS and Akt phosphorylation. The authors concluded that CO prevents hepatocyte apoptosis through redox mechanisms, leading to cytoprotection.
Kinobe et al. (2006, 188447)	Sheep Gravid and nongravid sheep and their near-term fetuses			There were no significant differences in hypoxic adult and hypoxic fetal sheep when compared to their normoxic controls.
Knuckles et al. (2008, 191987)	Mouse	4 h	Diesel emissions: 350 µg/m ³	Diesel exhaust enhanced vasoconstriction in veins but not arteries. It was suggested that this is through the uncoupling of eNOS.
Korres et al. (2007, 190908)	Human			Transient evoked otoacoustic emissions response and amplitude at 4,000 Hz was lower in neonates with prenatal exposure to cigarette smoke. There was no dose-dependent change in response depending on the amount cigarettes per day that was smoked.
Kreiser et al. (2004, 193948)	Human			End-tidal CO concentrations were lower in pregnant women with gestational hypertension and pre-eclampsia than normotensive women.
Lash et al. (2003, 193849)	Human Term placental chorionic villi from healthy or pre-eclamptic placentas			Infarcted areas of placenta had decreased HO expression (in pre-eclamptic placenta only).
Li et al. (2008, 187003)	Mouse ICR (CD-1) Pregnant			The effect of maternal LPS exposure on fetal liver HO was measured. HO-1 was upregulated in fetal livers post-LPS exposure, and this HO-1 upregulation was attenuated with the spin trap agent PBN, pointing to a ROS-dependent HO-1 upregulation post-maternal LPS treatment.
Liu and Fechter (1995, 076524)	Guinea pig Male		35 mL/kg (ip)	CO increased the compound action potential threshold at high frequencies. This could be blocked by inhibition of the glutamate receptor.
Loennechen et al. (1999, 011549)	Rat Sprague Dawley Female 220-240g	1 wk 1 wk 100 ppm and 1 wk 200 ppm	100 ppm 100-200 ppm	Endothelin-1 expression increased by 53% and 54% in the left and right ventricle, respectively, during the 2-wk exposure, and by 43% and 12% in the left and right ventricle, respectively, during the 1-wk exposure. Right ventricular to body weight ratio was increased by 18% and 16% in the 2-wk and 1-wk exposure groups, respectively. COHb levels were 23% and 12% in the 2-wk and 1-wk exposure groups, respectively.
Longo et al. (1999, 011548)	Rat uterine tissue and tail artery rings Sprague Dawley Human uterine biopsies		10 ⁻⁴ M	The addition of exogenous CO to isolated human and rat uterine tissue failed to induce relaxation of uterine tissue. Isolated rat aortic rings and tail artery rings from pregnant dams can be relaxed by submersion in exogenous CO solutions.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Lopez et al. (2008, 097343)	Rat Sprague Dawley	Pregnant rats exposed to CO GD5-GD20 (Group A) or GD5-GD20 plus PND5-PND20 (Group B); Group C (control air exposure). 10-18 h/day	25 ppm	CO exposure induced damage to the spiral ganglia neurons and inner hair cells, with oxidative stress seen in cochlear blood vessels. At PND20 groups A and B showed vacuolization of afferent terminals at the base of the cochlea. At PND3, group A showed decreased synapsin-1 staining of the efferent nerve terminals. At PND20, groups A and B showed decreased neurofilament-IR (staining) in type I spiral ganglia neurons and afferent nerve fibers. At PND12 and PND20, group B showed increased HO-1 and SOD-1-IR in blood vessels of the stria vascularis; group A was similar to controls. From PND3-PND20, there was increased iNOS and increased nitrotyrosine-IR in blood vessels of the cochlea.
Lopez et al. (2003, 193901)	Rat Sprague Dawley	PND6 to weaning (PND19-PND20)	12 or 25 ppm	In the cochlea, atrophy or vacuolization of the nerve cells that innervate the inner (not outer) hair cells was seen. Fibers of the 8th cranial nerve (internal auditory canal of the ARCO animals, 25 ppm) had distorted myelination and vacuolization of the axoplasm. In the organ of corti and spiral ganglion neurons, cytochrome c oxidase and NADH-TR were significantly decreased in 25 ppm exposure group vs control. Expression of the calcium-mediated myosin ATPase in the organ of corti and spiral ganglion neurons was significantly decreased in the 25 ppm CO exposure group vs controls.
Lund et al. (2007, 125741)	Mouse ApoE ^{-/-} Male High-fat diet	6 h/day, 7 days/wk, 7 wk	8, 40, or 60 µg/m ³ PM whole-gasoline exhaust; or filtered exhaust with gases matching the 60 µg/m ³ concentration. CO concentrations were 9, 50, and 80 ppm, corresponding to the 8, 40, and 60 µg/m ³ PM whole-exhaust exposures	Both whole-gasoline and filtered-gasoline exhaust increased aortic mRNA expression of matrix metalloproteinase-3 (MMP-3), MMP-7, and MMP-9, tissue inhibitor of metalloproteinases-2, endothelin-1 and HO-1 at 60 µg/m ³ . Aortas also showed increased immunostaining for MMP-9 and nitrotyrosine in 60 µg/m ³ PM whole exhaust and PM-filtered exhaust exposed groups. Aortic TBARS, a measure of lipid peroxidation, was also increased in all treatment groups.
Lund et al. (2009, 180257)	Mouse ApoE ^{-/-} Male High-fat diet	6 h/day, 1 or 7 days	Gasoline engine exhaust containing 60 µg/m ³ PM and 80 ppm CO	Gasoline exhaust exposure increased aortic MMP-2/9 activity at 1 and 7 days. Protein levels of aortic MMP-9, MMP-2, TMP-2 and plasma MMP-9 were also increased after 7 days. Lipid peroxidation in aorta, resulting from gasoline exhaust exposure, was inhibited by treatment with the antioxidant Tempol, while increases in mRNA for ET-1 and MMP-9 in aortas were inhibited by treatment with BQ-123, an antagonist of ETA receptor. Treatment with BQ-123 also reduced aortic MMP-2/9 activity in aortas following gasoline exhaust exposure. The authors concluded that ETA receptor pathway is a key mediator of gasoline engine exhaust effects in the vasculature.
Lyall and Myatt (2002, 193971)	Human			Women with pre-eclampsia produced term placenta with significant decreases in HO-2 vs women with healthy pregnancies.
Lyall et al. (2000, 193902)	Human (placentas from 8-to19-wk pregnancy and term placentas)			The use of a HO inhibitor ZnPP increased placental perfusion pressure. HO-1 and HO-2 were expressed in the placenta and placental bed and vary in expression over the course of pregnancy. HO may thus be involved in trophoblast invasion, placental function, and perfusion pressure.
Mactutus and Fechter (1984, 011355)	Rat Long Evans	Continuous exposure to CO over gestation	150 ppm	Acquisition as measured in a two-way conditioned avoidance (flashing light warnings followed by mild footshock) test failed to improve with age of in utero CO-exposed (150 ppm, dam COHb 15%) rats (male and female offspring) in contrast to air-exposed controls who improved with age/maturation, indicating a failure in the associative process of learning. The authors also found impairments in reacquisition performance, an index of retention, in PND31 rats that had received continuous in utero CO exposure. Prenatal CO exposure induced learning and memory deficits in male and female offspring.
McGregor et al. (1998, 085342)	Guinea pig	GD23-GD25 until term (approximately 68 days) 10 h/day	200 ppm	Aberrant respiratory responses (to asphyxia and CO ₂) of offspring with prenatal CO exposure. The authors hypothesized that this may be related to changes in the brainstem. COHb was measured in maternal (8.53 ± 0.6% vs 0.25 ± 0.1%) and fetal blood (13.0 ± 0.4% vs 1.6 ± 0.1%) from CO-treated vs controls.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
McLaughlin et al. (2001, 193823)	Human placenta			Various pathologies of pregnancy including IUGR and pre-eclampsia are associated with significant decreases in placental HO activity. The endogenous generation of CO in the placenta has been demonstrated in chorionic villi of term placenta.
McLaughlin et al. (2000, 015815)	Human placenta			Placental regional localization of HO was explored. The chorionic plate, chorionic villi, basal plate, and chorio-decidua had significantly higher HO activity than the amnion.
McLaughlin et al. (2003, 193827)	Human placenta			HO expression in various regions of term placentas was explored. Microsomal HO-2 protein content was not different between normotensive and milk pre-eclamptic pregnancies. There was increased expression of microsomal HO-1 protein in chorionic villi and fetal membranes from pre-eclamptic pregnancies vs normotensive pregnancies.
McLean et al. (2000, 016269)	Human placenta			HO activity was highest in the placenta near term.
Melin et al. (2002, 037502)	Rat Dark Agouti Male Model of right ventricle hypertrophy secondary to chronic hypoxia (HH 10 wk)	10 wk	50 ppm alone or concomitant with HH	Hb and hematocrit levels were increased above controls in HH rats, CO rats and HH+CO rats, with the increase due to the combined treatment significantly higher than the increase due to HH. COHb levels were 1.1% in controls, 1.3% in HH rats, 4.7% in CO rats and 9.1% in HH plus CO rats. HH treatment significantly increased right ventricular (RV) heart weight above controls while CO treatment had no effect on any postmortem heart weights. Combined treatment with HH+CO resulted in a significant increase in left ventricular plus septum (LV+S) weight and RV weight compared with HH treatment alone. Echocardiographic left ventricular morphology and mass also showed the greatest changes in the HH+CO group. Hemodynamic measurements of LV function demonstrated significant effects in the HH+CO group for left ventricular end diastolic pressure (LVESP), left ventricular maximal first derived pressure (+dP/dtLV), and left ventricular work (LVW) compared with controls. Hemodynamic measurements of RV function demonstrated significant effects in the HH group for right ventricular end systolic and diastolic pressure (RVESP, RVEDP), right ventricular maximal and minimal first derived pressure (+dP/dtRV, -dP/dtRV) and right ventricular work (RVW). CO significantly enhanced the effects of HH on RVEDP and significantly diminished the effects of HH on dP/dtRV and RVW. The authors concluded that CO intensified the HH-induce RV hypertrophy, increased LV weight, and induced severe hematological responses that could hamper adaptation.
Melin et al. (2005, 193833)	Rat Dark Agouti Male and female Model of right ventricle hypertrophy secondary to chronic hypoxia (HH, 10 wk) Half of the animals were exercise trained to induce LV hypertrophy	10 wk	50 ppm alone or concomitant with HH	In untrained animals, combined treatment with HH+CO led to increased LV+S and RV weights compared with HH treatment alone. HH+CO led to several changes in measured echocardiographic parameters, including increased anterior and posterior wall thickness in diastole (AWTd, PWTd), and to increased fraction of shortening. These effects were not seen with HH alone. In addition, RVEDP was enhanced in HH+CO compared with HH alone. HRV components were altered by HH+CO but not by CO alone.
Mereu et al (2000, 193838)	Rat Wistar	GD0-GD20 continuous CO exposure	150 ppm	In utero exposure to CO disrupted hippocampal LTP with concomitant HO-2 and nNOS reductions. The authors surmised that these changes may be related to the memory deficits seen in animals exposed to CO in utero.
Middendorff et al. (2000, 015842)	Human Adult males aged 65-75 yr Testicular tissue from orchietomy			Zn protoporphyrin (ZnPP) and Hb both significantly reduced seminiferous tubular cGMP generation, suggesting a role for CO in human testicular tissue.
Montagnani et al. (1996, 080902)	Rat Wistar Male pups	GD0-GD20	75 or 150 ppm	CO caused an increase in tetrodotoxin-induced inhibition of perivascular nerve stimulation PNS-evoked vasoconstriction, increased the time to NO-related relaxant effect by ACh, and decreased the contractile response evoked by ACh on resting tone.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Naik and Walker (2003, 193852)	Rat Sprague Dawley Male		210 µL of CO/100 mL of physiological saline solution	Endogenous CO-mediated vasorelaxation involved cGMP-independent activation of vascular smooth muscle large-conductance Ca ²⁺ -activated K ⁺ channels. However, exogenous CO vasodilation was cGMP dependent.
Ndisang et al. (2004, 180425)				Review of CO and hypertension. CO is a vasorelaxant due to activation of the big conductance calcium-activated potassium channels and soluble guanylate cyclase/cGMP pathway. Developmental stage and tissue type will determine which of these pathways plays more of a role in vasorelaxation.
Neggens and Singh (2006, 193964)	Mouse CD-1	GD8-GD18	500 ppm	Developmental toxicity of CO was attenuated by protein supplementation, i.e., protein supplemented animals (27%) showed a significantly lower incidence of fetal mortality vs 8% and 16% protein groups. Further, dietary restriction of both protein and zinc with CO exposure to during gestation increased the incidence of pup mortality and malformations including gastroschisis. Zinc supplementation to a protein-deficient diet in CO-exposed mice decreased fetal mortality and malformation.
Newby et al. (2005, 193966)	Human placental cells in culture			Term human placental cells were grown in cell culture under basal and hypoxic conditions to explore changes in HO expression. HO-1 was unchanged in cytotrophoblasts under hypoxia, but HO-1 was significantly decreased in hypoxic syncytiotrophoblasts. HO-2 was unchanged in either cell type with hypoxia. These cell culture data can give insight into what cell types might be responsive to hypoxia through the HO/CO system in the human placenta.
Odrich et al. (1998, 193958)	Guinea pig			Immunohistochemical localization of HO in guinea pig placenta showed that HO-1 staining was highest near term (PND62) and lesser at term or earlier in pregnancy. HO-1 was localized in the adventitial layer of fetal blood vessels.
Ozawa et al. (2002, 193841)	Rat Wistar Adult male			The role of HO-1 in spermatogenesis was explored. CdCl ₂ induced testicular HO-1 and reduced HO-2 protein in rats. Pretreatment with ZnPPiX attenuated CdCl ₂ -dependent apoptosis. Leydig cells use HO-1-derived CO to trigger apoptosis of pre-meiotic germ cells and modulate spermatogenesis under CdCl ₂ dependent oxidative stress.
Patel et al. (2003, 043155)	Rat Sprague Dawley Male 262 ± 30 g Isolated hearts	30 min	Buffer saturated with 0.01 and 0.05% CO	The ventricular glutathione content, both reduced and oxidized, decreased by 76% and 84% 90 min post-exposure to 0.01% and 0.05% CO, respectively. Treatment with antioxidants partially blocked the decreases in glutathione. Increased creatine kinase activity was observed in heart perfusate during and after treatment.
Penney et al. (1983, 011385)	Rat (strain not reported)	GD17-GD22	157, 166 or 200 ppm	In utero CO exposure induced decreased fetal body weight, decreased placental weight, increased wet heart weight at birth, and altered cardiac enzymes at birth.
Penney et al. (1982, 011387)	Rat COBS	GD0-GD32	350 ppm PND1-PND3, then 425 ppm PND4-PND7, then 500 ppm PND8-PND32	Postnatal CO exposure decreased body weight, to a greater extent in male pups. The heart to body weight ratio and left ventricle plus interventricular septum and right ventricle weight increased after birth in CO exposed pups. This persistent cardiomegaly was not explained by increasing in DNA or hydroxyproline.
Piantadosi (2002, 037463)				Reviews the biochemical activities of CO, including various heme protein binding. The review stresses the importance of the CO/O ₂ ratio in determining the physiological effects of CO.
Piantadosi (2008, 180423)				Reviews the physiologic responses to exogenous and endogenous CO and biochemical effects, including the binding to heme proteins, the generation of reactive O ₂ species, and activation-related signaling pathways.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Piantadosi et al. (2006, 180424)	Rat Sprague Dawley Adult male	1, 3, or 7 days	50 ppm or HH	COHb produced COHb levels of 4-5% (controls approximately 1%) and liver CO concentration of 30-40 pmol/mg wet weight (controls approximately 10 pmol/mg wet weight). Both CO and HH led to increased expression of hypoxia-sensitive proteins HO-1 and HIF-1 α and mitochondrial antioxidant protein SOD-2. CO caused a greater change in mitochondrial GSH/GSSG than HH. Only CO increased mitochondrial 3-nitrotyrosine and protein mixed disulfides. Mitochondria isolated from CO-exposed rats, but not from HH-exposed rats, showed an increase in the calcium sensitivity of the mitochondrial permeability transition (MPT). Exposure to CO or HH resulted in a loss of the ability of adenine nucleotides to protect mitochondria from MPT. This effect was restored in the presence of a strong reductant. The authors concluded that CO caused mitochondrial pore stress independently of its hypoxic effects
Prigge and Hochrainer (1977, 012326)	Rat Wistar, SPF	GD0-GD20	60, 100, 250, 500 ppm	Fetuses were collected by C-section after 21-days exposure. Significant increases in fetal heart weight were seen in fetuses exposed to CO in all dose groups. Fetal body weight was significantly decreased (NOAEL 125 ppm CO).
(Raub and Benignus, 2002, 041616)				Reviews the physiology of CO and the effects on the nervous system. It is estimated that COHb would have to rise to 15-20% before a 10% reduction in any behavioral or visual measurement could be observed.
Richardson et al. (2002, 037513)	Human Male		20% COHb	20% COHb did not influence O ₂ Mb binding indicated by unaltered deoxy-myoglobin signal. Resting skeletal muscle metabolic rate was unaffected by 20% COHb. VO ₂ max was decreased. No decrement in intracellular PO ₂ was found. 20% COHb altered exercising bioenergetics, pH, PCr, and ATP levels.
Ryter et al. (2006, 193765)				Reviews the basic science of exogenous and endogenous CO including HO-1 regulation. It also reviews some therapeutic applications for CO.
Sartiani et al. (2004, 190898)	Rat Wistar	In utero inhalation exposure	150 ppm	At 4 wk of age, the action potential duration APD of isolated cardiac myocytes from CO-exposed animals failed to shorten or mature as did the APD of control animals. Further, the two ion conduction channels I _{to} (transient outward current, K ⁺ -mediated) and I _{Ca,L} (L-type Ca ²⁺ current), which largely control the rat APD, were significantly different from control animals after CO exposure at 4 wk of age. All of these CO-dependent changes were no longer different from controls at 8 wk of age, showing a delayed maturation.
Schwetz et al. (1979, 011855)	Mouse CF-1 Rabbit New Zealand	7 or 24-h/day GD6-GD15 (Mice) GD6-GD18 (Rabbits)	250 ppm	In mice there was a significant increase in number of skeletal abnormalities in CO-exposed mice. Decreased birth weight in mice exposed to 24 h/day CO vs control. Increased birth weight in mice exposed to 7 h/day CO vs controls. No similar effects were seen in rabbits.
Singh et al. (1992, 013759)	Mouse CD-1	GD8-GD18	65, 125, or 250 ppm	CO exposure concomitant with a low-protein diet exacerbated the percent of skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was directly related to CO concentration and inversely related to maternal dietary protein levels. CO and maternal dietary protein restriction had a synergistic effect on offspring survival and an additive effect on malformations.
Singh (2006, 190512)	Mouse CD-1	6 h/day during the first 2nd wk of pregnancy	65 or 125 ppm	Modulating dam protein intake during in utero CO exposure altered pup mortality.
Singh et al. (1993, 013892)	Mouse Albino CD-1	GD8-GD18	65, 125, 250, or 500 ppm	Mice were given various protein diets (4, 8, 16, or 27% protein) during pregnancy, along with CO exposure. All concentrations of CO exposure within each maternal dietary protein level significantly increased the percentage of litters with malformations in a dose-dependent manner. CO exposure concomitant with a low protein diet exacerbated the percent of skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was directly related to CO concentration and inversely related to maternal dietary protein levels. CO and maternal dietary protein restriction had a synergistic effect on mouse offspring mortality and an additive effect on malformations.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Singh (2003, 053624)	Mouse Albino CD-1	GD8-GD18	500 ppm	CO decreased the mean implants per litter and increased the incidence of fetal mortality. Under low protein conditions, CO exposure increased the incidence of malformations (9.4% vs 0%) when Zn levels were normal and increased the incidence of gastroschisis (5% vs 0%) when Zn levels were low.
Singh and Scott (1984, 011409)	Mouse Albino CD-1	GD7-GD18	65, 125, 250, or 500 ppm	All concentration of CO decreased fetal weight in mouse pups. Near-term fetal body weight was decreased at GD18 in mice exposed from GD7-GD18 to 125, 250, and 500 ppm CO but not at 65 ppm CO.
Singh (1986, 012827)	Mouse Albino CD-1	GD7-GD18	65 or 125 ppm	Impaired aerial righting score at PND14 (65 and 125 ppm), impaired negative geotaxis at PND10 and righting reflex on PND1 (125 ppm)
Sitdikova et al. (2007, 180417)	Frog neuro-muscular junctions	20 min	96 µM	CO-induced acetylcholine release, without effects on the pre-synaptic action potential or functional properties of post-synaptic receptors in frog neuro-muscular preparations.
Song et al. (2002, 037531)	Human Primary human airway smooth muscle cells	0-48 h	10-250 ppm	CO inhibited SMC proliferation at concentrations from 50-500 ppm. The cell cycle arrest occurred at the G0/G1 phase of the cell cycle. CO increased expression of the cell cycle inhibitor p21Cip1 at 1 h and decreased expression of cyclin D1 over 24-48 h. The antiproliferative actions of CO were found to be independent of sGC, but instead exerted through the inhibition of ERK MAPK activation since 15 min exposure to 250 ppm CO blocked serum-mediated ERK phosphorylation.
Sorhaug et al. (2006, 180414)	Rat Wistar Female 169 ± 4.5 g	20 h/day, x 5 days/wk, x 72 wk	200 ppm	COHb was 14.7% in CO-exposed animals and 0.3% in controls. Total Hb was also increased in following CO exposure. CO caused no changes in lung morphology or pulmonary hypertension. No atherosclerotic lesions were found in aorta or femoral artery. Weight increases of 20% and 14% were observed in the right ventricle and left ventricle plus septum, respectively, indicative of ventricular hypertrophy following chronic CO exposure.
Stevens and Wang (1993, 188458)	Mouse C57/BI-6J Rat Sprague Dawley Hippocampal brain slices			HO inhibition blocked long-term potentiation but not long-term depression.
Stockard-Sullivan et al. (2003, 190947)	Rat Sprague Dawley	22 h/day, PND6-PND22	12, 25, 50, or 100 ppm	Using functional OAE testing and ABR showed that with perinatal CO exposure (50 and 100 ppm CO) there were significant decrements in OAE in CO-exposed animals. ABR showed no functional deficits with CO exposure. Using another otoacoustic test revealed significant attenuation of the AP of the 8th cranial nerve with CO exposure (12, 25, and 50 ppm CO) vs controls at PND22.
Storm and Fechter (1985, 011653)	Rat Long Evans	GD0-parturition	150 ppm	Prenatal CO exposure increased mean and total cerebellar norepinephrine concentration from PND14-PND42 but not in the cortex.
Storm and Fechter (1985, 011652)	Rat Long Evans	GD0-GD20	75, 150, and 300 ppm	CO transiently decreased 5HT and NE in the pons/medulla and increased NE in the cortex and hippocampus at PND42. CO dose-dependently reduced cerebellum wet weight. Maternal COHb: 2.5%, 11.5%, 18.5%, and 26.8% (0, 75, 150, and 300 ppm, respectively).
Storm et al. (1986, 012136)	Rat Long Evans	GD0-PND10	75, 150, and 300 ppm	CO decreased cerebellar weight (150-300 ppm at PND10, 75-300 ppm at PND21) and decreased total cerebellar GABA (150-300 ppm at PND10 and PND21). CO- exposed (300 ppm) cerebella had fewer fissures.
Styka and Penney (1978, 011166)	Rat Charles River Male	6 wk	400 ppm or gradual increase from 500 to 1,100 ppm	CO caused increased heart weight to body weight that regressed within a couple of mo after CO exposure. COHb: 400 ppm – 35%; 1,100 ppm – 58%

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Suliman et al. (2007, 193768)	Mouse C57BL/6 Wild-type and eNOS deficient Male Rat Embryonic cardiomyocytes H9c2 cells	1 h	50-1,250 ppm Or HH Or 100 mM dichloromethane	<p>One-h exposure of mice to 1,250 ppm CO increased cardiac mitochondrial content of all 5 respiratory complexes 24 h later. The volume density of interfibrillar mitochondria was increased by 30% after 24 h demonstrating that CO caused cardiac mitochondrial biogenesis. The CO concentration in heart increased from 9 pmol/mg to 50-150 pmol/mg in mice exposed to 50-1,250 ppm CO for 1 h. These levels declined to baseline by 6 h. Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) expression was increased 6 h following exposure to 50-1,250 ppm CO. Expression of DNA polymerase and mitochondrial transcription factor A (TFAM) was increased 6 and 24 h after exposure, while mitochondrial DNA was increased two- to threefold 24 h after exposure. CO activated gene expression of these proteins involved in cardiac mitochondrial biogenesis beginning at 2 h postexposure for PGC-1α, nuclear respiratory factors 1 and 2 (NRF-1 and -2) and at 6 h postexposure for TFAM. These effects were independent of NOS and not seen with HH. CO exposure resulted in phosphorylation of p38 MAPK and Akt at 2 and 6 h postexposure to 1,250 ppm CO for 1 h. Inhibition of p38 activation failed to inhibit the CO-mediated increase in cardiac mitochondrial biogenesis.</p> <p>In cell culture experiments, CO derived from dichloromethane metabolism resulted in increased cGMP, protein levels of SOD2, TFAM, NRF-1, NRF-2, PGC-1, mitochondrial ROS, Akt phosphorylation, and mitochondrial DNA. Inhibition of GC or PI3K/Akt but not p38 blocked the responses to CO. A role for mitochondrial H₂O₂ in Akt regulation was demonstrated. Mitochondrial H₂O₂ and the PI3K/Akt pathway were important mediators of TFAM expression.</p> <p>The authors concluded that CO exposure increased mitochondrial ROS, which promoted mitochondrial biogenesis in the heart.</p>
Sun et al. (2001, 026022)	Mouse Neuronal cultures prepared from the cerebral hemispheres of 16-day Charles River CD1 mouse embryos			Nb expression was increased by neuronal hypoxia in vitro and focal cerebral ischemia in vivo. Inhibiting Nb reduced neuronal survival after hypoxia whereas Nb overexpression enhanced neuronal survival.
Tattoli et al. (1999, 011557)	Rat Wistar Male and pregnant female	PND1-PND10	75 and 150 ppm	Cognitive function was assessed in rats after postnatal CO exposure at 3 and 18 mo of age. Postnatal CO exposure did not affect the acquisition and reacquisition of an active avoidance task. This is different from previous findings by the same laboratory, indicating that in utero exposure to CO (75 and 150 ppm) induced long-lasting learning and memory deficits.
Telfer et al. (2001, 193769)	Human Myometrium tissue obtained from gravid (pre-term [25- to 34 wk gestation], term not in labor or term in labor) and non-gravid women			cGMP was monitored in various myometrial tissues. cGMP was significantly higher than that from nonpregnant tissue and decreased at term, especially in tissue from laboring women.
Teran et al. (2005, 193770)	Rat Dahl/Rapp salt-sensitive rats Male		100 μ M	A high-salt diet for 1-4 wk resulted in increased aortic HO-1 protein expression, an increase in mean arterial pressure, and time-dependent inhibition of flow- and acetylcholine-mediated vasodilation in isolated gracilis muscle arterioles. A smaller degree of inhibition of acetylcholine-mediated vasodilation was observed with a low-salt diet for 1-4 wk. Pretreatment with a HO inhibitor restored these responses, but this effect was reversed in the presence of exogenous CO. Mean arterial pressure was decreased in intact animals fed a high-salt diet for 4 wk and then treated with a HO inhibitor. The authors concluded that the HO-derived CO contributed to the development of hypertension and the impairment of endothelium-dependent vasodilator responses in this model.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1994, 076459)	Rat Wistar Male	1 h Or	1,000 ppm Or	CO poisoning inhibited B ₂ integrin-dependent PMN adherence in heparinized blood obtained from rats immediately after exposure. Adherence was restored when platelet number was decreased. Adherence was also decreased when PMN from control animals were incubated with platelets from poisoned animals. Adherence of activated PMN was reduced in the presence of SOD and enhanced by NOS inhibition. Platelet production of NO was significantly greater while platelet NOS activity was significantly inhibited after poisoning. When whole blood or platelet-rich plasma was incubated with CO, PMN adherence was inhibited. The authors concluded that PMN B ₂ integrin activity was inhibited by CO-dependent release of NO from the platelets into the blood.
	Isolated blood cells	>1 h 30 min	1,000-3,000 and higher ppm 0.5 mL of pure CO	
Thom and Ischiropoulos (1997, 085644)	Ra Wistar Male	1 h 30 min or 2 h	20-1,000 ppm 10-20 ppm	Platelets isolated from rats exposed to 20-1,000 ppm CO for 1-h released NO in a dose-dependent manner. COHb levels were 0.7% in controls and 3.2%, 7.8% and 51.0% in 20, 100 and 1,000 ppm exposure groups, respectively. Isolated platelets released NO when incubated for 30 min with 20-100 ppm CO. NOS activity was not enhanced by 100 ppm CO. Platelets released NO in response to 10-100 ppm CO after 30-min pretreatment with a NOS inhibitor, suggesting that CO displaces NO from heme-binding sites. Longer incubations (2 h) with the NOS inhibitor led to a diminished response to 100 ppm CO. There appears to be a discrepancy in the results, depending on how NO was measured (electrode vs Greiss reaction). Endothelial cells released NO in response to 20-100 ppm CO. NOS inhibition blocked the response to 100 ppm CO. CO was found not to affect arginine transport or NOS activity in endothelial cells. Exposure to 40-100 ppm CO resulted in the release of short-lived oxidants. This response was blocked by NOS inhibition. Lysates from cells exposed to 50 and 100 ppm CO had increased nitrotyrosine content. This response was blocked by NOS inhibition. Cellular reduced sulfhydryls were not decreased by 100 ppm CO. Dihydrorhodamine 123 oxidation, a measure of peroxynitrite formation, was increased by exposure to 100 ppm CO. This effect was blocked by NOS inhibition. Cytotoxicity of CO was evaluated by the release of ⁵¹ chromium. Cytotoxicity was evident 4 h following a 2-h incubation with 100 ppm CO but not immediately after exposure. This response was not blocked by NOS inhibition, although NOS inhibition had protective effects under conditions of continuous CO exposure of 4 h. Exposure to 20 and 100 ppm CO for 2 h led to the loss of membrane integrity (measured by ethidium homodimer-1 staining) 18 h later. Results demonstrate that 10-20 ppm CO released NO from platelets and endothelial cells in vitro. Platelets from rats that inhaled 20 ppm CO also released NO in vitro. The authors suggested that CO-mediated NO release from platelets and endothelial cells resulted from disrupted intracellular scavenging for NO. They also suggested that peroxynitrite may have been generated in response to CO.
	200-290 g	1 h	10-100 ppm	
	Platelet-rich plasma from rats was used as the source of platelets Bovine pulmonary artery endothelial cells			

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1997, 084337)	Bovine pulmonary artery endothelial cells	30 min-4 h	10-100 ppm (11-110 nM)	<p>One-h exposure to 111-110 nM CO led to a dose-dependent increase in NO release, as measured by nitrite+nitrate. Significance was achieved at 22 nM (corresponding to an interstitial partial pressure of 20 ppm and a blood COHb level of 7%). NOS inhibition blocked the response to 110 nM CO. A dose-dependent increase in cellular nitrotyrosine was also observed following a 2-h exposure to CO, with significance achieved at 55 nM CO. NOS inhibition blocked the response to 110 nM CO. CO exposure failed to decrease the concentration of reduced sulphydryls but did result in the extracellular release of a short-lived oxidant species, which was blocked by NOS inhibition. Dihydrorhodamine oxidation, a measure of peroxynitrite formation, occurred in response to 110 nM CO, an effect which was blocked by NOS inhibition. Cytotoxicity of CO was evaluated by the release of ⁵¹chromium. Cytotoxicity was evident 4 h following a 2-h incubation with 110 nM CO but not immediately after exposure. This response was not blocked by NOS inhibition, although NOS inhibition had protective effects under conditions of continuous CO exposure of 4 h. Exposure to 110 nM CO for 2 h led to the loss of membrane integrity (measured by ethidium homodimer-1 staining) 18 h later. This response was blocked by NOS inhibition. Exposure to 110 nM CO had no effect on O₂ consumption, production of intracellular H₂O₂ or cellular redox activity. Exposure to 110 nM did not alter arginine transport or NOS activity. NO release from cells which had been pretreated with a NOS inhibitor and then exposed briefly to 5% CO was measured using a NO-selective electrode, suggesting that CO competed with intracellular binding sites of NO.</p> <p>The authors concluded that endothelial cells release NO and NO-derived oxidants in response to CO. A delayed cell death occurred following exposures to 22 nM and higher concentrations of CO.</p>
Thom et al. (1999, 016753)	Rat Wistar Male 200-290 g Some rats were fed a high cholesterol diet	1 h	50-1,000 ppm	<p>Nitrotyrosine immunoreactivity was found in aortic intima in rats exposed to CO for 1 h but not in controls. Nitrotyrosine content was quantitated and found to be increased in a dose-dependent manner following 1-h exposure to 50-1,000 ppm CO. The effect was significant at 50 ppm but the COHb content measured immediately after exposure was not different than controls. Platelet and neutrophil depletion did not alter nitrotyrosine content following CO exposure. Leukocyte adherence to the aorta occurred 18 h but not immediately after a 1-h exposure to 100 ppm CO. This effect was blocked by NOS inhibition. The influx of albumin from the microvasculature into skeletal muscle increased during the 3 h after exposure to 100 ppm CO but was not seen 18 h later. This effect was blocked by NOS inhibition.</p> <p>Rats fed a high-cholesterol diet and exposed to 100 ppm CO for 1 h had increased aortic nitrotyrosine content, which was not different than that in CO-exposed rats fed the standard diet. However, rats on the high-cholesterol diet had a six-fold increase in LDL oxidation immediately after 1-h exposure to 100 ppm CO. This effect was not blocked by NOS inhibition.</p> <p>The authors concluded that CO can alter vascular status by several mechanisms linked to NO-derived oxidants.</p>

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1999, 016757)	Rat Wistar Male 200-290 g	1 h	50-1,000 ppm	<p>Leakage of albumin into lung parenchyma occurred 18 h after rats were exposed to 100 ppm CO for 1 h. This response was not observed at earlier timepoints following CO exposure. This response was also observed using 50 and 1,000 ppm but not 20 ppm CO. Leakage resolved by 48 h. Furthermore, no leakage occurred when rats which were exposed to 100 ppm CO were pretreated with a NOS inhibitor. COHb levels were 0.9% in controls and 4.8%, 10.6% and 53.7% following 1-h exposure to 50, 100 and 1,000 ppm CO, respectively. Elevated free NO (determined by EPR) was observed in lungs of rats exposed to 100 ppm CO for 1 h. This effect was blocked when rats were pretreated with a NOS inhibitor. Lung H₂O₂ was elevated by exposure to 100 ppm CO for 1 h, and this effect was blocked when rats were pretreated with a NOS inhibitor. Elevated nitrotyrosine content was observed in lung homogenates 2-4 h following 1-h exposure of rats to 100 ppm CO. This effect was also blocked by pretreatment with a NOS inhibitor. No leukocyte sequestration was observed in lungs 18 h following exposure to 100 ppm CO. CO-induced lung leak was not affected by neutrophil depletion.</p> <p>The authors concluded that CO causes lung vascular injury which is dependent on NO.</p>
Thom et al. (2000, 011574)	Bovine pulmonary artery endothelial cells	40 min-2 h	11-110 nM (10-100 ppm)	<p>Increased uptake of ethidium homodimer-1, a measure of decreased membrane integrity and cell death, was observed in endothelial cells 18 h after exposure to 110 nM for 60-120 min. Exposures of 20-40 nM were ineffective in this regard. Ethidium uptake was also increased by 2-h exposure to 88 nM CO. Preincubation for 2 h with an inhibitor of eNOS, an antioxidant, and an inhibitor of peroxynitrite reactions blocked the CO-mediated cell death. Morphological changes in cells were observed 2 h following a 2-h exposure to 110 nM CO. Cell death induced by 110 nM CO was also blocked by inhibition of protein synthesis and inhibition of caspase-1 but of caspase-3. Caspase-1 activity was increased following 2-h exposure to 110 nM CO; this effect was blocked by inhibiting eNOS. Pre-exposure of cells to 11 nM CO for 40 min followed by a 3-h incubation period resulted in an increased level of MnSOD and protection against cell death 18 h following a 2-h exposure to 110 nM CO.</p> <p>The authors concluded that exposure to 11 nM CO led to an adaptive response which protected cells from injury and apoptosis resulting from NO-derived oxidants.</p>
Thom et al. (2001, 193779)	Rat	Until lost consciousness	1,000-3,000 ppm	<p>Neutrophils sequestration was observed in the brain vessels of rats exposed to high-dose CO. CO also led to increased nitrotyrosine formation in the brain vessels. These events were blocked by pretreatment with a peroxynitrite scavenger or a PAF receptor antagonist.</p>
Thom et al. (2006, 098418)	Human Rat Wistar Male Mouse C57B6J MPO-deficient Blood samples and brain tissue	1 h	Humans: Acute CO poisoning Rats and mice: 1,000-3,000 ppm	<p>In humans, COHb was 20-30.5%. Increased cell surface expression of CD18 and PAC1 was observed in neutrophils from people with CO poisoning. Increased surface-bound myeloperoxidase (MPO, indicative of neutrophil degranulation), increased plasma MPO, and more numerous platelet-neutrophil aggregates were also observed.</p> <p>Similar changes were observed in blood of CO-poisoned rats. Platelet depletion, inhibition of NOS, and inhibition of platelet integrin-dependent adhesion blocked these responses. Brains from poisoned rats had significant elevations in MPO, which could reflect either an increase number of neutrophils or an increase in neutrophil degranulation. Perivascular MPO and nitrotyrosine were CO-localized in brain. CO poisoning also resulted in altered brain myelin basic protein.</p> <p>Similar changes were observed in blood of CO-poisoned mice. MPO deficiency blocked the CO-mediated alteration in brain myelin basic protein.</p> <p>The authors concluded that exposure to CO triggers intravascular interactions between platelets and neutrophils that lead to neutrophil degranulation in experimental animals and people with CO poisoning.</p>

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thorup et al. (1999, 193782)	Rat Sprague Dawley Male 200-250 g		0.01-10 μ M	<p>Perfusion of isolated rat renal resistance arteries with CO-containing buffer (0.001-10 μM) led to the biphasic release of NO, peaking at 100 nM and declining to undetectable responses at 10 μM. Sequential pulses of 100 nM resulted in a blunting of NO release with consecutive pulses, consistent with a depletion of intracellular NO stores. NO release was dependent on arginine concentrations and was inhibited by pretreatment with a NOS inhibitor. Perfusion with 100 nM CO blocked carbachol-dependent NO release from vessels.</p> <p>Rats were treated with a HO-1 inducer, and renal resistance arteries were isolated 12 h later. Carbachol-induced NO release was smaller in the HO-1-induced rats compared with controls, suggesting that endogenous CO has a similar effect as 100 nM exogenous CO. This effect was reversed in the presence of excess arginine.</p> <p>Vasodilation was measured in blood-perfused afferent arterioles perfused with CO in solution. A biphasic vasodilatory response was observed as well as a blunted muscarinic vasorelaxation.</p> <p>CO (0.1-10 μM) suppressed the release of NO from purified recombinant eNOS in solution.</p> <p>The authors concluded that low levels of CO may release NO and elicit vasorelaxation and modulate basal vascular tone, while higher levels of CO may inhibit eNOS and NO generation.</p>
Tolcos et al. (2000, 015997)	Guinea pig	10 h/day over the last 60% of gestation	200 ppm	<p>Fetal and maternal COHb were 13% and 8.5%, respectively. Neurotransmitter systems were affected after CO exposure. The catecholaminergic system of the brainstem displayed significant decreases in immunoreactivity for tyrosine hydroxylase (TH), which was likely due to decreased cell number in specific medullary regions. The cholinergic system was also affected by prenatal CO exposure with significant increases in ChAT immunoreactivity of the medulla and no changes in muscarinic acetylcholine receptor.</p>
Tolcos et al. (2000, 010468)	Guinea pig	10 h/day for the last 60% of gestation	200 ppm	<p>Brains were collected at 1 and 8 wk of age. These data showed that CO exposure in utero sensitized the brain to hyperthermia at PND4 leading to generation of necrotic lesions in the brain and changes in neurotransmitter levels.</p>
Toyada et al. (1996, 079945)				
Tschugguel et al. (2001, 193785)	Human HUVEC			<p>CO was generated by primary endothelial cells from human umbilical veins and uterine arteries after exogenous 17-β estradiol administration.</p>
Vallone et al. (2004, 193993)	Mouse protein			<p>The authors presented the X-ray structure of CO-bound ferrous murine Nb. When CO binds, the heme group slides deeper into the protein crevice.</p>
Villamor et al. (2000, 015838)				
Vreman et al. (2000, 096915)	Human Umbilical cord (artery and vein) Rat Aorta, vena cavae, liver and heart			<p>HO activity was quantified in human umbilical cord and in the rat vasculature (aorta and vena cavae). Human umbilical artery and vein HO activity were equal. The rat aorta and vena cavae produced equal amounts of HO activity (wet weight/g tissue) but generated 3 times greater HO than the heart and 0.2 times of the liver. HO activity in rat vasculature was 3 times that of the human cord tissues. Use of the HO inhibitor CrMP effectively blocked HO activity in the rat liver and heart but was less effective at blocking HO activity in the human umbilical cord or the rat vasculature (only 50% effective). The activity of HO in the umbilical vessels may provide a role for CO in control of vasculature tone during pregnancy.</p>

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Vreman et al. (2005, 193786)	Mouse BALB/c	30 min	500 ppm OR Heme arginate 30 µmol/kg body weight i.v.	<p>Following CO exposure, COHb levels were 28%. Tissue concentrations of CO were as follows with control levels in parenthesis.</p> <p>Blood: 2648 ± 400 (45) pmol/mg Heart: 100 ± 18 (6) pmol/mg Muscle: 14 ± 1 (10) pmol/mg Brain: 18 ± 4 (2) pmol/mg Kidney: 120 ± 12 (7) pmol/mg Spleen: 229 ± 55 (6) pmol/mg Liver: 115 ± 31 (5) pmol/mg Lung: 250 ± 2 (3) pmol/mg Intestine: 9 ± 7 (4) pmol/mg Testes: 6 ± 3 (2) pmol/mg</p> <p>CO concentration relative to 100% blood: Lung: 9.4%, Spleen: 8.6%, Kidney: 4.5%, Liver: 4.3%, Heart: 3.8%, Brain: 0.7%, Muscle: 0.5%, Intestine: 0.3%, Testes: 0.2%</p> <p>Injection of heme arginate resulted in a threefold increase in CO excretion, reaching a maximum at 60 min. Animals were sacrificed at 90 min. COHb levels were 0.9%. Tissue concentrations of CO were as follows with control levels in parenthesis:</p> <p>Blood: 88 ± 10 (45) pmol/mg Heart: 14 ± 3 (6) pmol/mg Muscle: 7 ± 1 (10) pmol/mg Brain: 2 ± 0 (2) pmol/mg Kidney: 7 ± 2 (7) pmol/mg Spleen: 11 ± 1 (6) pmol/mg Liver: 8 ± 3 (5) pmol/mg Lung: 8 ± 3 (3) pmol/mg Intestine: 3 ± 1 (4) pmol/mg Testes: 2 ± 0 (2) pmol/mg</p> <p>CO concentration relative to 100% blood: Heart: 16% Spleen: 13% Lung: 9% Liver: 9% Kidney: 8% Muscle: 8% Intestine: 3% Brain: 2% Testes: 2%</p>
Weaver et al. (2007, 193939)	Human		Acute CO poisoning	<p>Mean COHb in humans with acute CO poisoning was 35%. Hyperbaric O₂ reduces cognitive sequelae in a randomized clinical trial of CO-poisoned patients. Risk factors for cognitive sequelae without hyperbaric O₂ included older age and longer CO exposures. Patients with loss of consciousness or high initial COHb levels should also be treated with hyperbaric O₂.</p>
Webber et al. (2003, 190515)	Rat (Strain not stated)	PND8-PND22	12.5, 25, or 50 ppm	<p>Immunostaining of c-Fos, a marker of neuronal activation in the nervous system, was followed. C-Fos immunoreactivity in the central IC was significantly decreased in the CO-exposed animals at both PND27 and PND75-PND77 over all dose groups of CO; immunostaining of other subregions of the IC were not affected by CO. These studies show exposure to CO during development can lead to permanent changes in the auditory system of rats that persist into adulthood.</p>

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Webber et al. (2005, 190514)	Rat (Strain not stated)	PND9-PND24	25 or 100 ppm	Neurofilament loss from the spiral ganglion neurons and somas after ARCO treatment was rescued (no detectable neurofilament loss) with low iron+CO (ARIDCO); ARID (low iron) treatment induced no change in neurofilaments. CuZn superoxide dismutase (SOD1) was significantly increased with CO exposure (ARCO) and rescued in ARIDCO animals; SOD1 was unchanged in low-iron-only animals (ARID). Low-iron treatment or CO exposure alone led to significant decreases in c-fos positive cell numbers of the central IC, but c-fos levels were unchanged after low-iron diet concomitant with CO exposure (ARIDCO).
Wellenius et al. (2004, 087874)	Rat Sprague Dawley 250 g Diazepam-sedated Model of acute MI induced by thermocoagulation	1 h, 12-18 h after surgery	35 ppm	CO exposure decreased ventricular premature beat frequency by 60.4% during the exposure period compared to controls. 1-h exposure to CAPs (318 µg/m ³) decreased ventricular premature beat frequency in specific subgroups. Neither CAPs nor CO had an effect on heart rate. There were no significant interactions between their effects when rats were exposed to both CO and CAPs.
Wellenius et al. (2006, 156152)	Rat Sprague Dawley 250 g Diazepam-sedated Model of acute MI induced by thermocoagulation	1 h, 12-18 h after surgery	35 ppm	Exposure to CO failed to increase the probability of observing supraventricular ectopic beats (SVEB). Exposure to CAPs (646 µg/m ³) for 1 h decreased the frequency of SVEB. There were no significant effects observed when rats were exposed to both CO and CAPs. Among a subset of rats with one or more SVEB at baseline, a significant decrease in number of SVEB during the exposure period was observed with either CO or CAPs exposure compared with controls.
Yoshiki et al. (2001, 193790)	Human			HO-1 localization in human endometrium and its changes in expression over the menstrual cycle were explored in this study. HO-1 was constitutively expressed throughout the menstrual cycle, and HO-2 was greater in the secretory than the proliferative phase of the menstrual cycle. HO-1 was localized to the epithelial cells and macrophages. HO-2 was found in endothelial cells and smooth muscle cells of endometrial blood vessels.
Yu et al. (2008, 192384)	Guinea pig Allergic rhinitis model using nasal ovalbumin sensitization			Indicators of allergic rhinitis were enhanced by treatment with a HO-1 inducer and decreased by treatment with a HO-1 inhibitor. Immunoreactivity for HO-1 was shown in the lamina of mucosa of sensitized guinea pigs. Endogenous CO may play a role in the inflammation process of allergic rhinitis.
Zamudio et al. (1995, 193908)	Human			Women living at high altitude had an increased risk of adverse pregnancy outcomes vs women living at lower altitudes.
Zenclussen et al. (2006, 193873)	Mouse CBA/J x DBA/2J			To evaluate the role of HO-1 in spontaneous abortion, a mouse model that spontaneously undergoes abortion (CBA/J x DBA/2J mice) was used with and without HO adenovirus treatment to see if pregnancy outcome could be modulated by changing HO concentration. Pregnancy outcome was significantly better (abortion rate significantly decreased) in mice overexpressing HO due to adenovirus transfer.
Zhang et al. (2005, 184460)	Rat Pulmonary artery endothelial cells	8-28 h	15 ppm	Exposure to 15 ppm CO during anoxia resulted in decreased phosphorylation of STAT1 and increased phosphorylation of STAT3 at 8-24 h. Similar responses were observed when 24-h anoxia was followed by a period of reoxygenation (0.5-4 h). DNA binding of STAT1 was decreased while that of STAT3 was enhanced by CO treatment during anoxia/reoxygenation. Exposure to 15 ppm during 8-24-h anoxia or 24 h anoxia followed by 0.5-4 h reoxygenation resulted in increased phosphorylation of Akt and p38 MAPK. Inhibitor studies demonstrated that activation of the PI3K pathway by CO was upstream of p38 MAPK activation during anoxia/reoxygenation. Similarly, the PI3K and p38 MAPK pathways were found to be upstream of STAT modulation. The anti-apoptotic effects of 15 ppm CO during anoxia-reoxygenation involved decreased FAS expression and decreased caspase 3 activity. These effects were dependent on activation of the PI3K, p38 MAPK and STAT3 pathways. The authors concluded that CO blocks anoxia-reoxygenation mediated apoptosis through modulation of PI3K/Akt/p38 MAPK and STAT1 and STAT3.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Zhang et al. (2007, 193879)	Mouse			A single dose of LPS administered to pregnant mice induced up-regulation of HO-1 but not HO-2 in the mouse placenta 12-48 h postLPS treatment. Pretreatment of mice with the spin trap agent PBN or the TNF α inhibitor pentoxifylline prevented the LPS-dependent HO-1 upregulation. Thus ROS may mediate the LPS-dependent upregulation of HO-1.
Zhao et al. (2008, 193883)	Mouse FVB			With pregnancy, there was an increased blood volume without a concurrent increase in systemic BP; this was accomplished by a decrease in total vascular resistance, to which CO contributed as determined by using HO inhibitors.
Zhuo et al. (1993, 013905)	Guinea pig Adult male			Hippocampal LTP of brain sections is significantly affected by CO exposure with ZnPP IX, a HO inhibitor, blocking hippocampal LTP.
Zuckerbraun et al. (2007, 193884)	Macrophages RAW 264.7 THP-1 cells, wild-type and respiration-deficient	10 min-24 h	50-500 ppm	Exposure of RAW macrophages to 250 ppm CO for 10-60 min increased ROS generation, measured as dichlorofluorescein (DCF) fluorescence. ROS generation at 1 h was dose dependent with significant effects observed at 50, 250 and 500 ppm CO. This response was not blocked with a NOS inhibitor. A 1-h exposure to 250 ppm resulted in decreased intracellular glutathione levels. CO treatment was found to block TNF α production and to enhance p38 MAPK phosphorylation in LPS-stimulated cells. These effects were diminished by pretreatment with antioxidants. The source of CO-derived oxidants was determined to be mitochondrial since respiration-deficient THP-1 macrophages, unlike wild-type cells, failed to generate ROS in response to 250 ppm CO. Furthermore, treatment of RAW cells with the mitochondrial complex III inhibitor antimycin C, blocked ROS generation in response to 250 ppm CO. Exposure of RAW cells to 250 ppm CO for 1 h inhibited cytochrome c oxidase activity by 50%. Exposure to 250 ppm CO for 6 h had no effect on cellular ATP levels or mitochondrial membrane potential. Antimycin C treatment was found to reverse the effects of CO on LPS-mediated responses (TNF α and p38 MAPK), suggesting that mitochondrial-derived ROS mediated the effects of CO. The authors concluded that CO increased the generation of mitochondrial-derived ROS.

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