Review of Health Effects Literature for Sub-Acute Carbon Monoxide Exposure and Health Effects

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REVIEW OF HEALTH EFFECTS LITERATURE FOR SUB-ACUTE CARBON MONOXIDE EXPOSURE AND HEALTH EFFECTS

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LIST OF ACRONYMS AND ABBREVIATIONS

AGA	American Gas Association
CO	carbon monoxide
COHb	carboxyhemoglobin
CPSC	Consumer Products Safety Commission
EH&E	Environmental Health & Engineering, Inc.
EPA	U.S. Environmental Protection Agency
HBO	hyperbaric oxygen
mg/m^3	milligrams per cubic meter
NAAQS	National Ambient Air Quality Standards
NIOSH	National Institute for Occupational Safety and Health
NOx	nitrogen oxide
OSHA	U.S. Occupational Safety and Health Administration
PM	particulate matter
ppm	parts per million
UL	Underwriters Laboratories, Inc.
WHO	World Health Organization

1.0 APPROACH TO CRITICAL REVIEW

1.1 BACKGROUND AND SCOPE

At the request of the Natural Gas Code and Standards Research Consortium sponsored by the American Gas Association (AGA), Environmental Health & Engineering, Inc. (EH&E) has conducted a critical review of the literature to characterize the strength of evidence for sub-acute carbon monoxide (CO) exposure and health effects. The CO Criteria Document, issued by the U. S. Environmental Protection Agency (EPA) in 2000, serves as a logical starting point for the current study, as it reviews CO exposure, dose, and related health effects and forms the basis for current regulatory standards involving CO. Since the Criteria Document presents the state of technical knowledge until 1998, this critical review focuses on evaluating the evidence in the literature for the subsequent time period between 1998 and 2006.

1.2 FRAMING THE QUESTIONS

CO is a ubiquitous by-product of incomplete combustion. It is also produced endogenously, through metabolism, in lesser amounts. CO is described as a colorless, odorless, and tasteless gas that is very stable. As an environmental pollutant, atmospheric, or indoor, CO enters the body through the lungs via inhalation and reacts readily with hemoglobin to form carboxyhemoglobin (COHb), which causes a reduction in the oxygen-carrying capacity of the blood and impairs the release of oxygen to organs and tissues. The COHb can be measured in a blood sample by conventional analytical methods; it is a highly specific biomarker of CO exposure and closely related to mechanisms of human toxicity. Exposure to CO leads to hypoxia, a condition characterized by oxygen depletion (WHO, 2000).

Because of the affinity of red blood cell hemoglobin to bind with CO, some environmental scientists hypothesize that low levels of CO in air could be of concern if exposures are prolonged, over periods of days to weeks. Effects at elevated levels commonly found both indoors and outdoors have been sufficient for some time now that standards have been established by the U.S. Occupational Safety and Health Administration (OSHA) for workers. Almost 15 years ago, the National Institute for

Occupational Safety and Health (NIOSH) recommended workplace standards setting maximum ceiling levels of 200 parts per million (ppm) and an eight-hour work shift integrated maximum level of 50 ppm. Both forms of the recommended standard are designed to prevent COHb levels from exceeding 5 percent to prevent psychomotor dysfunction.

The EPA's most recent review of the CO literature (through 1998) is presented in the 2000 CO Criteria Document. Based primarily on cardiovascular effects, the EPA Criteria Document supports a one-hour and eight-hour ambient CO standard that prevents susceptible persons (defined here as those individuals with pre-existing heart disease recognized from the onset of angina pectoris) in the general population from exceeding COHb blood levels of 2 percent. EPA's position is consistent with the World Health Organization (WHO) Regional Office for Europe in Copenhagen, Denmark (2000), which uses 2.5 percent COHb as an upper limit.

The dilemma with CO, which is similar to other pollutants, is the fact that exposures occur in other indoor environments besides the work space or ambient air. The CO Total Exposure Assessment Methodology (TEAM) study conducted by EPA in Denver and Washington, D.C. (Akland et al., 1985) demonstrates that CO exposures experienced during commuting or in restaurants and residences can exceed ambient levels. Residential exposures to CO are relevant because the high percentage of time that people spend at home contributes more to dose (integration of time and concentration). Furthermore, sources such as stoves, combustion driers, furnaces, water heaters, space heaters, grills, fireplaces, gasoline or diesel engines in attached garages, tobacco, and candles can elevate indoor CO above ambient levels. Finally, more than any other indoor environment, the home environment reflects the full spectrum of the United States population, including age, gender, and susceptibilities. There are no applicable air quality standards establishing safe levels for residences in the United States, and the 2000 EPA Criteria Document does not address the issue of chronic low-level exposures to CO.

The inhalation of CO diminishes the oxygen-carrying capacity of the blood. Acute events where CO concentrations in the air are very high (e.g., fires, faulty exhaust vents, or enclosed areas with internal combustion engines operating that are faulty or have

inadequate ventilation) can and have led to toxic levels of COHb even for short-duration exposures of minutes to hours. However, the impact of chronic CO exposure events on COHb buildup is neither included in the 2000 Criteria Document, nor well-documented in the scientific literature.

Given variability in susceptibility of the population, variability in air flow within a residence, the need for occupants to have sufficient cognitive and motor function to escape further exposure, and limited sensitivity of inexpensive CO detectors, a critical question arises: “What can be considered a “safe level” of CO for indoor residential environments?, ” where chronic exposures may be more likely? The AGA recommends 15 ppm, while the American Society of heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) suggests 9 ppm. Underwriters Laboratories (UL) and the Consumer Products Safety Commission (CPSC) standards for CO detectors (revised October 1998) require the ability of detectors to warn at three levels of concentration-duration combinations. For the different UL/CPSC standards for detectors, predicted levels of COHb are listed below, using a mathematical model for CO uptake.

CO Indoor Air	Duration	Approximate Resultant % COHb
15 ppm	30 days	3%
70 ppm	189 minutes	5%
150 ppm	50 minutes	7.5%

Consideration of key overarching questions related to low level CO exposure and dose and a critical review of the literature post the EPA Criteria Document of 2000 are warranted. In order to guide the review process, EH&E posed a specific set of key questions, summarized in Table 1.1.

Table 1.1 Key Questions During Critical Review of Carbon Monoxide (CO) Health Effects Literature	
Where We Are Today	
1	What represents a “sub-acute” CO exposure?
2	What is the current state-of-knowledge regarding sub-acute (i.e., chronic low-level) CO exposures and health effects?
3	What is the basis of the current standards to address sub-acute CO poisoning and health issues?
4	Is there evidence of greater susceptibility for specific sub-populations?
Where We Need to Go	
5	Is there sufficient new information that links the degree of chronic low-level CO exposure to health effects?
6	Is the available information of sufficient quality to warrant further action to protect public health?
7	What conclusions can be drawn at this time from a critical review of the health effects literature on sub-acute CO poisoning incidents and trends in human health data?

The study findings by EH&E are presented in the following manner. This section frames the technical questions around indoor levels of CO and detection requirements, based on health effects. Section 2.0 provides working definitions across a range of health effects, exposure levels and durations. Section 3.0 presents the criteria that were used to critically evaluate the literature, and subdivides the current compilation based on its relevance in addressing the questions that have been posed. Section 4.0 presents the findings from this study. A summary list of references is provided in Appendix A, and the literature citations are included separately in hardcopy and electronic form.

2.0 DEFINING CO HEALTH EFFECTS, EXPOSURE AND DOSE

The health and safety issues associated with acute, high-level CO poisoning are reasonably well understood. However, the potential effects from lower-level or sub-acute exposures to CO have not been systematically characterized to date. This study shifts the focus from reiterating the acute asphyxiating properties associated with elevated levels of blood CO to understanding the potential adverse impacts to other body systems (e.g., neurological, psychological). Hence, the current study is a compilation of the evidence and a technical evaluation of the quality of the evidence involving low levels of CO exposure and any associated health effects. From the key questions in Table 1.1, an important query emerges: what defines "sub-acute," in the context of CO exposure, dose, and health effects?

2.1 CARBON MONOXIDE HEALTH EFFECTS MODEL

The following medical model for CO summarizes the overall effect of CO exposure on human body systems:

- *Cardiovascular effects:* These are well characterized in medical practice and described in the clinical literature. They tend to be associated with acute exposures to CO, i.e., short, episodic events that result in an immediate impact on cardiac function.

- *Impaired oxygen function:* This involves chronic low-level exposures with damage to oxygen transport. The resultant impact on multiple organ systems continues to be under evaluation in the medical and research communities. The long-term efficacy of treatment regimens (normobaric vs. hyperbaric oxygen therapy) continues to be an actively debated area of clinical medicine.

- *Impaired central nervous system function:* The questions of reversible versus irreversible health effects are highly debatable at this time. Physiological mechanisms are not well understood and the involvement of multiple organ systems further complicates both the severity and the duration of impact.

The new frontiers for CO involve the functioning of the central nervous system, including clinical methods to measure and evaluate subtle sub-clinical changes, e.g., growth of basal ganglial lesions. The extent of measurable clinical changes is posited to be directly associated with the extent (duration) of exposure, and the CO dose, quantified in terms of COHb levels.

Working definitions are required to be consistent with published guidance that define acute exposures as one-time, immediate events on the order of minutes or hours, and chronic (sub-acute) events as exposures on the order of days, weeks, or more. The National Ambient Air Quality Standard (NAAQS) was initially developed to protect the most sensitive population sub-groups. However, guidance on sub-acute exposure limits is absent in the 2000 CO Criteria Document. Alternatively, *Indoor Air Pollution: An Introduction for Health Professionals* (1994), a reference document jointly issued by the American Lung Association, EPA, CPSC, and the American Medical Association, cites the related health effects over a range of concentrations, with COHb levels up to 5 percent as the limit below which "no statistically significant vigilance decrements [are experienced] after exposure."

Using a combined paradigm that includes health effects, exposure, and dose, acute, and sub-acute CO exposures may be classified in the following manner:

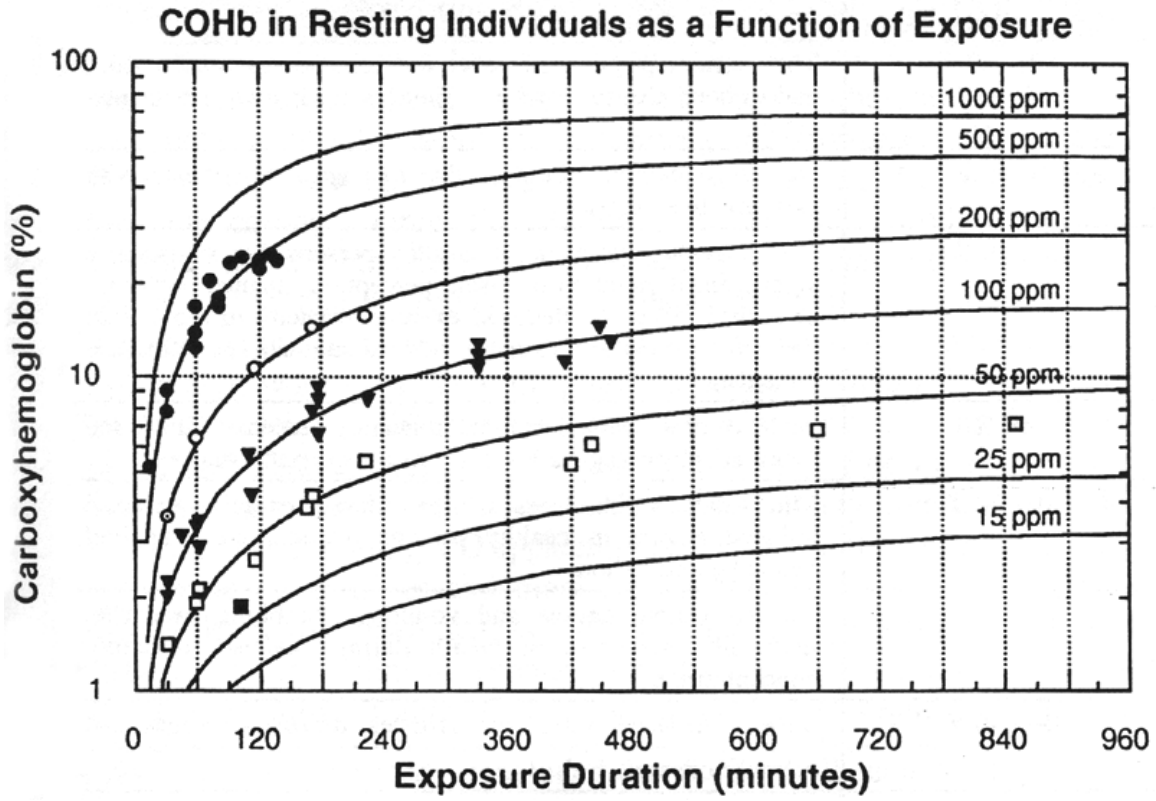
- **Clinical effects** at COHb levels of 20% or greater.
- **Sub-clinical impacts** on neurological/ visual systems up to 10% COHb.
- **Discernible, but not necessarily clinically significant, effects** at COHb levels less than 5%.

Additional analysis is necessary to refine these exposure ranges, and to characterize how these relate to the cutpoints suggested in the UL/CPSC guidelines for CO detectors.

2.2 EXPOSURE-DOSE MODEL

The Coburn-Forster-Kane exponential equation is a well known model that accounts for the known physiological variables involved in CO uptake. The graph in Figure 2.1

presents the relationship between ambient levels of CO in parts per million (ppm) as the range of exposures, and COHb levels in blood as a dose of %COHb (ambient concentrations and durations of exposure) for resting individuals.



From: Peterson, J.E. & Stewart, R.D. (1977) Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. J. Appl. Physiol., 39, 633-638.

Figure 2.1 Uptake of Carbon Monoxide by Normal Resting Humans
(The solid lines represent a mathematical model based on physiological principles and the symbols represent measurements of blood COHb.)

Mapping known exposure-dose effects onto Figure 1 identifies a region of the chart that can be classified as the “sub-acute zone” of CO exposure. A reasonable approximation ranges between a dose of 2% and 10% COHb.

2.3 EXPOSURE-DOSE LEVELS UP TO 10% CARBOXYHEMOGLOBIN

Under certain conditions, the measured levels of COHb can range from less than 0.5% to 10% for extended periods of time, based on endogenous CO production and environmental exposures, as summarized below.

Non-pregnant adults: endogenous CO production	0.4 – 0.7
Pregnant females: endogenous CO production	0.7 – 2.5
Non-smokers: endogenous plus environmental exposures	0.5 – 1.5
Nonsmoker workers in combustion environments[1]	up to 5%
Smokers	up to 10%

In order to protect non-smoking, middle-aged and elderly populations with documented or latent coronary heart disease from acute ischemic heart attacks, and to protect the fetuses of nonsmoking pregnant women, the WHO recommended that a COHb level of 2.5% should not be exceeded (WHO, 2000).

2.4 HEALTH EFFECTS DUE TO ACUTE AND SUB-ACUTE EXPOSURES

Earlier studies (prior to 1998) of sub-acute exposures provide limited data about CO levels that result in neurological and neurobehavioral health effects. It is accepted scientific knowledge that human environmental and occupational exposures to CO primarily affect those organs and tissues of the body that thrive on oxygen, i.e., the brain, the cardiovascular system, skeletal muscles (during exercise), and the developing fetus. Some effects are known to be reversible, while others result in long-term, irreversible damage. One consistency across the scientific literature is the recognition that observed effects of CO exposure result from complex interactions that may involve multiple organ systems over time.

At COHb levels exceeding 5 percent, researchers report a reduction in sustained attention and cognitive performance (Gale et. al., 1999, 2004). Following accidental exposures during acute CO events, neurological damage has been observed weeks after initial recovery. According to the 2000 CO Criteria Document, it is not known whether the late neurological sequelae such as intellectual deterioration, memory impairment, and brain damage result from long-term exposure to elevated ambient levels of CO (e.g., areas of high traffic). Understanding both neurological and neurophysiological health effects due to CO exposure is emerging as an area of research focus since the 2000 document.

[1] Firefighters, car drivers, police personnel, garage/tunnel workers, etc.

Acute CO poisoning causes both reversible neurological deficits, and severe, often delayed neurological damage. Summarized below are reported health effects over a range of approximate COHb levels as a result of acute exposures:

10% or higher	Headache, dizziness, with nausea and vomiting at higher levels.
40%	Coma and collapse
50 – 60%	Generally lethal

As reported by Laties (1979) and Bunnell (1988), low-level CO exposures and dose-effects on behavior were reviewed by Laties and Merigan (1979) and Benignus (1994). The earlier studies suggest that central nervous system deficits are noted in people with COHb levels as low as 3 – 5%. Although statistically significant, it is still not established if these are, or lead to, functionally significant or irreversible changes. Other psychomotor functional performance effects are reported as follows:

18% or less	Impairment of non-tracking vision or other behavioral functions in healthy young sedentary subjects is not significant.
5.1 – 8.2%	Psychomotor effects, such as reduced coordination, impaired tracking and driving ability, and less vigilance/ detection of small changes
5 – 20%	Reduction in cognitive performance (earlier studies)
7 – 10%	Visual tracking performance effects

These ranges do not consider impacts to potentially susceptible populations, e.g., children, adults with pre-existing health conditions, or neonates.

2.5 BASIS OF CURRENT EXPOSURE GUIDELINES

WHO: The 2000 WHO Regional Office for Europe has determined the following exposure guidelines based on this equation using time-weighted average exposures in a way such that the 2.5% COHb level is not exceeded.

- 100 milligrams per cubic meter (mg/m^3) (90 ppm) for 15 minutes
- 60 mg/m^3 (50 ppm) for 30 minutes
- 30 mg/m^3 (25 ppm) for 1hour

- 10 mg/m^3 (9 ppm) for 8 hours

The WHO guidelines also provide general statements about the health effects of long-term exposure to CO, including headache, memory defects, reduced productivity, sleep disturbances, vertigo, emotional distress, central and peripheral nervous system damage, and increased concentrations of chemical constituents in blood. The relevance of these statements for sub-acute exposures is discussed further in Section 3.0.

EPA: The Air Quality Criteria for Carbon Monoxide (2000) describes the regulatory background for permissible CO exposure limits in the United States. According to this Criteria Document, the EPA promulgated the following identical primary and secondary NAAQS for CO in 1971.

- 40 mg/m^3 (35 ppm) for 1 hour
- 10 mg/m^3 (9 ppm) for 8 hours

In 1980, EPA proposed changes to the criteria. After reevaluation of the scientific data concerning health effects associated with exposure to CO at or near ambient exposure levels, the EPA issued a final notice in 1985 announcing retention of the primary standard. Between 1987 and 1990, new studies about the effects of CO exposure on persons with angina were discussed, and a revised Staff Paper prepared by the Clean Air Scientific Advisory Committee (CASAC) was released in 1992. Based on the recommendations in the Staff Paper, the EPA issued a final decision in August 1994 that revisions of the CO NAAQS were not appropriate at the time. The 2000 Criteria Document describes how the Staff Paper reviewed the lower end of the exposure range to provide an adequate margin of safety from effects of clear concern.

The EPA Administrator determined that cardiovascular effects for persons with pre-existing health conditions (i.e., decreased time to onset of angina pain in adults with documented coronary artery disease) were the health effects of greatest concern. The scientific literature provided supportive evidence that adverse health effects occurred at exposures as low as 2.9 to 3.0% COHb. Other factors that were considered in evaluating the adequacy of the NAAQS involved work capacity reductions in athletes with COHb as low as 2.3%, the absence of CO exposure susceptibility data for sensitive populations

(e.g., children, adults with prior medical conditions), the acceptance that acute exposures to CO can be detrimental to fetal development, the concern about individuals with anemia or respiratory disease, and exposures to the elderly. The EPA acknowledged that central nervous system impairments were not well studied relative to CO exposure. With the data uncertainties, the less significant health endpoints, and less quantifiable data on other potentially sensitive groups, the lower end of the allowable exposure range was established at 2.0% COHb.

3.0 CRITICAL LITERATURE REVIEW

3.1 GENERAL APPROACH

Noting that the 2000 CO Criteria Document significantly lacked a thoughtful discussion or review of neurological/psychological, brain and cognitive behavior effects, this present review obtained all the available and relevant knowledge in this emerging field of study. Using the references in the CO Criteria Document as a starting point, EH&E developed a list of keywords and conducted a comprehensive search of the peer-reviewed literature for technical information related to sub-acute CO exposures and health effects for different sub-groups of the population. In addition, the gray (non-peer reviewed) literature e.g., internet, e-publications, etc., was also included in the review. As the searches were expanded, over 200 possible citations were identified. A refined search and preliminary review of content eliminated over half the initial references. For the time period between 1998 and 2006, approximately eighty citations appeared to be relevant. About three-fourths of those focused on clinical information, including diagnosis and treatment using a hyperbaric oxygen chamber, neurological changes to the brain, and psychomotor impairments. The remaining articles were not immediately relevant to the present work and were excluded from further consideration. A representative subset of the reference literature is included in this review.

In general, EH&E noted an increase in peer-reviewed publications between 1998 and 2006, specifically in the areas of central nervous system and neuropsychological effects. The sustained growth of literature in this field exceeded the number of references for cardiac effects (acute exposure) and indicated a research interest in areas not covered by the 2000 Criteria Document.

3.2 CRITERIA FOR CRITICAL REVIEW

EH&E obtained information from a variety of sources, summarized below:

- Peer-reviewed articles from U.S./Canadian and European journals
- Books on CO and/or other environmental pollutants
- Guidance documents from regulatory or quasi-government agencies
- Internet-based articles in non-peer reviewed electronic publications

- Internet-based publications or documents from alarm manufacturers or other vendors

Critical review of individual references consisted of the following questioning process:

a. Does the report include measures of chronic, sub-acute CO exposure?
b. Are measured levels of COHb documented?
c. Are health outcomes clear and consistent?

Evaluation of each literature citation was based on one primary criterion: Its relevance in addressing the questions posed in this inquiry. If an article provided good clinical knowledge and was technically sound, but did not meet the relevance criteria, it was excluded from further consideration.

The literature compilation was classified in terms of review articles, reviews of clinical and physiological symptoms, epidemiological studies, anecdotal case studies, books and publications, and general informational articles. The numerical breakdown is provided in Table 3.1. A critical review of the 65 references is summarized in matrix format as Appendix B.

Table 3.1 Classification of Literature for Critical Review

Type of Reference Article	Number of Citations, by Category	Number Relevant to Sub-acute Exposures	General Summary Notes
Reviews	14	8	Provide useful reference information across range of COHb levels and health effects.
Clinical reviews	15	2	Focus remains on acute exposures and treatment methods.
Epidemiological studies	13	3	Lack of exposure data.
Case studies	9	5	Ambient or COHb data available for anecdotal cases.
General informational articles	7	1	Insufficient detail.
Books and publications	3	3	Sections address challenges associated with sub-acute exposures and health effects.
Other (manuscripts/ editorials/test methods)	4	2	Unpublished information.
Total	**65**	**24**	**Overall lack of credible scientific sub-acute COHb exposure data.**

3.3 REVIEW ARTICLES

In a recent publication, Hopkins, Weaver and others (2006) reviewed the literature and reported on specific changes to the brain captured by MRI imaging, e.g., basal ganglion lesions, following acute CO exposure. They concluded that these lesions may be less common than previously reported. Gale and Hopkins (2004) continue to study the subsequent memory deficits associated with brain damage and report significant correlations between hippocampal volume (brain atrophy) and performance on nonverbal information processing activity.

In his review article, Weaver (1999) cited earlier works by Benignus (1996) and Amitai et al. (1998), and concluded that there is conflicting evidence that experimental CO exposures in healthy subjects, including low-level CO exposures, impair cognitive functions. A more recent review by Raub and Benignus (2002) provides updated guidance about the CO exposures needed for central nervous system effects, including a reduction in visual perception, manual dexterity, learning, driving performance, and

attention level. The authors stated that earlier literature reported that exposures of 5% COHb would be sufficient to effect various neurobehavioral deficits. However, recent research suggests that the COHb would have to increase to 15 – 20% before a 10% reduction in behavioral or visual impairment could be observed (Raub and Benignus, 2002).

A significant segment of the peer-reviewed literature relies heavily on health effects that they refer to as chronic, but are based on CO exposures that are initially acute. The body of peer-reviewed scientific literature that examines health effects from sub-acute CO exposures is extremely limited. Kao and Nanagas (2004, 2005, 2006) review exposure situations that present as acute CO poisoning events, and are followed by subsequent health effecgts e.g., dizziness, vomiting, or other generalized symptoms. According to the 2005 review, measured COHb levels up to 20 – 25% correlate well with gastrointestinal symptoms (nausea, vomiting), and neurologic symptoms (headache, dizziness, blurry vision). Further, they conclude that chronic clinical effects remain in question, and the evidence to substantiate health-based claims of is not compelling, primarily due to the inherent difficulties in quantifying both the degree of exposure and the degree of neurologic impairment (Kao and Nanagas, 2005).

3.4 CRITICAL PAPERS ON CLINICAL SYMPTOMS

The peer-reviewed literature reviewed fell into three logical categories of scientific information: emergency medicine, neurophysiology, and psychology. The majority of findings are reported by a common subgroup of physician and medical researchers with multiple citations and collaborative research work. Key examples include NB Hampson, RO Hopkins, LK Weaver, SR Thom, SD Gale, LW Kao, and KA Nanagas, among others.

The first knowledge category emerges from the field of Emergency Medicine, where various types of CO-exposed patients are treated for acute exposures with possible chronic sequelae. EH&E reviewed the following thirteen citations on how healthcare practitioners address CO exposures in the emergency room: Hampson et al. (2001); Durak et al. (2005); Hampson et al. (2005); Hampson and Hampson (2001); Gorman et al. (2003); Hampson (1999); Raub et al. (2000); Henz and Maeder (2005); Buckley et al. (2005); Hampson (1998); Hampson (2001); Hampson and Little (2005); Hampson

(2005). This segment of the literature acknowledges that acute CO poisoning continues to be an issue of concern, and that the treatment of hyperbaric oxygen (HBO) has been particularly beneficial for patients with unexpectedly high levels of exposure. The merits and specifics of the oxygen treatment regimen (intensity, frequency, hyperbaric vs. normobaric, etc.) continue to be actively debated among practitioners. Hampson has studied numerous population subgroups, including bingo players, firefighters, first responders in emergencies, and divers.

Most of Hampson's work continues to focus on the benefits of acute exposure treatment using HBO, and other researchers are beginning to explore the long-term effects of sub-acute exposure following a treated acute episode, using MRI imaging techniques (Durak et al. 2005). Henz and Maeder (2005) of Switzerland suggest that the immediate and delayed symptoms noted in acute CO poisoning may result from different pathogenic mechanisms; however, they do not offer sub-acute exposure estimates. Although the severity of exposure in Hampson's research refers to COHb levels at or exceeding 20%, the follow-on research does not quantify subsequent (reduced) exposure levels. Clearly, Hampson's extensive work in this area is commendable from the perspective of medical treatment regimens. Unfortunately, neither his efforts, nor the limited recent follow-up citations address any of the key questions of this review. Therefore, they are not relevant in the assessment of health effects due to sub-acute exposures and will not be evaluated further.

The neuropsychological literature consists of two compartments of knowledge, one that covers physical damage to the brain, and the other that focuses on cognitive impairments and functioning. EH&E reviewed nine citations that were relevant to this inquiry: Porter et al. (2001); Pavese (1999); Hopkins et al. (2006); Hopkins et al. (2001); Hurley et al. (2001); Gale and Hopkins (2004); Gale et al. (1999), and Weaver (1999), Raub and Benignus (2002). The efforts by Hopkins, Weaver, and Gale and their teams of researchers lead the state of knowledge in understanding the extent of measurable neurological damage following acute episodes of CO poisoning.

Another area of active research involves the psychology of patients exposed to CO. These include patients with depression and anxiety, or patients who seek occupational health assistance due to impaired work functions. As clinical neuropsychologists, Gale

and colleagues (1999, 2004) investigated brain-behavior relationships following CO exposures. They studied the effects of hypoxia on the brain and evaluated the neuropathologic changes with associated cognitive impairments, including impaired attention, memory, executive function, and mental processing speed. They also measured affective changes, e.g., depression and anxiety, and concluded that a multi-faceted clinical approach was necessary to integrate the neuropathological and neurobehavioral effects following CO exposure.

While both research areas provide valuable insights about the manifestations of CO poisoning across a variety of systems, EH&E did not find the reported CO exposure levels to be sub-acute. Chronic, long-term health effects were evaluated, based on initial COHb levels that were termed "severe," i.e., well above 20%.

3.5 ARTICLES ON POPULATION SUBGROUP EXPOSURES

The articles critically reviewed in this study include selected subgroups in the general population, e.g., children, the elderly, and people with specific medical impairments. Traffic-related air pollutant levels (including ambient CO) resulting in increased prevalence of asthma among children have been reported in the peer-reviewed literature, Guo et al. (1999), Yu et al. (2000), and Etzel (2000). Sub-acute CO exposure to the elderly has been reported as an issue of concern (Harper and Croft-Baker, 2004), or as anecdotal instances, but with no exposure information. Exposure of CO to smokers and non-smokers has been measured; however, given the pollutant mixture that is generated from smoking, the individual effect of CO remains unknown. Foster and colleagues (1999) reported on recurrent life-threatening events and lactic acidosis in an infant cause by chronic CO poisoning. The exposure levels, however, are not well-defined. In general, the knowledge on subpopulation CO exposures and health impacts tends to be anecdotal or based on case studies. In this review, exposure to exercising adults was not evaluated. In particular, a review of cardiovascular health effects was not conducted, as those effects result from acute CO exposure, not sub-acute levels. In summary, no systematic studies of sub-acute exposure to any subgroup were available for EH&E review.

3.6 ARTICLES ON PROLONGED CARBON MONOXIDE EXPOSURES

The review by EH&E uncovered a subset of articles in the peer-reviewed and gray literature that focused on prolonged exposure to sub-acute levels of CO. Townsend and Maynard (2002) report that the evidence of CO exposure on multiple organ systems is accumulating. The EH&E review identified additional research studies since 2002 that not only describe effects on the cardiovascular system, but also on other physiological systems, e.g. neurological, gastrointestinal, and ocular. Rottman et al. (1995) acknowledged that subtle neurological disturbances were not known to be permanent or reversible. Annane and colleagues (2001) reported that 97% of adults with mild symptoms of CO exposure were able to return to work within a month. Amitai et al. (1998) documented neuropsychological deficits and provided fair exposure information on CO levels. However, the study was based on acute, not chronic exposure. Another example is an article by Devine et al. (2002), who presented a well-designed case report of long-term chronic exposure. However, COHb information was not available. Whether long-term exposure to low concentrations can produce long-lasting effects on the brain is still inconclusive, and in some cases, contradictory.

Knobeloch and Jackson (1999) report three case studies of chronic CO poisoning, but with no COHb exposure levels. The National Electronic Injury Surveillance System All Injury Program (NEISS-AIP) examined fatal and nonfatal unintentional, non-fire related CO exposures between 2001 – 2003. Among the criteria for defining a non-fatal case was the required presence of a CO detector in the home. The limitations of this evaluation are characteristic of poorly-designed studies. Data on CO exposure sources was not available for a substantial percentage of cases. The estimates of non-fatal injuries were limited to emergency room visits and did not include any outpatient settings. For these and other compelling reasons, no conclusions could be drawn from this study.

The single reference with comprehensive coverage on the state of the science on CO toxicity until 2000 is the book edited by Penney (2000). The book includes excellent working definitions of low-level, sub-acute exposure, critically reviews case studies, and provides a smooth transition from acute to sub-acute CO exposure scenarios. Several authors cited in the EH&E review are referenced in the Penney book as well for their

earlier work. Penney arrives at conclusions that are generally consistent with EH&E's analysis.

3.7 UPDATE ON EXPOSURE IN INDOOR ENVIRONMENTS

There are numerous partially or completely enclosed microenvironments (e.g., indoor ice arenas, indoor motor shows) with insufficient ventilation, where the levels of exhaust pollutants from combustion engines may greatly exceed the common ambient levels. For indoor ice arenas, intermittent ice resurfacing with hydrocarbon-fueled equipment has produced average CO levels ranging from 2 – 152 mg/m^3 (2 – 132 ppm), compared to the mean values of several arenas being 40 – 46 mg/m^3 (35 – 40 ppm). Acute epidemic poisonings in ice arenas have documented CO concentrations as high as 170 – 405 mg/m^3 (148 – 354 ppm) (Pelham et al., 2001). In poorly ventilated homes with faulty or unvented combustion appliances, peak levels exceeding 115 mg/m^3 (100 ppm) have been measured. A significant amount of research has been done in Europe in the 1990s to characterize exposures to commuters (in vehicles, during subway rides, on bicycles, etc.). Environmental tobacco smoke in various indoor settings (homes, offices, vehicles, restaurants, recreational facilities) is another source that can raise the average CO concentration by up to 23 – 46 mg/m^3 (20 – 40 ppm) (WHO, 2000).

4.0 SUMMARY OF REVIEW FINDINGS

Based on a critical review of the CO health effects literature between 1998 and 2006, EH&E concludes the following:

- Impairment of cognitive and psychomotor abilities in CO exposures resulting in COHb of 5% is suggested in the literature (Amitai, 1998; Hampson, 2005).

- Sub-acute CO exposures and dose reconstruction is a fundamental limitation to meaningful interpretation of most studies.

- Studies of CO are confounded by the unquantified presence of co-contaminants. CO is always a result of incomplete combustion which is accompanied by other contaminants, including particulate matter (PM), polynuclear aromatic hydrocarbon, nitrogen oxide (NOx), among others. Thorough consideration of the co-contaminant hazards is lacking in the CO literature. An awareness of health effects literature for other air pollutants (NOx, PM, etc.) needs to be considered in studying the health effects of chronic CO exposure.

There is insufficient information in the published literature to assess the relevance of low-level chronic CO exposure to the development of systemic effects. The literature is confounded by reference to many studies that discuss chronic sequelae after an acute CO exposure. The studies are insufficient to assess potential sub-acute effects.

APPENDIX A

LITERATURE REFERENCE LIST

COMPILATION OF CARBON MONOXIDE RELATED HEALTH EFFECTS LITERATURE 1998 – 2006 (EH&E 14446)

Abelsohn A, Sanborn MD, Jessiman BJ, and Weir E. 2002. Identifying and Managing Adverse Environmental Health Effects: 6. Carbon Monoxide Poisoning. *Canadian Medical Association Journal*. 166(13): 1685 – 1690.

Amitai Y, Zlotogorski Z, Golan-Katzav V, Wexler A, and Gross D. 1998. Neuropsychological Impairment from Acute Low-Level Exposure to Carbon Monoxide. *Arch Neurol*. June 1998(55): 845 – 848.

Annane D, Chevret S, Jars-Guincestre MC, Chillet P, Elkharrat D, Gajdos P, and Raphael JC. 2001. Prognostic Factors in Unintentional Mild Carbon Monoxide Poisoning. *Intensive Care Med*. 2001(27): 1776 – 1781.

Ashley P, Anderson J, Menkedick JR, and Wooton MA. 2005. Healthy Homes Issues: Carbon Monoxide. *Healthy Homes Initiative Background Information*. 2005(12): 1 – 35.

Bartlett D. Understanding and Treating Carbon Monoxide Poisoning. *Elsevier Public Safety*. Lethal Exposure: 2 – 9.

Buckley, NA, Isbister GK, Stokes B, and Juurlink DN. 2005. Hyperbaric Oxygen for Carbon Monoxide Poisoning, A Systematic Review and Critical Analysis of the Evidence. *Toxicol Rev*. 24(2): 75 – 92.

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Eisinger DS, Dougherty K, Chang DP, Kear T, and Morgan PF. 2002. A reevaluation of Carbon Monoxide: Past Trends, Future Concentrations, and Implications for Conformity "Hot -Spot" Policies. *J. Air & Waste Manage. Assoc*. 2002(52): 1012 – 1025.

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Etzel RA. 2000. The "Fatal Four" Indoor Air Pollutants. *Pediatric Annals*. 29(6): 344 – 350.

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Foster M, Goodwin SR, Williams C, and Loeffler J. 1999. Recurrent Acute Life-threatening Events and Lactic Acidosis Caused by Chronic Carbon Monoxide Poisoning in an Infant. *PEDIATRICS*. 104(3): 1 – 3.

Gale SD, Hopkins RO, Weaver LK, Bigler ED, Booth EJ, and Blatter DD. 1999. MRI, Quantitative MRI, SPECT, and Neuropsychological Findings Following Carbon Monoxide Poisoning. *Brain Injury*. 13(4): 229 – 243.

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APPENDIX B

CRITICAL REVIEW MATRIX

Table B.1 Critical Review of Carbon Monoxide Literature—Sub-acute Exposures and Health Effects

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Abelsohn A, Sanborn MD, Jessiman BJ, and Weir E. 2002. Identifying and Managing Adverse Environmental Health Effects: 6. Carbon Monoxide Poisoning. *Canadian Medical Association Journal*. 166(13): 1685 – 1690.	Case study	COHb level 5%. Health effects: headaches. Gas furnace in basement.	Yes
Amitai Y, Zlotogorski Z, Golan-Katzav V, Wexler A, and Gross D. 1998. Neuropsychological Impairment from Acute Low-Level Exposure to Carbon Monoxide. *Arch Neurol*. June 1998(55): 845 – 848.	Case-control study	Acute low-level CO exposure 17 – 100ppm. Measured COHb 1 – 11%. Measured health effects: neuropsychological impairment.	Yes
Annane D, Chevret S, Jars-Guincestre MC, Chillet P, Elkharrat D, Gajdos P, and Raphael JC. 2001. Prognostic Factors in Unintentional Mild Carbon Monoxide Poisoning. *Intensive Care Med*. 2001(27): 1776 – 1781.	Clinical epidemiological study	Acute exposure. COHb >10% for smoker. COHb>5% for nonsmoker. Oxygen therapy. 97% return to work in 1 month.	No
Ashley P, Anderson J, Menkedick JR, and Wooton MA. 2005. Healthy Homes Issues: Carbon Monoxide. *Healthy Homes Initiative Background Information*. 2005(12): 1 – 35.	Monograph; summary report	Reported acute. Reported chronic.	Yes
Bartlett D. Understanding and Treating Carbon Monoxide Poisoning. *Elsevier Public Safety*. Lethal Exposure: 2 – 9.	Clinical review–Nursing	Focus on hyperbaric therapy.	No
Buckley, NA, Isbister GK, Stokes B, and Juurlink DN. 2005. Hyperbaric Oxygen for Carbon Monoxide Poisoning, A Systematic Review and Critical Analysis of the Evidence. *Toxicol Rev*. 24(2): 75 – 92.	Review	No COHb reported. Reported health effects. Assessment of treatment therapies.	No
Centers for Disease Control and Prevention. 2005. Unintentional Non-fire-related Carbon Monoxide Exposures – United States 2001-2003. MMWR Weekly, January 21, 2005. 54(02) 36-39. www.cdc.gov	Informational	No COHb levels. No CO exposure levels. Reported health effects.	No
Colome S, McCunney RJ, Samet JM, and Swankin D. Health Problems Caused by Other Combustion Products. 1994. *Indoor Air Pollution: an Introduction for Health Professionals.* EPA 402-R-94-007, 1994.	Publication	Reported COHb. Reported health effects.	Yes

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Cunnington AJ and Hormbrey P. 2002. Breath Analysis to Detect Recent Exposure to Carbon Monoxide. *Postgrad Med J*. 2002(78): 233 – 238.	Exposure test method	Breath CO levels for smokers, nonsmokers.	No
Devine SA, Kirkley SM, Palumbo CL, and White RF. 2002. MRI and Neuropsychological Correlates of Carbon Monoxide Exposure: A Case Report. *Environmental Health Perspectives*. 110(10): 1051 – 1055.	Case study	Reported chronic exposure to CO gas leak. Reported elevated indoor CO levels. No COHb. Measured health effects.	Yes
Devine SA, Kirkley SM, Palumbo CL, and White RF. 2002. MRI and Neuropsychological Correlates of Carbon Monoxide Exposure: A Case Report. *Environmental Health Perspectives*. 110(10): 1051 – 1055.	Case study	Acute exposure. Reported health effects. N.B.: second event discussed in paper.	No
Durak AC, Coskun A, Yikilmaz A, Erdogan F, Mavili E, and Guven M. 2005. Magnetic Resonance Imaging findings in Chronic Carbon Monoxide Intoxication. *Acta Radiol*. 2005(3): 322 – 327.	Clinical case-control study	Acute CO exposure. No COHb reported. Health effects: cerebral atrophy, neuropsychiatric findings.	No
Eisinger DS, Dougherty K, Chang DP, Kear T, and Morgan PF. 2002. A Reevaluation of Carbon Monoxide: Past Trends, Future Concentrations, and Implications for Conformity “Hot -Spot” Policies. *J. Air & Waste Manage. Assoc*. 2002(52): 1012 – 1025.	Informational	None.	No
Ernst A and Zibrak J. 1998. Carbon Monoxide Poisoning. *New England Journal of Medicine.* 339(22): 1603 – 1608	Review	COHb levels not reported. Health effects reported, e.g., delayed neuropsychiatric syndrome.	No
Etzel RA. 2000. The "Fatal Four" Indoor Air Pollutants. *Pediatric Annals*. 29(6): 344 – 350.	Informational	None.	No
Fierro MA, O’Rourke MK, Burgess JF. 2001. Adverse Health Effects of Exposure to Ambient Carbon Monoxide. Draft Manuscript. University of Arizona, College of Public Health, September 2001.	Draft manuscript	Reported CO exposure. Predicted COHb levels. Susceptible populations.	Yes
Fisher J. Carbon Monoxide Poisoning, A Disease of a Thousand Faces. *Chest*. 115(2): 322 – 323.	Clinical review	Health effects.	No

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Foster M, Goodwin SR, Williams C, and Loeffler J. 1999. Recurrent Acute Life-threatening Events and Lactic Acidosis Caused by Chronic Carbon Monoxide Poisoning in an Infant. *PEDIATRICS*. 104(3): 1 – 3.	Case study	Measured indoor CO. Reported elevated COHb. Health effects.	Yes
Gale SD, Hopkins RO, Weaver LK, Bigler ED, Booth EJ, and Blatter DD. 1999. MRI, Quantitative MRI, SPECT, and Neuropsychological Findings Following Carbon Monoxide Poisioning. *Brain Injury*. 13(4): 229 – 243.	Clinical review	Acute exposure. COHb 26%. Health effects: neuropathologic changes, multiple system impacts.	No
Gale SD and Hopkins RO. 2004. Effects of Hypoxia on the Brain: Neuroimaging and Neuropsychological Findings Following Carbon Monoxide Poisoning and Obstructive Sleep Apnea. *Journal of the International Neuropsychological Society*. 2004(10): 60-71.	Clinical review	Acute exposure. Health effects: neuropathologic impairments.	No
Gallagher F and Mason HJ. 2004. Carbon Monoxide Poisoning in Two Workers Using an LPG Forklift Truck Within a Coldstore. *Occupational Medicine*. 54(7): 483 – 488.	Case study	Acute exposure. COHb 17.8-35%. Health effects.	No
Gandini C, Castoldi AF, Candura SM, Priori S, Locatelli C, Butera R, Bellet C, and Manzo L. 2001. Cardiac Damage in Pediatric Carbon Monoxide Poisoning. *Clinical Toxicology*. 39(1): 45 – 51.	Case study	Acute exposure. COHb level 24.5%. Health effects.	No
Gorman D, Drewry A, Huang YL, and Sames C. 2003. The Clinical Toxicology of Carbon Monoxide. *Toxicology*. 2003(187): 25 – 38.	Clinical review	None. Reported health effects for acute exposures. Review of treatment options, including oxygen therapy.	No
Guido M. 2001. U.S. Ignores Auto Device That's Touted as Life-Saver. *Mercury News.* May 6, 2001.	Informational	None.	No
Guo YL, Lin YC, Sung FC, Huang SL, Ko YC, Lai JS, Su HJ, Shaw CK, Lin RS, and Dockery DW. 1999. Climate, Traffic-Related Air Pollutants, and Asthma Prevalence in Middle-School Children in Taiwan. *Environmental Health Perspectives*. 107(12): 1001 –1006.	Epidemiological study	Ambient CO levels. Asthma prevalence. No COHb.	Yes
Hampson NB. 2005. Trends in the Incidence of Carbon Monoxide Poisoning in the United States. *The American Journal of Emergency Medicine*. 2005(23): 838 – 841.	Review	None reported. Study reported decline in CO mortality from 1968 – 1998, effect of oxygen treatments.	No

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Hampson NB. 1998. Emergency Department Visits for Carbon Monoxide Poisoning in the Pacific Northwest. *The Journal of Emergency Medicine*. 16(5): 695– 698.	Clinical epidemiological study	No CO, COHb reported. Study evaluated number of Emergency Department visits.	No
Hampson NB and Little CE. 2005. Hyperbaric treatment of patients with CO poisoning in the US. *Undersea and Hyperbaric Medical Society, Inc.* 32(1): 21-26.	Clinical epidemiological study	None reported. Hyperbaric treatment facilities evaluated.	No
Hampson NB, Mathieu D, Piantadosi CA, Thom SR, and Weaver LK. 2001. Carbon Monoxide Poisoning: Interpretation of Randomized Clinical Trials and Unresolved Treatment Issues. *Undersea and Hyperbaric Medical Society, Inc*. 28(3): 157 –164.	Clinical review	None. Hyperbaric oxygen treatment options for undersea divers.	No
Hampson NB, Scott KL, Zmaeff JL. 2006. Carboxyhemoglobin measurement by hospitals: Implications for the diagnosis of CO poisoning. *Journal of Emergency Medicine*. 31(1): 13-16.	Clinical review	None. Study evaluates need for hospitals to measure blood COHb for diagnosis and treatment of CO poisoning.	No
Hampson NB, Weaver LK, and Piantadosi CA. 2005. "Low-Level" Carbon Monoxide Administration May Carry Risk. *American Journal of Respiratory and Critical Care Medicine*. 2005(172): 784 – 785.	Editorial	Reported indoor CO 500 ppm. Reported low-level CO 100 ppm. Reported health effects: neuropsychological impairment.	Yes
Hampson NB and Zmaeff JL. 2001. Outcome of Patients Experiencing Cardiac Arrest with CO Poisoning Treated with Hyperbaric Oxygen. *Annals of Emergency* Medicine. 38(1): 36-41.	Clinical epidemiological study	Acute mean COHb measured 31.7%. Health outcomes: death.	No
Hampson NB and Zmaeff JL. 2005. Carbon Monoxide Poisoning from Portable Electric Generators. *American Journal of Preventative Medicine.* 28(1): 123 – 125.	General – CO sources	None.	No
Harper A and Baker JC. 2004. Carbon Monoxide Poisoning: Undetected by Both Patients and Their Doctors. *Age and Ageing.* 33: 105-109.	Clinical review	Health effects.	No
Henz S and Maeder M. 2005. Prospective Study of Accidental Carbon Monoxide Poisoning in 38 Swiss Soldiers. *Swiss Med Weekly*. 2005(135): 398 – 406.	Case-control study	No indoor CO reported. Measured COHb 30.4%—acute. Reported health effects: immediate and delayed symptoms, different pathogenic mechanisms.	No

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Hopkins RO, Fearing MA, Weaver LK, and Foley JF. 2006. Basal Ganglia Lesions Following Carbon Monoxide Poisoning. *Brain Injury*. 20(3): 273 – 281.	Clinical review	Acute exposure. COHb 42.3%. Health effects: basal ganglia lesions.	No
Hurley RA, Hopkins RO, Bigler ED, and Taber KH. 2001. Applications of Functional Imaging to Carbon Monoxide Poisoning. *J Neuropsychiatry Clin Neurosci*. 13(2): 158 – 160.	Clinical review	Acute exposure. No COHb levels. Delayed neurological sequelae, MRI imaging changes.	No
Kao LW and Nañagas KA. 2006. Toxicity Associated with Carbon Monoxide. *Clin Lab Med*. 2006(26): 99 – 125.	Review	Reported acute. Reported chronic. Reported health effects.	Yes
Kao LW and Nañagas KA. 2005. *Med Clin N AM*. 2005(89): 1161 – 1194.	Review	Reported acute. Reported chronic. Reported health effects.	Yes
Kao LW and Nañagas KA. 2004. Carbon Monoxide Poisoning. *Emergency Medicine Clinics of North America*. 2004(22): 985 – 1018.	Review	Reported acute. Reported chronic. Reported health effects.	Yes
Kesler SR, Hopkins RO, Weaver LK, Blatter DD, Edge-Booth H, Bigler, ED. 2001. Verbal Memory Deficits Associated with Fornix Atrophy in Carbon Monoxide Poisoning. *Journal of the International Neuropsychological Society.* 7(5), 640-646.	Clinical review	Acute exposure. Mean COHb 21.4%. Health effects: at 6 months, significant decline in verbal memory; no decline in visual memory, processing speed, attention/ concentration.	No
Kleinman, MT. 2000. Carbon Monoxide: Evaluation of Current California Air Quality Standards with Respect to Protection of Children. Prepared for California Air Resources Board, California Office of Environmental Health Hazard Assessment. Irvine, CA:University of California Irvine Department of Community and Environmental Medicine.	Informational	Chronic CO exposure. Target COHb 2.5%. Predicted pediatric uptake of ambient CO. Reported health effects.	Yes
Knobeloch L and Jackson R 1999. Recognition of Chronic Carbon Monoxide Poisoning. *Wisconsin Medical Journal*. September/October 1999: 26 – 29.	Case studies-gas furnace exposures	Reported indoor CO. Reported chronic. No COHb. Health effects.	Yes

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Koster LA and Rupp T. 2003. Recognizing and Treating Carbon Monoxide Poisoning. *JEMS*. January 2003: 80 – 89.	Clinical review	Focus on hyperbaric therapy.	No
Kress T and Krueger D. 2004. Identifying Carbon Monoxide Poisoning. *Nursing*. 34(11): 68-69. www.nursing2004.com.	Case Study - Nursing	Acute exposure. COHb at 15%. Health effects.	No
Pavese N, Napolitano A, De Iaco G, Canapicchi R, Collavoli PL, Lucetti C, Gambaccini G, and Bonuccelli U. 1999. Clinical Outcome and Magnetic Resonance Imaging of Carbon Monoxide Intoxication. A Long-Term Follow-up study. *Ital J Neurol Sci*. 1999(20):171 – 178.	Clinical epidemiological study – acutely and chronically exposed cohorts	Acute COHb 10 – 53.6%. Chronic COHb 12.5 – 10.8%. Health effects: brain lesions, delayed neurological sequelae for 1 year.	No
Pelham TW, Holt TE, and Moss MA. 2002. Exposure to Carbon Monoxide and Nitrogen Dioxide in Enclosed Arenas. *Occup Environ Med*. 2002(59): 224 – 233.	Review	Recommended indoor CO limit of 20 ppm.	No
Penney DG, Editor. Carbon Monoxide Toxicity. Boca Raton, FL:CRC Press, Inc. 2000.	Book	Reported subacute CO. Reported subacute COHb. Reported health effects, exposure studies.	Yes
Perren A and Marone C. 2005. Remember 'A Posteriori Diagnosis' of Carbon Monoxide Poisoning. *European Journal of Emergency Medicine*. 12(5): 259 – 260.	Case study-mobile home exposure	Measured COHb. Health effects. Acute or chronic.	Yes
Porter SS, Hopkins RO, Weaver LK, Bigler ED, and Blatter DD. 2002. Corpus Callosum Atrophy and Neuropsychological Outcome Following Carbon Monoxide Poisoning. *Archives of Clinical Neuropsychology*. 2002(17): 195 – 204.	Clinical case-control study	Acute CO exposure. Mean COHb 22.4%. Health effects: significant atrophy and cognitive impairments.	No
Raub JA and Benignus VA. 2002. Carbon Monoxide and the Nervous System. *Neuroscience and Biobehavioral Reviews*. 2002(26): 925 – 940.	Review	Reported COHb 5% may not be sufficient to produce visual sensitivity reduction and neurobehavioral performance deficits. Reported COHb of 15 – 20% needed for 10% performance reduction measured.	Yes

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Raub JA, Mathieu-Nolf M, Hampson NB, and Thom SR. 2000. Carbon Monoxide Poisoning—A Public Health Perspective. *Toxicology*. 2000(145): 1– 14.	Review	Reported ambient CO. Reported COHb range. Reported health effects for acute and chronic exposures, e.g., neurological impairment.	Yes
Rottman J, Kaser-Boyd N, Cannis T, and Alexander J. 1995. Low-Level Carbon-Monoxide Poisoning: Inability of Neuropsychological Testing to Identify Patients Who Benefit from Hyperbaric Oxygen Therapy. *Prehospital and Disaster Medicine*. 10(4): 70 – 76.	Clinical case-control study	Low-level exposure reported. No COHb reported. Health effects reported. Hyperbaric therapy. Inconclusive finding.	No
Stefanidou M, Athanaselis S, and Koutselinis A. 2003. Carbon Monoxide: Old Poison—Recent Problems. *Legal Medicine*. July 2003: 253 – 254.	Editorial	Reported acute poisoning.	No
Tomaszewski C. 1999. Carbon Monoxide Poisoning. Early Awareness and Intervention Can Save Lives. *Postgraduate Medicine*. 105(1).	Clinical review	None.	No
Townsend CL and Maynard RL. 2002. Effects on Health of Prolonged Exposure to Low Concentrations of Carbon Monoxide. *Occup Environ Med*. 2002(59): 708 – 711.	Clinical review	Reported COHb 2.5 – 4%, health effects. Reported range of COHb, health effects.	Yes
Utah Poison Control Center. 2004. Carbon Monoxide Poisoning. *Utox Update*. 6(3): 1 – 4.	Informational	None.	No
Varon J and Marik PE. 1997. Carbon Monoxide Poisoning. *The Internet Journal of Emergency Intensive Care Medicine*. 1(2): http://www.ispub.com/journals/IJEICM/Vol1N2/CO.htm	Clinical review	Reported COHb, acute and sub-acute. Methylene chloride to CO in liver. Health effects reported over range of COHb levels.	Yes
Varon J, Marik PE, Fromm RE, and Gueler A. 1999. Carbon Monoxide Poisoning: A Review for Clinicians. *The Journal of Emergency Medicine*. 17(1): 87 – 93.	Review	Reported COHb levels. Reported health effects: disabling neuropsychiatric sequelae.	Yes

Table B.1 Continued

Literature Citation	Type	Measured vs. Reported CO, COHb, Health Outcomes	Relevance for Sub-acute Exposures
Weaver, LK. 1999. Carbon Monoxide Poisoning. *Critical Care Clinics* 15(2): 297-317.	Review	Reported low-level COHb to <10%. Health effects: conflicting evidence about extent of cognitive impairment.	Yes
Widdop B. 2002. Analysis of Carbon Monoxide. *Ann Clin Biochem*. 2002 (39): 378 – 391.	Review- COHb measurement methods	None.	No
World Health Organization. 2000. Chapter 5.5: "Carbon Monoxide Air Quality Guidelines" Air Quality Guidelines – Second Edition. WHO Regional Publications, European Series, No. 91. Copenhagen, Denmark: 2000.	Review	Reported ambient CO levels. Reported COHb levels. Reported health effects.	Yes
Wright J. 2002. Chronic and Occult Carbon Monoxide Poisoning: We Don't Know What We're Missing. *Emerg Med J*. 2002(19): 386 – 390.	Review	Reported acute. Delayed neurological sequelae.	No
Yoon SS, Macdonald SC, and Parrish RG. 1998. Deaths From Unintentional Carbon Monoxide Poisoning and Potential for Prevention with Carbon Monoxide Detectors. *Journal of the American Medical Association*. 279(9): 685 – 687.	Retrospective epidemiological study	None.	No
Yu O, Sheppard L, Lumley T, Koenig JQ, and Shapiro GG. 2000.Effects of Ambient Air Pollution on Symptoms of Asthma in Seattle-Area Children Enrolled in the CAMP Study. *Environmental Health Perspectives*. 108(12): 1209 – 1214.	Epidemiological study	Reported ambient CO. Reported health effects: asthma.	Yes

CO carbon monoxide
COHb carboxyhemoglobin
ppm parts per million