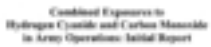

Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations: Initial Report

Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations, Committee on Toxicology, National Research Council

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Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations: Initial Report

Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

In support of the Health Hazard Assessment (HHA) for armored vehicles, the U.S. Army's Center for Health Promotion and Preventive Medicine (CHPPM) performed weapons-emissions testing for various firing scenarios. CHPPM evaluated emissions of carbon monoxide, hydrogen cyanide, oxides of nitrogen, sulfur dioxide, ammonia, and carbon dioxide. Generally, CHPPM evaluates the concentrations of these gases against the permissible exposure limits established by various agencies and organizations. Because military personnel in armored vehicles will be exposed to a mixture of gases, concerns were raised about potential additive or synergistic toxic effects, specifically the combined effects of simultaneous exposures to hydrogen cyanide and carbon monoxide, because both gases produce similar toxic effects. Because of these concerns, the Army prepared a report that provides guidance on assessing combined exposures to low levels of carbon monoxide and hydrogen cyanide. The Department of Defense (DOD) then requested that the National Research Council (NRC) independently evaluate the Army's proposed guidance on assessing combined exposures to hydrogen cyanide and carbon monoxide and recommend exposure limit guidelines for combined exposures to these chemicals. The NRC was asked to prepare two reports. For the initial report, the task was to determine whether the hazard presented from simultaneous exposures to hydrogen cyanide and carbon monoxide warrants a combined exposure assessment, and if so, whether the use of the hazard quotient approach is a reasonable method of assessment. The committee's second report, to be completed next year, will address the remainder of the task assigned to it (the complete statement of task is described in the summary of the report).

In response to DOD's request, the NRC convened the Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations. The members of the committee were selected by the NRC for their expertise in occupational health and medicine, physiology, pharmacokinetics, toxicology, inhalation toxicology, epidemiology, physiologically-based pharmacokinetic modeling, and risk assessment. Biographical information on the committee members is provided in the Appendix.

A draft of this initial report was reviewed by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Robert Goyer, University of Western Ontario; Sam Kacew, University of Ottawa; David Macys, Island County Health Department; and Deepak Bhalla, Wayne State University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Edward Bishop, HDR Engineering, Inc., appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all

review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Glenn Leach, Mathew Bazaar, Steve Kistner, and Col. John Rowe (all from the U.S. Army, Department of Defense). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. Other staff members who contributed to this effort are Ruth Crossgrove, senior editor; Aida Neel, program associate and Radiah Rose, senior editorial assistant. The committee particularly acknowledges Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

William E. Halperin, *Chair*
Committee on Combined Exposures to Hydrogen
Cyanide and Carbon Monoxide in Army Operations

Contents

Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations: Initial Report

Summary

The U.S. Army's Health Hazard Assessment (HHA) Program is a Medical Department initiative that supports the Army acquisition process by evaluating potential health hazards during the design and development of materiel systems. Weapons emissions evaluated by the program include carbon monoxide (CO), hydrogen cyanide (HCN), oxides of nitrogen, sulfur dioxide, ammonia, and carbon dioxide. Typically, these chemicals are evaluated on an individual basis against their respective medical criteria that may include military-specific standards. However, additive or synergistic toxic effects among the chemicals must also be considered. Therefore, the Army is considering the simultaneous exposures of crew members in enclosed vehicles to CO and HCN generated from firing of conventional munitions from a 30-mm cannon.

Both CO and HCN are well known toxicants with established guidelines for safe levels of exposure. Adherence to these guidelines for either of these toxicants alone leads to engineering designs, administrative controls, and use of personal protective devices to ensure an acceptable working environment. However, safe levels of exposure to each of the toxicants may need to be lower if the combined effects of exposure are additive or more than additive. Hypothetically, the design requirements could be based upon the toxicologic mechanisms of CO and HCN being independent, additive, or synergistic. The three different scenarios would lead to differences in the resulting designs for ventilation systems, etc.

The potential for combined exposures results from firing of guns in enclosed (but ventilated) spaces in a military environment such as armored tanks. Because of concerns for the health effects of the personnel simultaneously exposed to HCN and CO, the U.S. Army's Center for Health Promotion and Preventive Medicine prepared a report titled *Assessment of Combined Health Effects of Hydrogen Cyanide and Carbon Monoxide at Low Levels for Military Occupational Exposures*. That report provides guidance to assess combined exposures in HHAs of military systems.

The weight of available evidence indicates that the toxic effects of inhaled CO and HCN at lethal and incapacitating levels are additive. Whether similar additive effects hold true at lower concentrations and longer time periods that military personnel may experience, while also in the presence of other combustion gases, is not known. No relevant chronic or low-level exposure studies were found in the literature. In 1981, a military standard established the Army's COHb limits of 5% for aviation crew members to protect against visual effects and 10% for all other military personnel. The exposure criterion for HCN is the current American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLC) ceiling of 4.7 ppm on the basis of anoxia, central-nervous-system, irritation, lung, and thyroid effects.

In addition to singular or individual evaluations of CO and HCN, the following hazard quotient (HQ) approach using singular benchmarks was employed in the Army's HHA report.

$$\frac{\text{COHb\%}}{10\%} + \frac{\text{15-min avg. HCN (ppm)}}{4.7\ \text{ppm}} = \text{HQ}.$$

It assumed the effects at low levels were additive. An HQ equal to or greater than 1.0 indicated an overexposure.

The Army used the following criteria to evaluate the data involving combined exposures to CO and HCN: if both or either of the 10% COHb and 4.7 ppm HCN limits is exceeded, then the scenario fails and the HQ calculation is essentially not applicable. If COHb and HCN are within acceptable limits, then the HQ calculation is performed.

In 2005, the Department of Defense requested that the National Research Council evaluate the Army's proposed guidance for assessing the adverse effects resulting from combined exposures to low-levels of HCN and CO, and recommend exposure limit guidelines for combined exposures to these chemicals. In response, the National Research Council convened the Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations with oversight from the Committee on Toxicology to address the task assigned to it.

The committee's Statement of Task is as follows:

> An ad hoc committee under the oversight of the standing Committee on Toxicology (COT) will assess potential toxic effects from combined exposures to low-levels of HCN and CO. In its first report (i.e., this report), the committee will evaluate the Army's proposed guidance on assessing combined exposures. The ad hoc committee will specifically determine the following in its initial report:
>
> 1. Does the hazard presented from combined exposure to HCN and CO at low levels warrant their combined assessment or is the individual assessment of each chemical sufficiently protective?
> 2. If the combined exposure assessment of HCN and CO is warranted at low levels, is the hazard quotient approach, discussed in the technical context section, a reasonable method of assessment? Should it be modified or improved (i.e., use of a blood CN benchmark instead of the ACGIH TLV-C)?
>
> In its second report, to be completed next year, the committee will determine the following:
>
> 1. Is the approach discussed in the technical context section appropriate or an alternative assessment method should be developed and validated through either field or laboratory study?
> 2. What improvements are needed in the Army's proposed methodology for assessing these combined exposures? The committee will also provide recommendations that will yield more precise measurements of gases which might be useful in hazard assessment.
> 3. What exposure limit guidelines are appropriate for combined exposures to these chemicals?

THE COMMITTEE'S MAJOR CONCLUSIONS AND RECOMMENDATIONS OF THE INITIAL REPORT

After receiving a briefing from the Army and evaluating published literature on the adverse effects of CO and HCN, both individually and in combination, in animals and in humans, the committee arrived at the following overall conclusions and recommendations for its initial report.

Conclusions

- Based on the mechanisms of action of toxicity of CO and HCN and the supporting literature, it is likely that the toxicities of these two chemicals are additive, and therefore, the hazard presented from combined exposures to these chemicals should be assessed as a mixture and not singularly or individually.
- The use of the HQ approach proposed by the Army is reasonable in establishing exposure limits for personnel simultaneously exposed to CO and HCN.
- CO is assessed as an individual chemical in HHAs using the Coburn-Forster-Kane (CFK) equation for predicting the percent of COHb in blood. The use of the CFK model for the prediction of COHb levels related to air concentrations of CO is justified. The CFK model has been validated; however it has not been tested in environments with dynamically changing air concentrations, such as in an armored vehicle.
- The use of an air concentration for HCN in the HQ equation, as opposed to a blood level, is reasonable.

Recommendations

- The Army should conduct further neurological studies on sensory and motor performance at lower concentrations of HCN and CO because most studies on the combined toxicity of CO and HCN have been carried out at high concentrations and have focused on lethality and/or incapacitation; this makes it difficult to use those data to extrapolate to low-levels of exposures and more subtle toxicity end points of interest to the Army. The committee recommends that the Army assess the validity of the CFK model in the context of armored vehicles both using instantaneous measured data and various running averages.
- While the toxicity of combined exposures to HCN and CO is important to understand, the Army should also consider concurrent exposures to other chemicals, e.g., other combustion gases, diesel exhaust, which may have additional effects on the tank crew.

1

Introduction

The U.S. Army's Center for Health Promotion and Preventive Medicine (CHPPM) evaluates health hazards of materiel systems and considers that information in the design and development of materiel systems. CHPPM evaluates weapons emissions, including carbon monoxide (CO), hydrogen cyanide (HCN), oxides of nitrogen (NO_X), sulfur dioxide (SO_2), ammonia (NH_3), and carbon dioxide (CO_2). Generally, these emission gases are evaluated on an individual basis. CHPPM also considers additive or synergistic toxic effects among the chemicals. The Army is specifically concerned about the combined exposures to low-levels of CO and HCN of crew members in an enclosed armored vehicles from the firing of 30 mm cannons.

The literature (Levin et al. 1987; Levin et al. 1988; Chaturvedi et al. 1995) indicates that the toxic effects of inhaled CO and HCN are additive at lethal and incapacitating levels. Whether similar additive effects hold true at the lower concentrations and for longer time periods (lasting from several weeks to several years in worst-case scenarios) that military personnel may experience, while also in the presence of other combustion gases, is not known. No relevant chronic or low-level exposure studies were found in the literature. CO is assessed as an individual chemical in HHAs using the Coburn-Forster-Kane (CFK) equation (Smith et al. 1996) for predicting the percent of carboxyhemoglobin (COHb) in blood. A 1981 military standard (DOD 1981) established the U.S. Army's COHb limits of 5% for aviation crew members to protect against visual effects and 10% for other effects. This level was considered to be a safe level for healthy young people and had previously been used by the American Conference of Governmental Industrial Hygienists (ACGIH) (Smith et al. 1996; DOD 1972). Adverse motor neuron effects such as decreased coordination, tracking, and driving ability, were not present when COHb was below 10% of hemoglobin (ACGIH 2002). The exposure criterion for HCN is the current ACGIH Threshold Limit Value (TLV) ceiling of 4.7 ppm to minimize the potential for headache; nausea; nasal, throat, and pulmonary irritation; and enlargement of the thyroid gland, which can result from low concentration exposure (ACGIH 2001).

The following hazard quotient (HQ) approach using the singular benchmarks was employed, which assumed the effects at low levels were additive. An HQ equal or greater than 1.0 indicated an overexposure.

$$\frac{\text{COHb\%}}{10\%} + \frac{\text{15-min avg. HCN (ppm)}}{4.7\ \text{ppm}} = \text{HQ}.$$

When evaluating an actual test scenario using the stream of test data, the COHb level was calculated at the end of each data interval (3 or 5 seconds) using the instantaneous CO level and the COHb concentration from the end of the previous interval. The 15-minute HCN average was a running average calculated at the end of each data interval.

The 15-minute HCN average concentration was used because HCN exposures were observed to be transient and to quickly clear after a round is fired. CO concentrations exhibit a spike when a round is fired and also quickly decline but will begin to accumulate in the blood of exposed subjects after several rounds.

In addition to evaluating test data, the Army also provides predictions for proposed training and operational scenarios. The predictions are used for adjusting the proposed training and operational scenarios. The predictions are used for adjusting the proposed firing rates and patterns to keep weapons emissions exposure below the desired levels or verifying the need for use of personnel protective equipment. The predictions are based on the worst-case CO exposure levels per round (expressed in ppm-minutes) from the proposed hatch position/ventilation configuration. The build-up and decay of COHb is calculated over the course of the scenario. The HQ is then calculated with the highest estimated COHb value and highest value of the 15-minute running HCN average from the relevant scenario.

In summary, the Army used three criteria to evaluate the data. If one or both of the 10% COHb and 4.7 ppm HCN limits is exceeded, then the scenario fails and the HQ calculation is essentially not applicable. If COHb and HCN are within acceptable limits, then the HQ calculation is performed as the third criterion. The method employed allowed the HQ results to be consistent with the singular results. Although the Army assumes a linear relation between biological effects and COHb and HCN concentrations that may not be true, it was successful in providing an additional degree of protection above the singular benchmarks.

In 2005, the Department of Defense requested that the National Research Council assess the Army's proposed guidance for assessing the adverse effects resulting from the combined simultaneous exposures to low-levels of CO and HCN. The potential for combined exposures results from routine firing of guns in enclosed but ventilated spaces in the military environment such as armored tanks. In response, the National Research Council convened the Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations under the oversight of the Committee on Toxicology to assess the Army's proposed guidance.

Both CO and HCN are well known intoxicants with established guidelines for safe levels of exposure. Adherence to these guidelines for either of these intoxicants alone would lead to engineering designs, administrative controls, and use of personal protective devices. These controls would ensure an acceptable working environment. Safe levels of exposure to each of the intoxicants may be lower if the combined effects of exposure are additive to more than additive. Hypothetically the design requirements could be predicated based upon the toxicological mechanisms of CO and HCN being independent, additive, or synergistic. The three different scenarios would lead to variation in the resulting designs for ventilation systems, etc.

The committee's Statement of Task is as follows:

> A committee of the National Academies' Committee on Toxicology will assess potential toxic effects from combined exposures to low-levels of CO and HCN and evaluate the Army's proposed guidance on assessing combined exposures in Health Hazard Assessments (HHAs) of military systems. The committee will specifically determine the following:
>
> - Does the hazard presented from combined exposure to HCN and CO at low levels warrant their combined assessment or is the individual assessment of each chemical sufficiently protective of health?
> - If the combined exposure assessment of HCN and CO is warranted at low levels, is the HQ approach, discussed in the technical context section, a reasonable method of assessment? Should it be modified or improved (i.e., use of a blood CN benchmark instead of the ACGIH TLV-C)?
> - Is the approach discussed in the technical context section appropriate or an alternative assessment method should be developed and validated through either field or laboratory study?

- The committee will also provide recommendations for making improvements in the Army's proposed methodology for assessing these combined exposures. The committee will also provide recommendations that will yield more precise measurements of gases which might be useful in hazard assessment.

THE COMMITTEE'S FIRST REPORT

The committee divided its work into two reports. In the first report due by September 2007, the committee considers whether the hazards presented from combined exposures at low levels warrant a combined assessment. The committee then considers whether the HQ approach is a reasonable approach to assessment of the combined exposures. The committee approached its task by reviewing the toxicity data on CO and HCN singularly and in combination. The committee also heard presentations from representatives of academe, EPA, and ATSDR. The committee relied primarily on published peer reviewed data.

THE COMMITTEE'S SECOND REPORT

In the second report, the committee will determine the following:

1. Is the approach discussed in the technical context section appropriate or an alternative assessment method should be developed and validated through either field or laboratory study?
2. What improvements are needed in the Army's proposed methodology for assessing these combined exposures? The committee will also provide recommendations that will yield more precise measurements of gases which might be useful in hazard assessment.
3. What exposure limit guidelines are appropriate for combined exposures to these chemicals?

2

Mechanisms of Carbon Monoxide and Hydrogen Cyanide Toxicity

The mechanisms of carbon monoxide (CO) and hydrogen cyanide (HCN) toxicity are reviewed in Chance (1965); Coburn et al. (1965); Wilson et al. (1972); Coburn and Forman (1987); and Lam and Wong (2000). CO binds to reduced hemoglobin with a much higher affinity (200 times greater) than does O_2. The formation of carboxyhemoglobin (COHb) results in a shift of the oxyhemoglobin (O_2Hb) dissociation curve (this plots increases in O_2Hb versus the partial pressure of O_2 [PO_2]), which inhibits delivery of O_2 from peripheral capillaries into tissues thus producing a decrease in the PO_2 inside cells (tissue hypoxia). Molecular O_2 has numerous functions in cells, but the major function is that it binds to the mitochondrial terminal cytochrome, cytochrome C oxidase (a complex that includes cytochrome a3), and accepts electrons that flow through a series of different cytochromes (electron chain transport) coupled to oxidative phosphorylations, formation of adenosine trisphosphate (energy formation) and oxidation of reduced compounds like nicotinamide adenine dinucleotide-reduced (NADH) which control the redox state. The cytoplasmic redox state is coupled to many cellular metabolic functions including acid formation (lactic acid). A COHb-evoked decrease in mitochondrial PO_2 below a threshold level limits or inhibits O_2 binding to cytochrome a3 and electron chain transport. Mechanisms of CO toxicity, therefore, include decreases in energy formation and changes in the redox state which results in cellular metabolic acidosis. CO also binds to reduced cytochrome a3, but the binding affinity is so low that this does not occur in intact humans or animals.

The Coburn-Forster-Kane (CFK) equation allows calculation of rates of pulmonary uptake resulting from increases in ambient PCO, and reversal when CO is removed from inspired air, as well as steady state COHb values. The major factors are alveolar ventilation, a term that defines rate of uptake from alveolar gas to pulmonary capillary blood (the pulmonary diffusing capacity). Because CO has a relatively low solubility in water and a low diffusion coefficient, uptake is limited by diffusion, a major reason for the slow uptake of inhaled CO. Following a sudden steady state increase or decrease in inhaled CO at a normal PO_2 and resting ventilation, it takes 4 to 5 hours to reach a steady state COHb. For an exercising human, CO uptake is increased and steady state COHb values are achieved more rapidly. Under conditions where CO exposures are rapidly changing, such as occurs in the enclosed environment of the tank cabin during gun firing, spike changes in CO concentration are buffered both by the high lung volume compared to tidal volumes, as well as the slow uptake into pulmonary capillary blood. Under conditions where ambient CO concentrations are changing rapidly, the use of the CFK equation to calculate COHb levels needs to be verified with blood COHb measurements. There is evidence for effects of small but biologically significant increases in COHb in the range of 5 to 10% saturation on human mental functions including automobile driving reflexes and visual function. In some animal experiments time-dependent tolerance to large increases in COHb occurred and it is possible that military personnel exposed to CO over several days or weeks might develop tolerance. There is evidence for tolerance to CO toxicity, and, of course, altitude hypoxia, so it is likely tolerance to CO would develop. There are no data, human or animal studies, on tolerance to small concentrations of HCN. Whether or not

tolerance is important during combined exposures of CO and HCN at concentrations found in the tank cabin should be given a high priority for future research.

HCN is a weak acid with a pka of 9.3; therefore at physiological pH ionization is minimal. Although HCN is a highly reactive compound and is known to form simple salts with alkali earth cations and ionic complexes of varying strengths with metal cations, the major mechanism of toxicity arises from its reversible binding to an iron containing heme group of cytochrome a3 with resulting inhibition of mitochondrial electron chain transport, decreased energy formation and changes in the cellular redox state producing metabolic acidosis. As with O_2, HCN binds to heme Fe^{2+} in reduced cytochrome a3. However, in the presence of O_2 when the iron in cytochrome a3 is rapidly oxidized, its affinity for binding of HCN increases markedly. Threshold HCN concentrations that inhibit mitochondrial electron chain transport are not known. Unlike CO, HCN does not induce tissue hypoxia defined as a decrease in tissue PO_2. Indeed, under conditions of HCN-evoked inhibition of O_2 consumption, tissue PO_2 must increase, explaining the known decrease of O_2 extraction from capillary blood during HCN poisoning. HCN is miscible with water and has a high effective "solubility" in body fluids and tissues. Thus, ambient HCN is absorbed via the skin as well as the lung. However, pulmonary uptake is most important. Pulmonary uptake is determined by ventilation and blood flow and its high effective solubility in blood. Since the kinetics of HCN uptake have not been accurately determined, our knowledge is based on a few measurements of blood HCN levels in animals and humans which suggest rapid uptake reaching steady state values in minutes rather than hours as occurs with CO. Because some HCN taken up in pulmonary capillary blood binds to methemoglobin (MetHb) forming cyanmethemoglobin, blood levels reflect the presence of MetHb as well as free HCN. Since MetHb content (usually only a few "percent" of total hemoglobin content) is variable in different humans, one can not precisely equate blood content to the partial pressure of HCN which determines peripheral tissue HCN concentrations and should most closely relate to the toxicity of this gas. HCN is rapidly metabolized via several pathways, the most important being the irreversible reaction of HCN with thiosulphate to form thiocyanate. Thiocyanate is then rapidly excreted in urine. Thiocyanate itself has tissue toxicity. The relatively small "percent" of body HCN excreted via the lungs indicates a very low partial pressure of this gas in pulmonary capillary blood and that most absorbed HCN is bound. After humans suffered from smoke inhalation, half of the peak HCN content in blood was lost over 20 to 60 minutes. Unlike the case for CO toxicity there are no reports that relate small HCN exposures, such as measured in tank cabins, to human abilities.

The apparent additivity of CO and HCN toxicity is explained by CO binding to hemoglobin evoking tissue hypoxia plus HCN binding to both reduced and oxidized cytochrome a3. There are possible interactions that occur during combined CO and HCN poisoning which influence their apparent additivity: (a) Does the presence of one of the gases influence pulmonary uptake of the other gas? In animal experiments large concentrations of HCN stimulated carotid body-driven ventilation which would increase uptake of CO. There is evidence that CO, as well, may stimulate the carotid body. (b) Since HCN-evoked inhibition of mitochondrial O_2 consumption results in increases in tissue and mitochondrial PO_2, HCN might blunt effects of concomitant CO poisoning which operates by evoking decreases in tissue PO_2.

RECOMMENDATIONS

Tests should be conducted to determine blood COHb and air CO concentrations before and after multiple test firings over several days; pre- and concurrent-exposure to CO from other sources such as smoking and engine exhaust, should be considered in evaluating test exposures. There is evidence for tolerance to CO toxicity, and, of course, altitude hypoxia, so it is likely tolerance to CO would develop. There are no data, human or animal studies, on tolerance to small concentrations of HCN. Whether or not tolerance is important during combined exposures of CO and HCN at concentrations found in the tank cabin should be given a high priority for future research.

3

A Brief Review of Hydrogen Cyanide and Carbon Monoxide Toxicity

Data on sublethal exposures and time to incapacitation for HCN and CO gases alone and combined are available for experimental animals and humans. However, data addressing subtle differences (e.g. attention deficits, decreases in hand and eye coordination, and decreases in fine movements) in performance, relevant to setting guidelines for human exposure, are sparse. For HCN, inhalation toxicity studies that involve human exposures are old, often anecdotal, and lack analytically measured concentrations. Human exposures with measured concentrations are limited to occupational reports, but these studies lack correlation between exposure concentrations and symptoms. Animal studies were generally conducted at high concentrations and also lack good dose-response information (Lam and Wong 2000; NRC 2002). Few studies measured cyanide concentration in the blood.

Concentrations of CO that produce incapacitation are extremely high, and it is difficult to correlate exposure concentrations with COHb formation. Data for combined exposure to HCN-CO involve laboratory animal studies and were generally conducted at high concentrations, i.e., concentrations that produce incapacitation or death. Recent inhalation studies, considered relevant to setting human exposure guidelines for military unique occupational exposures, i.e., performance degradation rather than incapacitation or death, are reviewed below.

HYDROGEN CYANIDE

Selected occupational monitoring studies show that exposures have been to concentrations up to an average of 10 ppm (Hardy et al. 1950; Maehly and Swensson 1970; El Ghawabi et al. 1975). Although many of these studies did not address health effects, symptoms that were reported appeared attributable to the long-term effect of cyanide on the thyroid gland. In animal studies, times to incapacitation for the monkey ranged from 8 to 19 minutes at concentrations of 156 to 100 ppm, respectively (Purser et al. 1984). A concentration of 60 ppm for 30 minutes had only a non-biologically significant depressive effect on the central nervous system of monkeys (Purser 1984). For the rat, incapacitation (EC_{50} for loss of righting reflex) occurred at 10 minutes at an exposure concentration of 170 ppm (Levin et al. 1987) and, in another study, at 5 minutes at 184 ppm and at 35 minutes at 64 ppm (Chaturvedi et al. 1995; see also Crane et al. 1989; Sanders et al. 1994). Respective blood cyanide concentrations in the Chaturvedi et al. (1995) study were 2.3 and 4.2 µg/mL. In a third study, incapacitation of rats exposed to 95 ppm HCN occurred at 44 minutes (Hartzell et al. 1985a,b). Lethal (LC_{50}) values in the rat range from approximately 500 ppm for a 5-minute exposure to 100-140 ppm for a 60-minute exposure (NRC 2002).

There are studies that show that HCN can be absorbed through the skin, with effects up to and including lethality. For that reason, the ACGIH has used a skin notation since 1961, stating that a significant fraction of the total absorbed dose of HCN can occur via this route to produce systemic effects. However, the committee concludes that exposure from this route of exposure is not likely to be significant

so as to be considered in the development of allowable concentrations used in the hazard index calculation.

Guidelines for human exposure to HCN have been developed by several agencies. Following a review of the literature on occupational exposures, a National Research Council Subcommittee concluded that a 1-hour exposure to HCN at 8 ppm should cause no more than mild headache in healthy adults (Lam and Wong 2000). The American Conference of Governmental Industrial Hygienists Ceiling value, a concentration that should not be exceeded during any part of a working exposure, is 4.7 ppm (ACGIH 1996). The National Institute for Occupational Safety and Health (NIOSH) short-term exposure limit is also 4.7 ppm, and the Immediately Dangerous to Life and Health (IDLH), a 30-minute exposure, is 50 ppm (NIOSH 2005). The Occupational Safety and Health Administration Permissible Exposure Limit (OSHA) is 10 ppm (NIOSH 2005). A guideline value considered safe for the general public includes the 1-hour Acute Exposure Guideline Level-1 (AEGL-1) of 2.0 ppm (NRC 2002).

CARBON MONOXIDE

Data on correlations between exposure concentrations and levels of blood COHb are lacking. A number of sources including Coburn and Forman (1987), WHO (1999), and EPA 2005 reviewed COHb levels in the blood of smokers and symptoms in healthy adults associated with COHb levels in the blood. A physiologic background concentration of 0.5-0.8% is due to endogenous formation. A concentration of 5% COHb may be found in one pack/day smokers, and concentrations of 10-15% in two and three pack/day smokers. Up to 10% COHb has no appreciable effect except shortness of breath on vigorous exertion. Concentrations of 10-20% may result in symptoms such as headache. As concentrations of COHb increase from 30 to 70%, successive symptoms reported are headache, fatigue, dizziness, confusion, unconsciousness, and possibly death. A concentration of 80% COHb is rapidly fatal. Clinical studies with humans indicate that a COHb of about 34-56% are not lethal in healthy adults EPA 2005. CO levels in homes are usually lower than 9 ppm, but may range up to 30 ppm in homes with wood stoves. Levels inside motor vehicles are generally around 9-25 ppm, but may range up to 35 ppm EPA 2005.

In a study with cynomolgus monkeys exposed to 900 ppm CO, no signs of intoxication occurred during the first 20-25 minutes (corresponding to COHb of about 16-21%) (Purser and Berrill 1983). At 25 minutes, the animals' performance in a behavioral test was significantly decreased. At 30 minutes the monkeys were lying down. In rodent studies, incapacitation in rats exposed to CO occurred at 5 and 35 minutes at concentrations of 5706 and 1902 ppm, respectively. Blood COHb values were 81 and 71%, respectively (Chaturvedi et al. 1995). Hartzell et al. (1985a,b) reported a higher value, incapacitation at 8000 ppm at 5.1 minutes. Blood levels were not reported. Lethal (LC_{50}) data in the rat ranges from a 5-minute value of 10,000-14,000 ppm to a 60-minute value of approximately 4000 ppm EPA 2005.

Guidelines for human exposure to carbon monoxide include the following: ACGIH 8-hour TLV-TWA of 25 ppm; NIOSH 8-hour TWA of 35 ppm and IDLH of 1200 ppm; OSHA PEL of 50 ppm; 1-hour Emergency Response Planning Guidelines (ERPG-1) of 200 ppm; and the NRC Emergency Exposure 1-hour Guidance Level of 400 ppm.

4

Summary of the Effects of Combined Exposure to Carbon Monoxide and Hydrogen Cyanide and Recommendation for Combined-Exposure Risk Assessment

As discussed previously, certain Army operations such as firing ammunition generate toxic gases. In a confined environment, exposure of Army personnel to these gases could pose a health concern. CO and HCN are the toxic gases of major concern, but analyses show that the time-weight-average concentrations of these two gases are low and generally do not exceed OSHA's permissible exposure limit or ACGIH's Threshold Limit Value for these two gases (Bazar 2006). However, since both compounds can induce hypoxia in tissue and the primary targets are the brain and the heart (Pitt et al. 1979), the U.S. Army is concerned about the potential for the combined effects of exposures to low concentrations of these gases to produce performance decrements. The present assessment of the toxicity of CO + HCN co-exposures could provide a guideline to the Army for evaluating the hazard of exposures in a confined environment and implementing mitigation procedures.

CO and HCN are two of the toxic gases of major concern produced in fires and other combustion events (Esposito and Alarie 1988, Sanders et al. 1994). Smoke can kill victims outright or produce physical incapacitation. Postmortem analyses of blood samples collected from victims revealed that in some victims, inhalation of either CO or HCN could not have been the sole cause of death (Esposito and Alarie 1988). The effects of combined exposure to CO and HCN have been subjected to intensive investigation. Investigations have centered on lethality or incapacitation, and these were assessed by exposing animals simultaneously to both gases at concentrations below their individual effect levels (at concentrations of CO and HCN, which produce no effects), or by studying the shortening of time to death (Td) or incapacitation (Ti) when animals were exposed to the effect levels of both gases. The biological interaction of combined exposure to CO and HCN can be studied by investigating the fractional effective concentrations (FECs) of the two compounds (Crane et al. 1989). If the sum ($\sum$FEC) is equal or close to 1, the combined effects are said to be additive; if the sum is greater than 1, the effects are said to be synergistic; if the sum is less than 1, the effects are said to be antagonistic or less than additive, or to have no interaction (Crane et al. 1989).

The results of examining the CO + HCN interaction in a very large rodent study conducted by the National Bureau of Standards (NBS) under the sponsorship of the U.S. Army Medical Research Institute led the investigators to conclude that the lethal effects of combined exposure were additive (Levin et al. 1987, 1988). These results were consistent with the conclusions of earlier NBS studies (Levin et al. 1988). In a study similar to the NBS investigations, Esposito and Alarie (1988) also demonstrated that the combined lethal effects of CO + HCN were additive. Additive effects were also observed by Lynch (1975) and Kaplan (1988) in animals exposed to CO + HCN. Instead of testing the combined effects by exposing animals to predetermined durations (T) and gaseous concentrations (C), Yamamoto and

Kuwahara (1981) exposed rats to various combinations of CO and HCN concentrations and recorded the C x T values when animal deaths occurred; the results also led these authors to conclude that the combined effects were additive.

Several studies were carried out by the Civil Aerospace Medical Institute (CAMI) of the Federal Aviation Administration (Oklahoma City, OK); Sanders et al. (1994) and Chaturvedi et al. (1995) reported that the Ti for combined CO + HCN exposure in rodents was shortened compared with the Ti for individual gas exposures; these observations led the authors to conclude that the combined effects were additive. The results of an earlier study conducted at CAMI led Smith et al. (1974) to come to the same conclusion.

Higgins et al. (1971) observed no additive toxicity in animals exposed to CO followed by HCN. However, additive lethal effects might not have been detected because of the great variation in the data points; the large confidence limits may have prevented detection of the combined biological effects of CO + HCN.

Moore's group concluded that the combined lethal effects in CO-exposed mice given lethal doses of cyanide salt by intraperitoneal injection were synergistic (Norris et al. 1986). However, the fact that the two compounds were given by different routes, resulting in different toxicokinetics, coupled with the fact that the data were not rigidly analyzed. A similar study by Moore's group examining biochemical variables in blood showed that some results were additive and others were synergistic (Moore et al. 1991). Pitt et al. (1979) studied effects of CO and cyanide on cerebral blood flow (CBF) and oxygen consumption in anesthetized and CO-exposed dogs, to which cyanide was given by slow intravenous infusion. The exposure concentrations were comparable to those that produce physical incapacitation. These authors concluded that the combined effects of co-exposure on CBF and cerebral conductance were additive.

The weight of evidence on combined exposures to CO and HCN supports the conclusion that the effects of these toxic gases are additive. However, the exposure concentrations that were used to investigate the combined effects were high in efforts to observe lethality or physical incapacitation. As pointed out above, the U.S. Army is concerned about the potential for the combined effects of exposures to low concentrations of these gases to produce performance decrements. In assessing the toxicity of these two compounds, it is prudent to expect that the additive effects of combined exposure observed with high concentrations would occur in subjects exposed to low concentrations. The hazard quotient or hazard index should be used for calculating the risk of the CO+HCN combined exposures.

$$\text{Hazard Quotient or Hazard Index} = \frac{[CO]exp}{[CO]al} + \frac{[HCN]exp}{[HCN]al}.$$

where [CO]exp and [HCN]exp are exposure concentrations, and [CO]al and [HCN]al are allowable concentrations.

For the blood, COHb% and the 15-min average [HCN] are the variables measured and 10% COHb and 4.7 ppm HCN are the Army's current allowable values, and the equation becomes

$$\text{Hazard Quotient} = \frac{\text{COHb\%}}{10\%} + \frac{\text{15 min avg. HCN (ppm)}}{4.7 \text{ ppm}}.$$

The appropriateness of the Army's current level of 10% for CoHb and 4.7 ppm for HCN will be evaluated in the committee's final report, which is likely to be finalized in September 2008.

5

Pharmacokinetics and Mathematical Modeling for Assessing Toxicity of Mixtures of Chemicals

Several approaches exist that could be used to evaluate the hazard presented by co-exposure to CO and HCN. It is commonly believed that the chemicals act independently if exposure to Chemical B does not change the severity of the toxic response to a given exposure to Chemical A. This is normally the case if the two chemicals cause their respective toxicities following entirely unrelated modes of action, the physiological, biochemical, or other series of processes that cumulatively cause toxic responses. When the modes of action share common elements, potential for non-independence in the combined dose response curve exists. Where this occurs, the non-independence can take a form of sub-additive, additive, or super-additive (also sometimes called synergistic effects). An additive response generally occurs when the dose response curves to the individual chemicals are parallel and can be added together to predict the combined response. A sub-additive response occurs when the combined response is somewhat less than expected through simple addition but greater than the response expected from either chemical alone. The super-additive response occurs when the combined response is greater than simple addition of the individual responses occurs. Mathematical approaches have been developed for these respective approaches; however, the choice of which approach to use is driven by the review of literature indicating which mode of interaction occurs.

As reviewed earlier in this report, there are several studies that indicate that high doses of HCN and CO may exert additive toxic responses. The underlying mode of action for toxicity of CO and HCN share some common elements; therefore, additive responses are plausible. Few reports suggested super-additive, sub-additive, or independent responses. However, these toxicity studies conducted were generally at very high exposure levels and extrapolation to relatively low levels is required. It is uncertain whether the response to the mixture would be additive at the levels germane to the assessment of combined exposures at low levels. For pharmacokinetic as well as pharmacodynamic reasons, potential for super-additive responses for any mixture is more likely as dose increases; thus, when additive responses may exist at high dose, it is unlikely that super-additive responses would occur in the range of extrapolation. The possibility that independence or sub-additive responses may occur cannot be discounted. However, in light of the weak database of relevant studies, the committee agrees that assuming an additive response is the most reasonable approach.

While other mathematical approaches may exist, by far the most common approach for assessing the combined hazard to chemical mixtures is the "hazard quotient" (HQ), which is also called the "hazard index" (HI) This approach is endorsed for use in applications such as this application by the U.S. Environmental Protection Agency (EPA 2000), American Conference of Governmental Industrial Hygienists (ACGIH 2006), the U.S. Occupational Safety and Health Administration (29 CFR 1910.1000 [2007]), and the Agency for Toxic Substances and Disease Registry (ATSDR 2004). EPA recommends the HQ for mixtures where toxicity is dose additive, which is consistent with the current hazard evaluation. Specifically**,** EPA (2000) defines a HI for the assessment of combined exposure to components of a mixture as the sum of quotients of exposure to each component divided by the Acceptable Level for that chemical. The generic formula for the HI is:

$$HI = \sum_{i=1}^{n} \frac{E_i}{AL_i}$$

where HI = hazard index, E = exposure level to component i, and AL = acceptable level to component i.

If the HI exceeds 1.0, overexposure is indicated. ACGIH, OSHA and ATSDR's formulations are mathematically identical. The assumption that underlies the validity of the use of this model is that the shapes of the dose response curves (or more precisely, the exposure-response curves) are similar.

One unique aspect of the Army's proposed implementation of the HQ is the use of an internal measure of dose (COHb) with an external measure of dose (HCN in air). However, as COHb is a measure of dose rather than response, the combination of an internal and external measure of dose appears to be consistent with EPA guidance.

The Army proposes using the Coburn-Foster-Kane (CFK) equation to calculate carboxyhemoglobin (COHb) levels from CO air data that can be measured in real-time. The real time monitoring of CO provides an exceptional ability to observe the pulsitile spikes (seconds) in the ambient air in the armored vehicle after the cannon is fired. The changes in COHb are much slower, on the order of minutes to a few hours. Factors controlling the rate of change of CO binding to hemoglobin are CO concentration in the air, breathing rate (workload), and the diffusion rate of CO into lung blood. The CFK model has been validated, but as with any model, is not always accurate and typically has not been tested in environments such as in armored vehicles where the air concentration changes dynamically. Due to the fact that COHb changes over a slower time course than air concentrations, use of a running fifteen minute average for air CO would likely be more appropriate although has not been thoroughly analyzed. The committee recommends that the Army assess the validity of the CFK in the context of armored vehicles both using instantaneous measured data and various running averages. This should take into account the typical firing intervals, including the rapid firing sequences and the sequences of infrequent firing that are representative of actual conditions. After firing a round, the gases are at a peak and decline in concentration due to ventilation. When rounds are fired more frequently, exposures increase in parallel. Thus, the exposure is rarely if at all at steady state, and almost always subject to short peaks and declining levels. The ability of the exposure assessment strategy to detect a potential overexposure will therefore depend in large part on the appropriate selection of an averaging interval. The use of running averages for HCN exposure assessment copes with this difficulty by ensuring that a short peak exposure is not missed, i.e., selection of start and stop times for averaging are essentially moot since every configuration is calculated. The use of the internal measure of dose, via the CFK equation's calculation of % COHb likewise copes with the highly intermittent exposure by calculating an integrated measure of dose through the biomarker, wherein the biological process serves as the means of integration.

An alternate to mathematical models such as the HQ is the use of physiologically based pharmacokinetic (PBPK) modeling. PBPK has been used to understand interactions between individual chemicals found in a chemical mixture once the chemical mixture has entered the body of laboratory animals or humans. Inhaled solvents have received the greatest attention with PBPK modeling. Solvent toxicity of a chemical mixture such as central nervous system effects may be governed by the brain: blood partition coefficient for each chemical, while other toxicities are mediated by the formation of reactive metabolites. The use of PBPK models to predict the metabolic clearance of solvent mixtures from the body has received the greatest attention (Haddad et al. 2001) by quantitatively describing the competitive metabolism of each solvent by the same enzymatic system (e.g., P450 isoforms). The impact of solvent mixtures on individual solvent pharmacokinetics is governed by the exposure level of each solvent in the solvent mixture, chemical specific properties of each solvent such as its affinity for the metabolizing enzyme and thermodynamic properties (blood: air and tissue: blood partition coefficients).

While a PBPK model has addressed CO as a byproduct of solvent metabolism, currently there are no PBPK models for CO and HCN mixtures. In the case of CO and HCN, a computational research effort designed to understand possible mechanistic interactions (hypothesis generation) between CO and HCN is warranted.

The Army reports that exposures to HCN appear to be low most of the time such that HCN may not contribute substantially to the HQ calculation for HCN and CO. By implication, if this is true, then HCN exposures may not warrant assessment. In practice if a chemical is 5% or less of occupational exposure limit as a maximum exposure, the chemical may be considered as minor contributor to the toxicity of a mixture of chemicals. In the current assessment, it is not clear that HCN exposure is low enough to warrant the elimination of monitoring activities, and as long as HCN is monitored, it should be included in the HQ calculation.

6

Appropriateness of Measurement of Blood or Air Levels of Cyanide

The question has been asked if blood cyanide levels would be a more appropriate biomarker of toxicity risk than ambient air cyanide levels. It should first be noted that there is little human data for non-lethal endpoints with good measurements of either air or blood levels (reviewed in ATSDR 2006; NRC 2002). Most of the data on these gases are old and based on chronic occupational exposures to low levels of airborne hydrogen cyanide. In most of these reports symptoms were either absent or minor in nature. There are considerable data on blood cyanide levels in lethalities, primarily from fire victims where carbon monoxide was also present. Most authorities conclude that whole blood cyanide levels >1 mg/L may cause major symptoms or lethality, although reported levels in deaths have ranged from 0.4 to 230 mg/L (Rehling 1967). In summary, there is not good human data relating either blood levels or air levels to relevant endpoints of interest in the present situation.

That said there appear to be several reasons to think that measurement of air levels is a better benchmark to use in assessing the combined toxicity of cyanide and carbon monoxide in a hazard quotient model. First, measurement of hydrogen cyanide in air can apparently be done in real time as judged by the data presented by the military. There are no reported rapid or simple methods for the determination of cyanide in biological fluids (ATSDR 2006). Second, using blood cyanide levels as a biological marker for sub-lethal effects is complicated by the rapid metabolism of cyanide in vivo. The initial half-life of cyanide in humans is estimated to be 20-60 minutes (ATSDR 2006). When levels are very high, as in potentially lethal exposures, there is an initial rapid decline followed by a slow terminal elimination with half-lives ranging from 19-66 hours for the terminal phase (ATSDR 2006). Thus timing of blood sampling would be crucial in interpreting the results. Cyanide undergoes first pass metabolism that further complicates the interpretation of blood levels. Third, there is a problem with which blood fraction to use in analysis. Whole blood (WB) samples are more stable than plasma or serum samples, where there can be a significant decline in cyanide levels in stored samples over a period of hours (Alarie 2002; Ballantyne 1976). In WB most cyanide resides within the red blood cell. Thus WB levels may be a poorer marker of toxicity if obtained before equilibrium has been reached between the plasma cyanide and red blood cell cyanide (Alarie 2002). Plasma cyanide levels appear to correlate better with clinical effects, but suffer from the stability problem, even if stored at appropriate temperature. In any case virtually all authorities recommend that cyanide levels be measured as soon as possible after collection in order to avoid declining values. This would create a significant logistical problem if blood levels were to be used as the biomarker.

Finally it should be noted that factors other than acute environmental exposure may influence cyanide levels measured in blood. The most important of these is smoking history. There are numerous reports in the literature documenting variable increases in cyanide in blood as a result of smoking (Cailleux et al. 1988). There are also reports of increased blood cyanide levels in some populations whose diet includes large proportions of certain cyanogenic foods (Mlingi et al. 1992).

In summary, there seems to be no compelling reason why blood measurements of cyanide would be a better predictor of toxicity than measurement of ambient air levels. The added difficulties associated with the measurement and interpretation of blood cyanide levels would suggest that this measurement should not be selected as a routine monitoring methodology.

7

Conclusions and Recommendations

In requesting that this project be carried out, the major concern of the army is the health of personnel during certain military operations, particularly the firing of guns in tanks which can result in the generation of toxic gases. The most relevant of these are carbon monoxide (CO) and hydrogen cyanide (HCN). The questions being asked are whether the adverse effects of these chemicals are additive or synergistic in nature and whether an assessment of their combined risk can be calculated using the hazard quotient approach (HQ) with the equation:

$$HQ = \frac{COHb\%}{10\%} + \frac{\text{15 min avg. HCN (ppm)}}{4.7 \text{ ppm}} .$$

If so, this approach would be used to establish limits of exposure for these personnel; that would be important in the design and operation of the tanks.

As noted above, the mechanisms by which CO and HCN exert their toxic effects are multiple, have been well studied as individual agents, and continue to be investigated. While their exact mechanisms and characteristics for absorption, distribution, metabolism and excretion may be different, nevertheless, it is not unreasonable to suspect that the effects of these two chemicals on oxygen delivery and utilization would have an additive effect.

Based on the extensive review of the literature of studies in animals on this interaction, the committee concluded based on the weight of evidence that the effects of the two chemicals were additive. The committee recommends that the hazard quotient approach be utilized. However, one of the limitations in making this conclusion is that most of the studies were carried out in animals using high levels of cyanide, which were greater than 100 ppm or high levels of CO that were in the range of one to several thousand parts per million compared with low levels of interest with cyanide at less than 5 ppm or CO at less than 100 ppm and extreme end points, such as incapacitation or death. Thus there needs to be a caveat in the extrapolation of these results to low levels of exposure (less than 5 ppm for HCN and less than 100 ppm for CO) and more subtle effects such as decrements in performance of the tank crew. While a theoretical case could be made perhaps for a less than additive effect based on, for example, changes in respiration and gas uptake, the committee believes that it is prudent to expect that the additive effect of the combined exposure observed with high concentrations would occur if subjects were exposed to low concentrations (less than 4 ppm for HCN and concentrations of CO producing carboxyhemoglobin [COHb] levels of 10%).

While there have been a number of reports on the interaction of cyanide and CO and the potential interaction has been well recognized in respect to fires, the human literature is not helpful in defining adverse blood levels of cyanide alone or in combination with CO. In most cases, either the exposures were very high and/or the measurements of exposure, particularly cyanide, were questionable. It is difficult to find studies which carefully correlated exposures, blood levels and adverse effects. Furthermore, available studies do not address subtle effects, such as decrements in performance, relevant to setting guidelines for human exposure. While guidelines for limiting exposure to CO and cyanide have

been published by governmental and professional groups, they have the same limited databases, especially for the interaction.

As noted, since the actions of the two toxicants apparently are additive, the use of the hazard quotient approach proposed by the army is appropriate. The use of the Coburn-Foster-Kane (CFK) model for the prediction of COHb levels related to air concentrations appears to have a solid scientific basis. Since the spikes observed in air levels of CO within the tank during firing scenarios were of such short duration taking into account respiratory rate and tidal volume, the committee concluded that it was not overly concerned about them in comparison with longer, possibly increasing, COHb levels. However, because of conditions where ambient CO concentrations are changing rapidly, it is recommended that the use of CFK equation to calculate COHb levels needs to be verified with blood COHb measurements. It was also noted by the Army that their monitoring data from gun firing scenarios would suggest that cyanide levels would be expected to be below levels of concern most of the time. That, is they would normally not be expected to add substantially to the hazard quotient.

An ancillary question was whether or not the blood level of cyanide, rather than air exposure, should be used in the hazard quotient calculation. The committee concluded that use of a blood level would be problematical based on the lack of good data to support a model such as the CFK model for CO. Furthermore, there is no simple method for determining cyanide levels in blood, and there are a number of technical difficulties in obtaining and handling blood samples. In addition, the rapid metabolism of cyanide makes correlation of air levels and blood levels difficult. Finally there are a host of confounding environmental factors which may influence cyanide levels. The committee, therefore, recommends that the Army continue to use the air level for cyanide rather then a blood level.

Because most studies on the combined toxicity of CO and HCN have been carried out at high concentrations and have focused on lethality and/or incapacitation, which makes extrapolation to the low-levels of exposure and more subtle toxicity end points of interest to the Army is difficult. Therefore, the Army should conduct neurological studies of sensory and motor performance at lower concentrations of HCN and CO.

In conducting its review and evaluation, the committee provides the following additional recommendations for the army to consider. One is to search relevant military documents regarding exposure and biological monitoring that may not be in the open, published literature, especially with regard to cyanide levels. A second is that the Army should consider that, while the binary system is important, other potential exposures such as exposure to diesel combustion products may need to be considered with respect to health of the tank crew.

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Appendix

Biographical Information on the Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations

William E. Halperin is professor and chairman of the Department of Preventive Medicine and Community Health at the UMDNJ New Jersey Medical School. He received his M.D., M.P.H., and Dr.P.H. from Harvard University. Previously, Dr. Halperin was deputy director of the National Institute for Occupational Safety and Health. His research interests are in occupational medicine, occupational epidemiology, and public health surveillance. Dr. Halperin was a member of the NRC Committee on Risk Assessment Methodology, and served as a member of the Committee on Toxicology's Subcommittee on Spacecraft Water Exposure Guidelines, Subcommittee on Ethylene Oxide, and Subcommittee on Jet Fuels, Panel on Emergency Exposure Guidance Levels. He also served as a member of the IOM Committee to Survey the Health Effects of Mustard Gas and Lewisite. Dr Halperin is certified by the American Board of Preventive Medicine and the American Board of Occupational Medicine. He is currently the chair of the NRC Committee on Toxicology.

Gary P. Carlson is professor of toxicology and associate head of the School of Health Sciences at Purdue University. He received his Ph.D. in pharmacology from the University of Chicago. He was chairman of the NRC Subcommittee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents. He is currently serving on the NRC's Committee on Toxicology. He is chairman of the Society of Toxicology's Board on Publications, and previously served as chairman of its Education Committee. Dr. Carlson is currently the secretary of the Society of Toxicology. He has served on EPA's Joint Advisory Board/Science Advisory Panel Committees on (1) Cholinesterase Inhibition and (2) Cholinesterase and Aldicarb and on the EPA Science Advisory Board's Panel on Drinking Water. Dr. Carlson has also served on the board of scientific counselors of the National Toxicology Program (NTP), and as chair of the NTP Technical Reports Review Committee. He is an associate editor of the Journal of Toxicology and Environmental Health and serves on the editorial board of the Journal of Toxicology.

Ronald F. Coburn is professor of physiology at the University of Pennsylvania. He received his M.D. from North Western University in 1957. He has done extensive research on carbon monoxide. He was the chairman of the Panel on Carbon Monoxide from 1972-1975. He received the N.I.H. merit award in 1997. He previously served on the NRC Committee on Medical and Biological Effects of Air Pollutants (1972-1976). Dr. Coburn is on the editorial boards of American Journal of Physiology, Journal of Applied Physiology, Pulmonary Pharmacology, and Lung.

James E. Dennison is a Certified Industrial Hygienist and owner of Century Environmental Hygiene LLC, Fort Collins, CO. Dr. Dennison received his Ph.D. in Environmental Health Toxicology from Colorado State University. His doctoral thesis involved physiologically-based pharmacokinetic modeling (PBPK) of complex mixtures of gasoline in rats. He has worked with the National Advisory Committee on Acute Exposure Guideline Levels (AEGLs) committee performing PBPK modeling of CNS

depressants to help establish AEGL values for several chemicals. He performs consulting work as a Certified Industrial Hygienist providing advice on testing, evaluation, and control of chemical agents such as heavy metals, solvents, pesticides, and biological materials. He currently serves as the vice chair of the Biological Monitoring Committee of the American Industrial Hygiene Association.

Jeffrey W. Fisher is a Professor in the Department of Environmental Health Science, College of Public Health at the University of Georgia (UGA). He joined the University of Georgia in 2000 and served as Department Head of the Department of Environmental Health Science from 2000 to 2006. He now serves as Director of the Interdisciplinary Toxicology Program at UGA. He spent most of his career at the Toxicology Laboratory, Wright Patterson AFB, where he was Principal Investigator and Senior Scientist in the Toxics Hazards Division and Technical Advisor for the Operational Toxicology Branch. Dr. Fisher research interests are in the development and application of biologically based mathematical models to ascertain health risks from environmental and occupational chemical exposures. Dr. Fisher's modeling experience includes working with chlorinated and non-chlorinated solvents, fuels, PCB, pyrethroids and perchlorate. Dr. Fisher has published over 100 papers on pharmacokinetics and PBPK modeling in laboratory animals and humans. He has served on several panels and advisory boards for the DoD, ATSDR, USEPA and non-profit organizations. He is a member of the National Academy of Sciences subcommittee on Acute Exposure Guideline Levels (2004-present) and is a Fellow of the Academy of Toxicological Sciences.

James J. McGrath is professor emeritus at Texas Tech University Health Sciences Center, Lubbock, TX. He received his Ph.D. from Indiana University in 1968. Dr. McGrath served at EPA's Office of Risk Assessment and was awarded a Silver Star in recognition of work in evaluating the world's health and toxicology literature for relevancy to standard setting for diesel exhausts and worked on Air Quality Criteria for Carbon Monoxide, and also served as a consultant for Indoor Air Quality for the EPA's new campus. He served as a principal author for the EPA's Air Quality Criteria for Particulate Matter for several chapters. He is serving (or has served) on the editorial boards of American Journal of Physiology, Science, Molecular Pharmacology, Journal of Applied Toxicology, Journal of Toxicology and Environmental Health, Toxicology Letters, and CRC Press. He has served on the Society of Toxicology's Inhalation Toxicology specialty section.

Chiu-Wing Lam is a senior toxicologist at Wyle Laboratories in Houston, TX. He received his Ph.D. in toxicology from the University of Rochester in 1983. He is a diplomate of the American Board of Toxicology. He has drafted numerous toxicological risk assessment documents on spacecraft maximum allowable concentrations (SMACs) since 1990. The SMAC values (for time durations ranging from 1 hr to 180 days) are valuable guidelines to NASA for their space station and space shuttle documents. He also drafted the hydrogen cyanide SMAC document. Dr. Lam has conducted numerous toxicological assessments of payload and utility chemicals used in Space Shuttle and Space Station, providing consultations to NASA flight surgeons, safety engineers, and payload customers on toxicological issues.

George C. Rodgers is professor of pediatrics at the University of Louisville, Kentucky. He received his Ph.D. in 1964 from Yale University and received his M.D. in 1975 from the State University of New York, Syracuse. He is board certified in pediatrics and medical technology. He is a member of the National Advisory Committee on Acute Exposure Guideline Levels; he was the chemical manager for the carbon monoxide AEGLs document that was reviewed by the NRC. He also served on the American Society of Safety Engineers, Z390: Accredited Standards Committee on Hydrogen Sulfide Safety Training. He is a fellow of the American College of Medical Toxicology. He is on the editorial board of Poisindex. He was a member of the Firefigthers Safety Act Technical Committee. He was president of the American Association of Poison Control Centers. He has served on committees of governmental agencies, such as EPA, ATSDR, and CDC.

Sylvia Talmage is a senior toxicologist at Summitec Corporation, a contractor for Oak Ridge National Laboratory. She received her Ph.D. from the University of Tennessee. She is a diplomate of the American College of Toxicology. She served on the NRC Subcommittee for the Review of the Risk Assessment of Methyl Bromide. She previously served for 26 years at Oak Ridge National Laboratory, where she performed numerous toxicological risk assessments for hazardous chemicals. She is the author of numerous acute exposure guideline level (AEGL) documents that were reviewed by the NRC. She also drafted the hydrogen cyanide AEGL document. She has also provided advice to EPA and the U.S. Army on matters related to toxicology and risk assessment.