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

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COMBINED EXPOSURES

TO HYDROGEN CYANIDE AND CARBON MONOXIDE IN ARMY OPERATIONS: FINAL 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 U.S. Army's health hazard assessment for armored vehicles, the Health Hazard Assessment (HHA) Program of the Army's Center for Health Promotion and Preventive Medicine (CHPPM) performs weapons-emissions testing for various firing scenarios. HHA evaluates potential exposures from emissions of carbon monoxide (CO), hydrogen cyanide (HCN), and other combustion gases within the compartments of weaponized armored vehicles. Generally, HHA evaluates the concentrations of these gases against the permissible exposure limits established by various agencies and organizations. Because military personnel in armored vehicles are exposed to a mixture of gases, the Army assessed the potential additive or synergistic toxic effects, specifically the combined effects of simultaneous exposures to HCN and CO, which produce similar toxic effects. The Army prepared a report titled *Assessment of Combined Health Effects of Hydrogen Cyanide and Carbon Monoxide at Low Levels for Military Occupational Exposures* that provides guidance on assessing combined exposures to low levels of CO and HCN (Bazar 2006). The U.S. Department of Defense (DOD) then requested that the National Research Council (NRC) independently evaluate the Army's proposed guidance on assessing combined exposures to HCN and CO and recommend approaches to developing exposure limit guidelines for combined exposures to these chemicals.

In response to DOD's request, the NRC convened the Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations, which prepared this report. 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 Appendix A.

The committee was asked to prepare an initial report and a final report. For the initial report, the task was to determine whether the hazard presented from simultaneous exposures to HCN and CO warrants a combined exposure assessment, and if so, whether the use of the Army's hazard quotient approach is a reasonable method of assessment. That report was published earlier this year (see NRC 2008) and is summarized in Chapter 1 of this report. This, the final report, addresses the remainder of the committee's task (described in Chapter 1 of this report).

A draft of this final 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: William Cain, University of California, San Diego; Tee Guidotti, George Washington University; Rogene Henderson, Lovelace Respiratory Research Institute; Sam Kacew, University of Ottawa; Bernard Schwetz, formerly with the U.S. Department of Health and Human Services; and Kenneth Still, Occupational Toxicology Associates, Inc.

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.

As part of its information gathering for this final report, the committee heard presentations from DOD representatives and other experts on issues related to low-level mixed exposure to CO, HCN, and other substances in armored vehicles. The committee gratefully acknowledges the valuable assistance provided by the following persons: Mathew Bazaar, Michael Chapman, Stephen Kistner, Timothy Kluchinsky, Glenn Leach, and Michael Leggieri, Jr. (all from DOD). The committee also received valuable information from Vernon Benignus, U.S. Environmental Protection Agency; Thomas Limero, Wyle Laboratories; and James Stuhmiller, L-3 Communications. Committee member Chiu-Wing Lam recused himself from the committee's discussions of the use of portable multi-agent monitors to assess the environment inside of weaponized armored vehicles.

We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), and Susan Martel, senior program officer, for their helpful comments. Other staff members who contributed to this effort are Raymond Wassel, project director; Ruth Crossgrove, senior editor; Mirsada Karalic-Loncarevic, manager of the Technical Information Center; Radiah Rose, senior editorial assistant; Patrick Baur, research assistant; and Korin Thompson, project assistant. Kulbir Bakshi was the project director for this study when the committee prepared its initial report. 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

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COMBINED EXPOSURES

TO HYDROGEN CYANIDE AND CARBON MONOXIDE IN ARMY OPERATIONS: FINAL REPORT

Summary

Military personnel in weaponized armored vehicles are exposed to combustion by-products generated from propellants used to fire the vehicle's guns. Personnel may also be exposed concurrently to other substances, such as diesel exhaust, present in the vehicle compartment, despite the use of mechanical ventilation. In response, the U.S. Army assessed possible additive or synergistic toxic effects from potentially harmful substances. Specific attention was given to the combined effects of simultaneous low-level exposures to carbon monoxide (CO) and hydrogen cyanide (HCN), because both gases produce similar adverse effects.[1]

Weapons emissions evaluated by the Health Hazard Assessment (HHA) Program of the Army's Center for Health Promotion and Preventive Medicine (CHPPM) include CO, HCN, and other gases. These chemicals are typically evaluated on an individual basis against medical criteria, which may include military-specific standards. However, additive or synergistic toxic effects among the chemicals were also considered. Because it found an increased potential for adverse effects on personnel simultaneously exposed to HCN and CO, CHPPM prepared a report titled *Assessment of Combined Health Effects of Hydrogen Cyanide and Carbon Monoxide at Low Levels for Military Occupational Exposures*. The report provides guidance to assess combined exposures in HHAs of military systems.

The Army found that the weight of available evidence indicates that the adverse effects of CO and HCN at lethal and incapacitating concentrations inhaled over periods of about 30 minutes or less are additive. However, for exposures occurring at lower and varying concentrations over periods of several weeks to perhaps several years, it is not known whether military personnel, while also in the presence of other combustion gases, may experience similar additive effects. No relevant chronic or low-level exposure studies were found in the literature. In 1981, a military standard established the Army's carboxyhemoglobin (COHb) limits of 5% for aviation crew members to protect against adverse visual effects and 10% for all other military personnel. The Army uses the Coburn-Forster-Kane (CFK) equation to estimate the percentage of COHb in the blood of military personnel in armored vehicles based on measurements of CO in the air inside of the vehicles. The exposure criterion for HCN is the current American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) ceiling of 4.7 parts per million (ppm) on the basis of anoxia, central-nervous-system irritation, and lung and thyroid effects.

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

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

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

The U.S. Department of Defense (DOD) requested that the National Research Council (NRC) assess the Army's proposed guidance for assessing the adverse effects resulting from the combined simulta-

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[1] Both compounds can induce hypoxia in human tissue, and the primary targets are the brain and heart.

neous exposures to low levels of CO and HCN in weaponized armored vehicles. The NRC was asked to prepare two reports. In response, it 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.

THE COMMITTEE'S INITIAL REPORT

In its first report, *Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations: Initial Report*, completed in 2008, the committee evaluated whether the adverse effects from combined exposure to HCN and CO at low levels warrant their combined assessment or whether the individual assessment of each chemical is sufficiently protective. If the combined exposure assessment of HCN and CO at low levels is warranted, the committee would determine whether the HQ approach is a reasonable method of assessment and whether it should be modified or improved.

The committee concluded the following in its initial report:

- The toxic effects of CO and HCN are probably additive, and, therefore, the effects from combined exposures to these chemicals should be assessed as a mixture and not individually.
- Until further findings suggest otherwise, the use of the HQ approach proposed by the Army is reasonable in establishing exposure limits for personnel simultaneously exposed to CO and HCN.
- The use of the CFK equation for the prediction of COHb levels related to air concentrations of CO is appropriate.
- The CFK equation has not been adequately evaluated in environments with dynamically changing air concentrations, such as in a weaponized armored vehicle.
- The use of an air concentration for HCN in the HQ equation, as opposed to a blood concentration, is reasonable.

The committee recommended that the Army assess the validity of the CFK equation in the context of weaponized armored vehicles using instantaneous measured data and various running averages. It also recommended that the Army conduct further neurologic 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 to assess more-subtle effects of interest to the Army. Finally, the committee recommended that the Army consider concurrent exposures to other chemicals (for example, other combustion products and diesel exhaust), which may have additional effects on the armored-vehicle crew.

THE COMMITTEE'S FINAL REPORT

For this, its second report, the committee was asked to address whether the approach discussed in the technical context section of the Army's proposed guidance is appropriate or whether an alternative assessment method should be developed and validated through either field or laboratory study. The committee was also asked to provide recommendations for making improvements in the Army's proposed method for assessing these combined exposures. The committee was asked to recommend methods for obtaining more precise measurements of gases that might be useful in exposure assessment and to recommend approaches for developing exposure limit guidelines for combined exposures to these chemicals.

As stated in its first report, the committee concludes that consideration should be given to the potential interaction between HCN and CO that could affect crew performance and health. This conclusion is based primarily on the possible additivity of the effects of both chemicals on attentiveness and reaction times. However, there is not enough evidence available at this time for the committee to make a conclusive assessment. In addition, the assessment is complicated by the presence of other combustion products released both from weapons firing and from use of vehicle fuel, and the committee recognizes that the potential toxic effects of those other products, especially in combination with CO and HCN, may also be important. Hence, although the committee still considers the HQ approach to risk assessment valid, and it reiterates its recommendation that the approach be used until further findings suggest otherwise, the committee concludes that additional information is needed to better understand possible synergisms between CO, HCN, and other combustion products that could help refine this risk assessment.

From a practical standpoint, to deal with the problem of possible synergy with respect to decrements in performance, it is necessary to understand how low concentrations of CO and HCN would act individually. This understanding will require additional information from studies specifically designed to examine such effects as attentiveness and reaction times. The information could then be used as a framework for follow-up studies on combinations of the two agents to determine whether there are interactions involving any of those effects.

The exposure information provided to the committee by CHPPM focused mainly on CO. As noted in the committee's initial report, the Army reported that exposures to HCN appear to be low most of the time, indicating that HCN may not contribute substantially to the HQ calculation for HCN and CO. As a result, the committee focused much of its consideration on CO with the understanding that actual exposures involve a multi-chemical mixture.

Major Conclusions and Recommendations

Portable Multi-Agent Monitors

To determine whether the air quality inside armored-vehicle cabins can meet exposure guidelines under deployment conditions, the Army test fires the vehicles' weapons and measures the concentrations of potentially harmful gases resulting under various operational scenarios. Samples are collected by using an innovative autosampling device consisting of long probes that draw a sample from infantry equipment into a nearby building for rapid analysis using spectrophotometry. As an alternative to the current use of fixed gas-monitoring instruments, portable gas monitoring instruments convey numerous advantages, including availability of real-time results and lower cost. Portable instruments are specifically available for measuring CO and HCN and are routinely used for measuring these chemicals in confined spaces. The direct-reading instruments can provide data transfer to a laptop computer, which would calculate potential COHb concentrations as well as an HQ index. The results of the direct-reading instruments would need to be verified periodically to determine whether the results were reasonably accurate and free of interferences. The instruments would also need to be carefully assessed in terms of sensitivity.

Assessing the Validity of the CFK Equation

The committee concluded that, although use of the CFK equation is appropriate in the context of weaponized armored vehicles, it has not been adequately evaluated in environments with dynamically changing CO concentrations. The committee recommends that the Army conduct experiments on human subjects to address the effects of rapid changes in inspired CO concentration at a constant rate of ventilation; rapid changes in ventilation at a constant inspired CO concentration; and simultaneous increases in inspired CO concentration and ventilation on CO uptake, venous blood COHb, and COHb predicted by the CFK equation. These experiments will assess the validity of the CFK equation at low or spiking levels of CO or under conditions of rapid changes in human ventilation.

Possible Human Performance Degradation Resulting from CO Exposure

In view of the lack of sufficient neuropsychological data and the inconsistencies in existing data, the committee recommends that the Army consider controlled experiments on human subjects using scenarios and concentrations of CO relevant to combat conditions. The experiments could be done best with vehicle simulators in an atmospheric chamber (or less desirably with face-delivery systems) where scenarios, CO concentrations, temperature, and humidity could be individually controlled. Such experiments should be designed to seek a dose-response relationship between CO and COHb so that levels of blood COHb are less than 10%. The experiments should examine neuropsychological end points, such as visual and reaction-time decrements, relevant to real-life scenarios in armored vehicles.

Alternatively, experiments could be done in an actual vehicle with standardized measures of performance under battlefield conditions. Such experiments, however, are unlikely to give definitive results because of multiple uncontrollable variables, such as heat, workload, and stress.

Possible Human Performance Degradation Resulting from Combined Exposures to CO and HCN

As more data become available on the actual combined exposure concentrations of CO and HCN and the durations of such exposures, the Army should consider the possibility that exposures to other chemicals, including ammonia, particulate matter, and components of diesel exhaust, might affect the interaction of CO and HCN. It should arrange for review of the information by an independent body to assist in setting priorities on such interactions, including those that may be synergistic.

Other Possible Deleterious Effects from CO and HCN Exposures

Both CO and HCN are known to affect respiratory rates, and the presence of these agents could result in an increased uptake of CO and other toxic gases. The data on such complex mixtures are insufficient to ascertain whether any such effects are functionally relevant to battle conditions. The Army should consider close and systematic surveillance of vehicle crews to identify any exacerbation of conditions affecting pulmonary efficiency (for example, asthma) or any increased risk of sudden death, myocardial infarction, or other significant medical problems.

Seeking Advice from Additional Perspectives

The Army performs an important role in ensuring that the health of personnel in armored vehicles is not compromised by co-exposures to CO and HCN during weapons firing. CHPPM's activity related to the development of new models for armored vehicles and the use of test-firing scenarios to mimic possible crew exposures to CO, HCN, and other gases could benefit substantially from greater communication with and feedback from groups involved with personnel training and field deployment. Such groups include the Army's Human Factors Engineering Program, instructors associated with training armored-vehicle crews in the field, crew members themselves, and health personnel involved with those crews during actual deployment. These groups could serve as valuable resources regarding the signs and symptoms associated with actual experiences in the different uses of these vehicles and under varying ventilation conditions.

Human Subjects Research

The committee's recommendations given in this report include experiments that would expose humans to CO concentrations that are within the range of typical conditions encountered by military personnel when firing weapons from inside armored vehicles. It is important to note that these studies involving research on human subjects must comply with federal and other applicable regulations for the protection of human subjects of research. Protocols for research involving human subjects should receive approval by a certified Institutional Review Board.

1

Introduction

The U.S. Army's Health Hazard Assessment (HHA) Program of the Center for Health Promotion and Preventive Medicine (CHPPM) is designed to identify and eliminate health hazards or to reduce them to some acceptable level during the life-cycle management of materiel systems. Although the Army operates mechanical ventilation systems in the vehicle compartments of its armored vehicles, military personnel within these vehicles are still exposed to low levels of combustion by-products generated from propellants used to fire the vehicle's guns. Personnel may also be exposed concurrently to other substances present in the vehicle compartment, such as diesel exhaust. HHA 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).

The Army assessed the potential additive or synergistic toxic effects of these substances. Specific attention has been given to the combined effects of simultaneous low-level exposures to CO and HCN because both gases produce similar toxic effects. As a result, the Army prepared a report titled *Assessment of Combined Health Effects of Hydrogen Cyanide and Carbon Monoxide at Low Levels for Military Occupational Exposures* that provides guidance on assessing combined exposures to low levels of CO and HCN (Bazar 2006).

CO is assessed as an individual chemical in the Army's HHA using the Coburn-Forster-Kane (CFK) equation (Smith et al. 1996) for predicting the percentage of carboxyhemoglobin (COHb) in blood.

$$\%COHb_t = \%COHb_0\,(e^{-t/A}) + 218\,(1 - e^{-t/A}) + [1/B + P_{I_{CO}}/1{,}316],$$

$$A = M\,V_b\,[O_2Hb]\,(1/D_{L_{CO}} + (P_B - P_{H_2O})/\dot{V}_A)/\overline{Pc}_{O_2},$$

$$B = [1/D_{L_{CO}} + (P_B - P_{H_2O})/\dot{V}_A],$$

where t = time (minutes); 0 = beginning of exposure; $P_{I_{CO}}$ = partial pressure of CO in inhaled air;
M = equilibrium constant for the reaction $CO + O_2Hb \rightarrow COHb + O_2$; V_b = blood volumn;
$D_{L_{CO}}$ = pulmonary CO diffusing capacity; P_B = barometric pressure; P_{H_2O} = partial pressure of water;
$\dot{V}_A$ = alveolar ventilation rate; and $\overline{Pc}_{O_2}$ = mean O_2 tension in the pulmonary capillary blood.

A DOD 1981 military standard established the Army's COHb limits of 5% for aviation crew members to protect against visual adverse effects and 10% for other effects. The 5% level was considered a safe level for healthy young people and had previously been used by the American Conference of Governmental Industrial Hygienists (ACGIH) (DOD 1972; Smith et al. 1996). Adverse motor neuron effects, such as decreased coordination, 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 parts per million (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).

In addition to the individual threshold levels, the Army uses the following hazard quotient (HQ) approach, which assumes the effects of CO and HCN at low levels are additive. An HQ equal to or greater than 1.0 indicates an overexposure.

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

To determine whether the air quality inside armored-vehicle cabins can meet the exposure guidelines under deployed conditions, the Army test fires the vehicles' weapons and measures the concentration of potentially harmful gases resulting under various operational scenarios. When an armored vehicle is first tested, no personnel are usually in the cabin and weapons are fired remotely. Before, during, and after firing, air is sampled remotely from the crew compartments and concentrations of specific gases are measured. Subsequent testing involves weapons firing by personnel within the vehicle cabin followed by air sampling and analysis (Bazar and Kluchinsky 2008; M. Bazar CHPPM, personal commun., September 23, 2008). To evaluate the stream of test data, the Army calculates COHb levels at the end of each data interval (3 or 5 seconds) using the instantaneous CO concentrations and the COHb concentration from the end of the previous interval. The 15-minute (min) HCN average is based on a running average calculated at the end of each data interval. The 15-min HCN average concentration is used because HCN exposures have been observed to be transient and to clear quickly after a round is fired. CO concentrations exhibit a spike when a round is fired and also quickly decline, but COHb begins to accumulate in the blood of exposed subjects after several rounds.

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

In summary, to assess the potential for health effects of CO and HCN combined exposures at low levels, the Army first determines if either or both of the limits of 10% COHb or 4.7-ppm HCN are exceeded. If so, the scenario fails and the HQ calculation is not needed. If COHb and HCN are within acceptable limits, then the HQ calculation is performed; the scenario fails if the HQ equals or exceeds 1.0. The method used allows the HQ results to be consistent with the single results.

In 2005, the Department of Defense (DOD) requested that the National Research Council assess (NRC) the Army's proposed guidance for assessing the adverse effects resulting from the combined simultaneous exposures to low levels of CO and HCN in weaponized armored vehicles. The NRC was asked to prepare two reports. In response, the NRC 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. The committee's Statement of Task is presented in Box 1-1.

THE COMMITTEE'S INITIAL REPORT

In its initial report (NRC 2008), the committee evaluated the Army's proposed guidance on using the HQ approach as part of its HHAs of military systems. The committee concluded in its initial report

BOX 1-1 Statement of Task

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 carbon monoxide (CO) and hydrogen cyanide (HCN).

In its first report, the committee will evaluate the U.S. Army's proposed guidance on assessing combined exposures in Health Hazard Assessments (HHAs) of military systems. The ad hoc committee will specifically determine the following in its first report:

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 and, if the combined exposure assessment of HCN and CO is warranted at low levels, is the hazard quotient approach, discussed in the Army's technical context section, a reasonable method of assessment? Should it be modified or improved (that is, the use of a blood HCN benchmark instead of the ACGIH TLV-C[1])?[1]

In its second report, the committee will address the following:

Is the approach discussed in the technical context section of the Army's proposed guidance appropriate or should an alternative assessment method be developed and validated through either field or laboratory study?

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, and recommend approaches for developing exposure-limit guidelines for combined exposures to these chemicals.

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[1] ACGIH TLV-C refers to a Threshold Limit Value ceiling issued by the American Conference of Governmental Industrial Hygienists.

that the toxic effects of CO and HCN are likely additive, and, therefore, the effects presented from combined exposures to these chemicals should be assessed as a mixture and not individually.

The literature (for example, Levin et al. 1987, 1988; Chaturvedi et al. 1995) indicates that the toxic effects of inhaled CO and HCN are additive at lethal and incapacitating levels. However, for exposures occurring at lower and varying concentrations over periods of several weeks to perhaps several years, it is not known whether military personnel, while also in the presence of other combustion gases, may experience similar additive effects. Although a number of reports on the interaction of HCN and CO have been done and the potential interaction has been well recognized in respect to fires, the human literature is not helpful in defining adverse blood concentrations of HCN alone or in combination with CO. In most cases, the exposures were very high and/or the measurements of exposure, particularly to HCN, were questionable. Animal studies mostly used high levels of HCN that 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 HCN at less than 5 ppm or CO at less than 100 ppm. Furthermore, available studies do not address subtle effects, such as decrements in performance, that are relevant to setting guidelines for human exposure. Although guidelines for limiting exposure to CO and HCN have been published by governmental and professional groups, they have the same limited databases, especially for the interaction. Therefore, the possibility that independence or subadditive 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. In assessing the toxic effects 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. Therefore, the committee concluded that until further findings suggest otherwise, the Army's use of the HQ approach or hazard index is reasonable in establishing exposure limits for personnel simultaneously exposed to CO and HCN. The committee stated that the HQ should be used for calculating the risk of adverse effects from exposure to CO and HCN combined. The approach involves assessment of CO exposure using the CFK equation.

The CFK equation has not, however, been evaluated in environments with rapidly changing CO concentrations, such as in the air within crew compartments of armored vehicles. Therefore the committee recommended that the Army assess the validity of the CFK model in that context.

Regarding HCN, the committee considered available evidence of HCN toxicity and the appropriateness of measurements of blood or air concentrations of HCN in the HHA. The committee identified several reasons why measurement of air concentrations is a better benchmark to use (for example, the lack of reported rapid or simple methods for the determination of HCN in biologic fluids). Also, there seemed to be no compelling reason why blood measurements of HCN would be a better predictor of adverse effects than measurement of ambient air concentrations. The added difficulties associated with the measurement and interpretation of blood HCN concentrations indicated that this measurement should not be selected as a routine monitoring method. Therefore, the committee concluded that the Army's use of air concentrations of HCN, rather than blood HCN concentrations, in the HHA is reasonable. Also, the committee recommended that the Army conduct further neurologic studies on sensory and motor performance at low concentrations of HCN and CO. In addition, the committee recommended that the Army consider concurrent exposures to other chemicals that may have additional effects on the armored-vehicle crew.

THE COMMITTEE'S FINAL REPORT

The exposure information provided to the committee by CHPPM focused mainly on CO. As noted in the committee's initial report, the Army reported that exposures to HCN appear to be low most of the time, indicating that HCN may not contribute substantially to the HQ calculation for HCN and CO. As a result, the committee focused much of its consideration on CO with the understanding that actual exposures involve a multi-chemical mixture.

In the committee's final report, Chapter 2 discusses whether there is a role for the use of portable multi-agent monitors to assess the armored-vehicle environment during varied operations.

Chapter 3 discusses the types of experiments needed to answer whether the CFK equation is valid (1) for assessing COHb levels at low and or spiking levels of CO or (2) under conditions of rapid changes in ventilation. Appendix B reviews past assessments of using the CFK equation for estimating various exposure concentrations, durations, and conditions. Appendix C provides details on methods for additional experiments recommended by the committee to assess the CFK equation.

Chapter 4 discusses whether there is dose-related performance degradation resulting from exposure to CO. Chapter 5 discusses whether there is dose-related performance degradation resulting from combined exposures. Chapter 6 discusses the potential for other deleterious end points of these exposures. Each of the chapters also recommends studies that may provide useful information for developing exposure limit guidelines for combined exposures.

Chapter 7 presents considerations for the Army as it moves forward in developing exposure guidelines. The chapter also considers environmental factors that might modify responses to CO exposure that are not currently taken into account by the Army, and it discusses whether computational models could be used to assess the effect of multiple exposures.

2

Is There a Role for the Use of Portable Multi-Agent Monitors to Assess the Armored-Vehicle Environment During Varied Operations?

Traditional air measurement methods generally consists of trapping the chemical of interest on a medium, shipping samples to a fixed laboratory, and analyzing the samples with an instrument. The ability of various media to trap chemicals effectively varies but, on the basis of method validation, is usually sufficient. Instrumental methods can be quite sensitive and fairly specific, but specificity is not always universal (Todd 2003). At one site where the Center for Health Promotion and Preventive Medicine (CHPPM) conducts testing on hydrogen cyanide (HCN) and carbon monoxide (CO), samples are collected using an innovative autosampling device consisting of long probes that draw a sample from infantry equipment into a nearby building for rapid analysis using spectrophotometry. This system provides advantages in terms of near-real-time analysis but also introduces variables in the sampling process, including sample-line loss and timing issues. In awareness of such variables, CHPPM conducts quality-control procedures to calibrate its spectrometers using certified gas standards at known concentrations. Gas standards are also introduced at the end of the sample lines, and the concentrations are measured to assess the condition of the lines and to check for leaks (M. Chapman, U.S. Army Aberdeen Test Center, unpublished material, 2008).

The method used for analysis by CHPPM does not appear to correspond to published National Institute for Occupational Safety and Health (NIOSH) or Occupational Safety and Health Administration (OSHA) methods, which would be preferred over unpublished methods. The NIOSH method for CO analysis is a direct-reading instrumental method (NIOSH 1996). OSHA uses direct-reading instruments (OSHA 1993) or gas chromatography (OSHA 1991) for CO analysis. NIOSH methods for HCN analysis include ion chromatography, ion-specific electrode, and spectrophotometry of a specially prepared sample (NIOSH 1994a,b, 2003), and OSHA recommends an ion-specific electrode method (OSHA 1988). None of these methods appears to be used by CHPPM.

Use of direct-reading instruments as an alternative to CHPPM's sampling and analytic system could be an improvement for the reasons previously noted. Typically, direct-reading instruments have a response time of a second or less, meaning that the digitally reported result is essentially instantaneous and represents the current exposure concentration. The cost of the instruments is low compared with laboratory-scale analytic instruments.

Numerous portable gas-monitoring instruments are readily available from commercial companies. Instruments are specifically available for measuring CO and HCN and are routinely used for measuring these chemicals in such environments as confined spaces, fires, and combustion environments. Although these instruments are subject to interferences from other chemicals that may be present, when used with appropriate caution and verification, they convey numerous advantages over fixed gas-monitoring instruments, including availability of real-time results and lower cost (Todd 2003).

The results of the direct-reading instruments would need to be periodically verified using an alternative sampling method, preferably a NIOSH or OSHA method that involves a fixed analytic laboratory. The purpose of the verification would be to determine whether the results were reasonably accurate and free of interferences. Direct-reading instruments would be self-contained (that is, the units would not need to be tethered to an analytic laboratory to measure and record ambient concentrations), providing more flexibility in the location of data collection. The instruments would also need to be assessed carefully in terms of sensitivity. For example, one widely available instrument has a reporting limit for HCN and CO of about 1 part per million, but at the low end of the reporting range, precision may be an issue **(**Draeger Safety, Inc. 2002**).**

Another advantage of the direct-reading instruments is the potential for real-time data evaluation or interpretation. Direct-reading instruments can provide data transfer to a laptop computer. With some programming, it may be possible to have data automatically uploaded to spreadsheet-type software that would be able to calculate the carboxyhemoglobin levels corresponding to any desired averaged exposure as well as to a hazard index. The system could probably be set to alarm at any desired level of single chemical exposure or mixture exposure. Finally, such a system consisting of portable direct-reading instruments and laptop computers could potentially be deployed during field exercises or even combat.

3

Is the Coburn-Forster-Kane Prediction Equation Valid at Low or Spiking Levels of Carbon Monoxide or Under Conditions of Rapid Changes in Ventilation?

HISTORY OF VALIDATION OF THE COBURN-FORSTER-KANE EQUATION

The Coburn-Forster-Kane (CFK) equation accurately predicted increases in blood carboxyhemoglobin (COHb) in resting male subjects during carbon monoxide (CO) exposures (constant 8.5 to 1,000 parts per million [ppm]; Peterson and Stewart 1975), during 60-second (sec) exposures to high CO concentrations (Tikuisis et al. 1987a), and during exercise in subjects breathing a constant CO concentration (Tikuisis et al. 1992) (see Appendix B). Tikuisis et al. (1987b) compared measured venous COHb and computed COHb using the CFK equation under conditions in which inspired CO was changed by evoking transient changes in inspired CO concentrations of 500-2,000 ppm and over times as short as 60 sec. Because of slow lung wash-in after CO was added to inspired air and wash-out after CO was discontinued, alveolar CO concentrations were constantly changing, but no sudden changes were studied. Computed COHb, obtained by using a "normalized" alveolar CO concentration that was obtained by integration, closely followed measured values. These investigators also showed that, in subjects exercising at constant different workloads during CO uptake for times as short as 60 sec, measured increases in venous COHb could be precisely computed using the CFK equation. In general, the above studies used inspired CO concentrations in excess of those found in the cabin air of armored vehicles.

NEED FOR VALIDATION OF THE CFK EQUATION UNDER CONDITIONS FOUND IN ARMORED-VEHICLE CABIN AIR

The committee was provided with several examples of CO concentration profiles representing the inside of armored-vehicle cabins during the test firing scenarios. These few examples show spikes in CO concentration lasting several seconds after weapons had been fired. Following multiple firings, there are gradual increases in inter-spike CO concentrations, followed by similarly gradual decreases in CO concentration after firing ceases due to ventilation of cabin air. The small number of examples provided to the committee illustrates considerable variability in CO concentration tracings, where spikes following firings were 25-2,500 ppm and interspike CO concentrations reached 100-500 ppm. These few examples are not necessarily representative of all scenarios, as CO concentrations within the cabin can vary depending on opened or closed hatches, operating ventilation fans, wind conditions, or armored-vehicle movements, as well as the history of weapons firings (M. Bazar, CHPPM, personal commun., September 23, 2008). Although it is established that the CFK equation can be used to predict blood COHb after 60- to 75-sec constant CO exposures or during slow changes in inspired CO concentrations, there are no data in the literature from experiments that replicate the rapid changes in CO concentrations measured in armored-vehicle cabins, that is, CO spikes of a few seconds durations. There are also no results reported in the literature from experiments that replicate changes in pulmonary ventilation found in armored-vehicle personnel. Two issues need to be addressed:

- Do the high CO concentrations found during spikes influence CO uptake, and how can these data be used to obtain a relevant "normalized" inspired CO to plug into the CFK equation?
- Do increases in workload and ventilation in armored-vehicle personnel augment CO uptake? Previous studies used inspired CO concentrations in excess of those found in armored-vehicle cabins, and data need to be obtained using lower CO concentrations.

The committee recommends that the Army conduct three types of experiments using human subjects to address those issues. Details on methods for each experiment are provided in Appendix C.

- Experiment 1. Effects of rapid changes in inspired CO concentration at a constant rate of ventilation. This experiment will have one part that addresses the relationship of inspired CO concentrations to CO uptake. The other part will evaluate the CFK equation.
- Experiment 2. Effects of rapid changes in ventilation at a constant inspired CO concentration.
- Experiment 3. Effects of simultaneous increases in inspired CO concentration and ventilation on CO uptake, venous blood COHb, and COHb predicted by the CFK equation.

The CFK equation could be evaluated by using animals, such as dogs or cats. However, there are numerous practical arguments against substituting animal data for human data: (1) animal testing would require anesthesia, and the animals could not exercise; (2) animal testing would require development of new approaches. Because experimenters would probably not have previous information in the diffusion capacity and other pertinent variables, they would need to be measured; (3) whereas equipment for conducting experiments using human subjects is already present in pulmonary-function laboratories, such equipment would need to be developed and/or procured for a comparable animal study; (4) the study of effects of increases in ventilation could be performed using animals but would be associated with decreases in arterial oxygen tension and increases in blood pH, which could complicate findings; (5) the results from animal experiments would not be as relevant to the Army's questions as would results obtained using human subjects; and (6) unlike the case for humans, there is no database from previous animal studies to which to relate results.

4

Is There Dose-Related Performance Degradation Resulting from Exposure to Carbon Monoxide?

In the context of this analysis, performance can be divided into physical performance and neuropsychological and neurophysiologic performances, such as reaction times, visual changes and short-term memory.

Physical performance in humans has been studied at various concentrations of carboxyhemoglobin (COHb). There appears to be a linear reduction in maximal workload with increasing COHb concentrations up to at least 20% COHb (Ekblom and Huot 1972). These effects are accentuated by heat, altitude, and anemia (Horvath et al. 1988; Bunnell and Horvath 1989; Kapoor et al.1997; Kleinman et al. 1998). At submaximal workloads, these effects are not seen at low-to-moderate COHb concentrations (Ekblom and Huot 1972).

Aronow and Cassidy (1975) and Allred et al. (1989) studied physical performance of patients who had coronary artery disease and who breathed CO to increase their COHb levels prior to moderate exercise. The researchers found that onset of ST segment elevations (determined using electrocardiography) and angina pectoris occurred sooner when COHb levels were at about 4% saturation or greater, as compared with the control group. This effect was a function of venous blood COHb% saturation. The researchers found that a value of about 4% COHb resulted in 12% and 7% decreases in exercise times for onset of ST segment elevation and onset of angina, respectively.

Of perhaps more relevance to the military scenario are the potential effects of carbon monoxide (CO) on neuropsychological and neurophysiologic performance measures. The effects of CO on neuropsychological and neurophysiologic performance in humans have been reviewed by several authors (Benignus 1994; Wong 1994). There is clearly conflicting data in this area. Although many studies that appear to be well done do not show effects until COHb levels are in the range of 10-20% (Stewart et al. 1973; Benignus and Otto 1977; Hudnell and Benignus 1989), many other studies show effects in the 3-6% range (Beard and Wertheim 1967; Wright et al. 1973; Putz 1979; Gliner et al. 1983;). There is no clear explanation for the discrepancies in these results. Although variability is probable among individual subjects, this factor alone is unlikely to account for the substantial differences in these studies. Methodologic differences, including lack of blinding in some studies, are also probably responsible for some of the inconsistencies observed. Benignus and others (Benignus et al. 1987, 1990; Benignus 1994) have estimated from animal and human data that central-nervous-system (CNS) hypoxia, and presumably neuropsychological and neurophysiologic effects, should not occur at COHb levels below 16-23%. Because of these discordant results, there is no clear dose-response association for relevant neuropsychological effects at low-to-moderate COHb levels.

A dose-response relationship for various neurobehavioral end points is apparent in animals and humans at COHb levels above 10% (Benignus 1994). The committee is unaware of any validated models that will predict biologic effects from CO exposure under circumstances relevant to the needs of the Army and in the presence of other CNS active gases, such as hydrogen cyanide (HCN) and carbon dioxide (CO_2). In the absence of reliable definitive data at low-to-moderate CO concentrations and in order to provide a safety margin for neuropsychological and neurophysiologic effects and potential cardiovascular effects, governmental groups have generally chosen to rely on the studies reporting effects at low levels when setting standards for critical tasks (Wong 1994).

Recommendation Information provided to the committee by the Army indicates that exposure scenarios in armored vehicles deployed in battle are expected to generate COHb levels less than 10% in vehicle personnel (M. Bazar and T. Kluchinsky, CHPPM, personal commun., April 14, 2008).

In view of the lack of reliable and relevant neuropsychological data and the inconsistencies in existing data at levels in this range, the committee recommends that the Army consider controlled human experiments using scenarios and exposure concentrations of CO relevant to combat conditions. Such experiments should be designed to seek a dose-response relationship at CO and COHb levels at less than 10% and with neuropsychological end points, such as visual and reaction-time decrements relevant to real-life scenarios in enclosed armored vehicles. It would not be feasible to measure these same end points in a meaningful way in exposure experiments using animals (also see discussion in Chapter 3). Also, the lack of consistent neuropsychological and neurophysiologic data precludes the use of computational models to estimate expected changes in human performance with increased COHb.

Controlled human experiments could be done best with vehicle simulators in an atmospheric chamber (or less desirably with face-delivery systems) where scenarios, CO concentrations, temperature, and humidity could be individually controlled. The Army will also need to control for "background" CO exposure from smoking and other sources. If these studies were done under controlled conditions, the Army would need to decide whether to model a scenario of rapid CO buildup or slow CO buildup, because the physiologic effects, and subsequent behavioral responses, might be different for these two scenarios. The small number of subjects who can practically be tested will likely be a limiting factor in these experiments, but given the current state of existing data, such controlled experimentation is the only conclusive way to assess the qualitative and quantitative risks of performance degradation resulting from in-vehicle CO release. Alternatively, experiments could be done in a test vehicle with standardized measures of performance under battlefield conditions. Such experiments, however, are unlikely to give definitive results due to multiple uncontrollable variables, such as heat, workload, and stress.

Attention should be paid to assessment of armored-vehicle crews for medical conditions that might adversely affect any performance degradation from CO or other hypoxia-producing conditions (for example, high altitude). Such conditions would also include diseases affecting pulmonary efficiency (for example, asthma and chronic obstructive pulmonary disease), cardiac diseases that can increase the risk of cardiac dysrhythmias or dysfunction, and blood diseases that can affect oxygen transport (for example, anemia and hemoglobinopathies). The committee acknowledges that the Army probably currently screens for some or all of these conditions in its crews.

5

Is There Dose-Related Performance Degradation Resulting from Combined Exposures to Carbon Monoxide and Hydrogen Cyanide?

As stated in its first report, the committee concludes that consideration should be given to the potential interaction between hydrogen cyanide (HCN) and carbon monoxide (CO) that could affect crew performance and health. This conclusion is based primarily on the possible additivity of the effects of both chemicals on attentiveness and reaction times. However, there is not enough evidence available at this time for the committee to make a conclusive assessment. In addition, the assessment is complicated by the presence of other combustion products released both from weapons firing and from combusting vehicle fuel, and the committee recognizes that the potential hazardous effects of these other products, especially in combination with CO and HCN, may also be important. Hence, although the committee still considers the hazard quotient approach to risk assessment valid, and it reiterates its recommendation that the approach be used until further findings suggest otherwise, the committee concludes that additional information is needed to better understand possible synergisms between CO, HCN, and other combustion products that could help refine this risk assessment.

The information available on exposures to low levels of these substances is scarce at best. A review of the literature suggests that, aside from reports on overexposures due to fires or suicides, there is a dearth of published studies on the neurobehavioral effects of HCN in humans and essentially nothing in nonhuman primates. There may also be epidemiologic data that could be helpful in addressing the effects of low concentrations of CO and HCN combined, but the committee is unaware of any recent experimental information in the current published literature that would directly assist in resolving this question with respect to the low concentrations of interest to the Army.

The studies conducted to date on co-exposures to CO and HCN primarily in animals have focused on high levels of exposure. There is the possibility of a synergism between the two chemicals at these levels. The committee discussed this potential problem with respect to the exposures in weaponized armored vehicles and concluded that the interaction, based on the known mechanisms of action of these agents, is more likely to be additive than synergistic if neither agent alone is the driver for the adverse effect. However, the problem cannot be addressed with greater certainty because of the inability to extrapolate to the low-exposure concentrations with respect to humans. Few studies have been conducted on other possible modes of interaction—for example, an effect of either agent, alone or in combination, on such factors as respiratory rate increases, in addition to possible increases in respiration based on workload.

From a practical standpoint, to address the likelihood of synergy with respect to possible decrements in performance, it is necessary to understand how low concentrations of CO and HCN would act individually. This understanding will require additional information from studies specifically designed to examine such effects as attentiveness and reaction times. The information could then be used as a framework for follow-up studies on combinations of the two agents to determine whether there are interactions involving any of those effects. Experiments on combined human exposures to CO and HCN, similar to those suggested in Chapter 3 for CO alone, would be ideal; however, the health risks posed to the subjects due to the high toxicity of HCN would likely be unacceptable. An alternative would be to design neurobehavioral experiments in nonhuman primates to test the effect of HCN in combination with CO.

An additional or alternative approach considered viable by the committee is to conduct field studies in actual armored vehicles, where CO and HCN would be measured simultaneously along with crew performance (for example, reaction times). As stated in Chapter 4, however, such field experiments are unlikely to give definitive results because of multiple uncontrollable variables.

Recommendation The committee recommends that, as more data become available on the actual combined exposure concentrations of CO and HCN and durations of such exposures, the Army seeks to understand how exposures to additional chemicals might affect the interaction of CO and HCN. Examples of additional chemicals are ammonia, particulate matter (including combustion-derived nanoparticles), and other components of diesel exhaust. Furthermore, it recommends that information or experimental results related to such potential interactions be reviewed by an independent body to assist in setting priorities on such interactions, including those that might be synergistic.

6

Are There Other Deleterious Effects of Varying Exposures to Carbon Monoxide and Hydrogen Cyanide?

We have considered the direct effects of carbon monoxide (CO) and hydrogen cyanide (HCN) on both physical and neuropsychological and neurophysiologic performance. It is clear from the medical literature that there are other direct and indirect effects of both CO and HCN in humans that might be relevant to human performance, either acutely or chronically. For example, CO may play a role in normal neurotransmission and vasomotor control; however, the pathophysiologic effect of low-level exposures is not yet well understood (EPA 2000).

Perhaps the best studied is the effect of CO inhalation on cardiac function. Several studies have looked at risks of cardiac dysrhythmia in patients with coronary artery disease (CAD) exposed to CO (Hinderliter et al. 1989; Sheps et al. 1990, 1991; Chaitman et al. 1992; Dahms et al. 1993). Carboxyhemoglobin COHb levels below 6% did not appear to exert significant effects on rhythm. However, 6% COHb resulted in an increased frequency of complex premature ventricular beats in the CAD patients (Chaitman et al. 1992; Dahms et al. 1993). Effects were more pronounced with advancing age. Another group of studies looked at exercise tolerance in CAD patients during CO exposure (Sheps et al. 1987; Adams et al. 1988; Allred et al. 1989a,b; Allred 1991; Kleinman et al. 1989; Chaitman et al. 1992; Dahms et al. 1993). Most of these studies have shown decreased exercise tolerance in CAD patients at COHb levels in the 3-4% range, a range commonly found in smokers. Although not specifically studied, other cardiac diseases, such as congenital heart disease and congestive heart failure, with the potential for hypoxia would probably show similar effects. At least one human study has suggested that chronic CO exposure in the occupational setting may contribute to the development of arteriosclerotic heart disease with aging (Stern et al. 1988). Although no similar studies have been done on HCN, it probably would have similar effects at concentrations capable of producing mild tissue hypoxia. These effects should be considered, given the existing data on CO and HCN concentrations within armored vehicles and the uncertainty about comprehensive screening of crew members.

There are few data in the medical literature relating to the effects of chronic or frequent intermittent exposure to either CO or HCN. Epidemiologic studies**,** primarily in the occupational literature, have suggested that chronic exposure to HCN may result in the formation of enlarged thyroid glands and hypothyroidism (El Ghawabi et al. 1975; Blanc et al. 1985). Chronic headaches, tremors, chronic fatigue, and changes in smell and taste have also been reported (Radojicic 1973; El-Ghawabi et al. 1975; Blanc et al. 1985). The incidence of these effects and the magnitude of exposure required to produce them are unknown. It is also not known whether these effects have occurred or may occur under the conditions of interest to this study.

Similar data from the literature on CO suggest that chronic occupational exposure can result in chronic headaches, chronic fatigue, sleep and memory problems, vertigo, and emotional problems (Beck

1936; Alistair et al. 2000; Penney 2000). Again, the incidence of these effects and the conditions necessary for their occurrence are not known. It is also not known whether these effects have occurred or may occur under the conditions of interest to this study.

CO and HCN are the major toxic gases considered in this report; however, the committee recognizes that other gases, such as oxides of nitrogen and sulfur dioxide, are produced during the combustion process and from other sources within armored vehicles. Both CO_2 and HCN are known to affect respiratory rates (Peterson and Stewart 1975; Purser et al. 1984), and the presence of these agents could result in an increased uptake of CO and other toxic gases. Data on such complex mixtures are insufficient to ascertain whether any such effects are functionally relevant to the questions the committee has been asked to address.

Recommendation The Army should consider close and systematic surveillance of vehicle crews with the intent of identifying any increased risk of sudden death, myocardial infarction, or other significant medical problems.

7

Moving Forward

The U.S. Army performs an important role in ensuring that the health of personnel in armored vehicles is not compromised by co-exposures to carbon monoxide (CO) and hydrogen cyanide (HCN) during weapons firing. Given the current weight of evidence, the committee clearly supports the Army's Center for Health Promotion and Preventive Medicine (CHPPM) hazard quotient approach, as indicated in the first report. (The committee recognizes that alternative approaches may provide additional insights into the conjoined effects of exposure to two or more substances. However, until further findings suggest otherwise, we are confident that the hazard quotient approach provides an appropriate method for establishing exposure limits for combined exposures.) This chapter provides several issues the Army should consider as it moves forward in developing exposure guidelines and taking other actions to eliminate or control health hazards to military personnel.

CHPPM's efforts are focused on testing armored vehicles during the design phase (prior to deployment). Weapons are fired under various controlled scenarios to estimate exposures that crew members might experience within deployed vehicles. As a result of its discussion with various Department of Defense representatives, it became clear to the committee that the Army's health-hazards-assessment activity in relation to the development of new models of armored vehicles and the use of scenarios to mimic possible crew exposures to CO, HCN, and other gases could benefit substantially from greater communication with and feedback from groups involved with personnel training and field deployment. These groups may include the Army's Human Factors Engineering Program, instructors associated with training armored-vehicle crews in the field, and health personnel involved with those crews during actual deployment. These groups could serve as valuable resources regarding the signs and symptoms associated with actual experiences in the different uses of these vehicles and under varying ventilation conditions. Feedback might yield information obtained from crew members, either real or perceived, on specific functional decrements in the field. Because the design or modification of the Army's armored vehicles is an iterative process, the committee concludes that the Army's future efforts to detect and mitigate potentially hazardous exposures within armored vehicles could benefit from advice, both positive and negative, from additional perspectives.

EXPOSURE AND EFFECTS RESEARCH

The committee identified the need for human experiments to assess the validity of the Coburn-Forster-Kane (CFK) equation at low or spiking concentrations of CO or under conditions of rapid changes in ventilation. The committee also identified the need for human experiments to investigate the effects of CO exposures on neuropsychological end points, such as visual and reaction-time decrements, relevant to real-life scenarios in armored vehicles. The experiments that we recommend would expose humans to concentrations of CO that are within the range of typical conditions encountered by military personnel when firing weapons from inside armored vehicles. It is important to note that these studies involving research on human subjects must comply with federal and other applicable regulations for the protection of human subjects of research. Protocols for research involving human subjects should receive approval by a certified Institutional Review Board.

OTHER CONSIDERATIONS FOR FUTURE RESEARCH

As more data become available as a result of the committee's recommended experiments, DOD should consider how other factors may affect the relationship between exposure and effects.

Factors That May Modify Effects of Carbon Monoxide

Because of the weakness of the database regarding adverse effects of small increases in body CO on brain functions, such as those involved in decision making and alertness, it is not possible at this time to make conclusions about the extent to which environmental factors, such as temperature and humidity, can confound relationships between CO exposures and performance. However, environmental factors can alter CO uptake that can potentially translate into adverse effects of CO.

Effect of Altitude

The partial pressure of oxygen (O_2) in the ambient air is reduced as altitude increases. This, in turn, reduces the partial pressure of O_2 in the inspired air as well as the volume of O_2 transported to human tissues by hemoglobin in the blood. The result is tissue hypoxia, the severity of which is determined by the absolute altitude. As described by the CFK equation, CO both competes with O_2 for hemoglobin, thus reducing the amount of O_2 that can be transported, and increases the affinity of hemoglobin for O_2 so that O_2 is released less readily in the tissues. Thus, reduced O_2 transport to the tissues due to altitude may be further reduced by inhaled CO (McGrath, 2000). The resulting tissue hypoxia would be exacerbated by stress and altitude-induced hyperventilation, which would increase CO uptake and cause respiratory alkalosis, further reducing O_2 transport to the tissues. Thus, possible adverse effects from CO exposure of military personnel within armored vehicles might be amplified at altitude.

Effect of Previous High Exposure to CO

CO uptake at a given inspired CO concentration might possibly decrease as a result of increased carboxyhemoglobin (COHb) in tobacco smokers or as a result of previous exposure to high inspired CO concentrations due to previous gun firings. It will be important to consider the extent to which adaptation via tobacco smoking may protect soldiers against detrimental effects of small increases in COHb due to CO uptake secondary to cannon firings.

Use of Computational Models to Assess Multiple Exposures

Future computational efforts for estimating the health risks posed by exposure to combustion products in armored vehicles could include evaluation of the Toxic Gas Assessment (TGAS) model. The TGAS models (versions 1.0 and 2.0) were developed to predict the onset of death or immediate incapacitation resulting from the inhalation of gases released during fires (for example, CO, HCN, nitrogen dioxide, hydrochloric acid, acrolein, and carbon dioxide) at high concentrations and in any combination, as well as from a decrease in available O_2 (Stuhmiller et al. 2006). Thus, TGAS models account for several factors that influence the breathing rate. The TGAS models would probably need to be restructured and calibrated to estimate the combustion-product-exposure conditions presented to the committee and also to estimate internal dosimetrics, such as COHb resulting from CO exposure.

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Appendix A

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

William E. Halperin is professor and chair 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 National Research Council (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 Institute of Medicine's 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 former associate head of the School of Health Sciences at Purdue University. He received his Ph.D. in pharmacology from the University of Chicago. He is currently serving on the NRC Committee on Toxicology. Previously, he was chair of the NRC Committee on Toxicology's Subcommittee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents. Dr. Carlson has served as secretary of the Society of Toxicology, chair of the society's Education Committee, and chair of its Board on Publications. He has served on the U.S. Environmental Protection Agency (EPA) 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 Northwestern University in 1957. He has done extensive research on carbon monoxide. He was the chairman of the Panel on Carbon Monoxide from 1972 to 1975. He received the National Institutes of Health Merit Award in 1997. He previously served on the NRC Committee on Medical and Biological Effects of Air Pollutants (1972-1976). Dr. Coburn has served on many editorial boards including *Physiological Review, American Journal of Physiology*, and *Journal of Applied Physiology*.

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) performing PBPK modeling of central-nervous-system 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 co-director of the Center for Security of Agriculture and the Environment. He is also department head and professor in the Department of Environmental Health Science, College of Agricultural and Environmental Sciences at the University of Georgia (UGA). He joined UGA 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 Air Force Base, where he was principal investigator and senior scientist in the Toxics Hazards Division and technical advisor for the Operational Toxicology Branch. Dr. Fisher's research interests are in the development and application of biologically based mathematical models to ascertain health risks from environmental and occupational chemical exposures. His modeling experience includes working with chlorinated and nonchlorinated 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, Agency for Toxic Substances and Disease Registry, EPA, and nonprofit organizations. He is a member of the NRC Committee on Toxicology's Committee on Acute Exposure Guideline Levels (2004 to 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. 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*. He also served as a consultant for indoor air quality for EPA's new campus. He served as a principal author for EPA's *Air Quality Criteria for Particulate Matter*. 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 scientist–toxicologist with Wyle Laboratories in Houston, working for the Johnson Space Center Toxicology Group. He received his Ph.D. in toxicology from the University of Rochester in 1983. He is a diplomat of the American Board of Toxicology. He has drafted numerous toxicologic risk assessment documents on spacecraft maximum allowable concentrations (SMACs) since 1990. The SMAC values (for time durations ranging from 1 hour to 180 days) are valuable guidelines to the National Aeronautics and Space Administration for assessing air quality in its space station and space shuttle documents. He also drafted the hydrogen cyanide SMAC document. Dr. Lam has conducted numerous toxicologic assessments of payload and utility chemicals used in space shuttles and space stations, providing consultations to NASA flight surgeons, safety engineers, and payload customers on toxicologic issues, including toxicities of potential combustion products of nonmetallic materials used in the spacecraft.

George C. Rodgers is professor of pediatrics at the University of Louisville. 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. Dr. Rodgers 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 and was president of the American Association of Poison Control Centers. He has served on committees of governmental agencies, such as EPA, ATSDR, and the Centers for Disease Control and Prevention.

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 diplomat 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 toxicologic 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 provided advice to EPA and the U.S. Army on matters related to toxicology and risk assessment.

Appendix B

Previous Applications of the Coburn-Forster-Kane Equation to Predict Carboxyhemoglobin Levels Resulting from Varying Carbon Monoxide Exposures

The Army uses the Coburn-Forster-Kane (CFK) equation to calculate carboxyhemoglobin (COHb) levels from measured carbon monoxide (CO) air concentrations. It was pointed out in the committee's first report (NRC 2008) that the use of COHb levels for assessing the risk of exposure to CO and the use of the CFK equation have a solid scientific basis. However, due to CO released by firing weapons during combat operations or battlefield training sessions, army personnel can be exposed in the confined environment of the vehicle cabin to these very high pulsatile spikes of CO, each lasting for a few seconds. Because this distinctive pattern of intermittent exposures to pulsatile spikes of relatively high concentrations of CO is unusual, the use of the CFK equation for this exposure scenario is further reviewed by the committee.

The CFK equation was originally developed by Coburn and his colleagues (Coburn et al. 1965) for the study of the endogenous production of CO. It has been widely validated and adopted to predict the COHb levels in humans exposed to CO under various conditions (Peterson and Stewart 1970, 1975; Tikuisis et al. 1987a,b, 1992). The COHb values determined experimentally generally agree well with the theoretical values predicted using the CFK equation. The exposure regimens of some of these studies to validate the CFK equation are discussed here so that the criteria for application of the CFK equation for assessing Army personnel exposed to CO can be substantiated or refined.

Before the CFK equation was formulated by Coburn et al. in 1965, many attempts were made by others to describe the CO concentration in the body mathematically. Several of these regression equations, together with the CFK equation, were tested for goodness of fit by Peterson and Stewart (1970) in their large-scale CO study in which human test subjects were exposed to concentrations (1 to 1,000 ppm), including the range reported by the Army. The authors concluded that the CFK equation provided the best fit to the experimental COHb data. In this study, Peterson and Stewart also included an intermittent or discontinuous exposure regimen of 3 h and 1 h of CO exposure separated by a 2-h non-exposure period, and another exposure regimen in which CO concentration gradually increased from ambient level to 1,000 ppm in a 2-h period and was held at this level for another hour. According to the authors, the agreement between the experimental COHb data and the values predicted by the CFK equation were "astonishingly good."

Peterson and Stewart (1975) carried out another large human study consisting of a series of 50 experiments in which male and female subjects were exposed to various CO concentrations (50 to 200 ppm) for various exposure durations (0.33 to 5.25 h) while they exercised at rates ranging from sedentary to 300 kilopond meters per minute (kpm/min). Using data for individual body weights and heights, the blood volumes and resting lung diffusivity for CO for all 22 subjects were estimated. The baseline (nonexposed) COHb level and hemoglobin value of each subject were measured. Of these 22 subjects, 15 participated in several exercise levels and their alveolar ventilation rates (6.2-17 liters per minute [L/min]) were measured. All of these individual variables were used for the calculation of COHb values using the CFK equation; the affinity constant, M, was assumed to be 218 and the endogenous CO production rate to be 0.007 milliliters per minute (mL/min) for all subjects. Peterson and Stewart concluded that the CFK equation predicts COHb concentrations equally well for sedentary subjects and exercising individuals; during exercise, the alveolar ventilation rate changed by a factor of 2.5 from the sedentary level but did not alter the fit of the CFK equation to the experimental data. The authors further noted that the work rate (300 kpm/min) for this level of exercise is equivalent to the work rate of an individual who consumes oxygen at 10 L/min or to the work rates of many industrial workers. The CFK equation also predicts values for men and women equally well. To test the goodness of fit of the CFK equation to predict COHb for other exposure scenarios, Peterson and Stewart extrapolated from these experimental data with CO concentrations of 8.7, 25, 35, 50, 200, 500, and 1,000 ppm and concluded that the CFK equation fit the resulting data very well. From these observations and the results of their previous studies investigating discontinuous or intermittent CO exposures, Peterson and Stewart concluded, "Even though the CFK equation has not been completely tested at all levels of all parameters (and such testing is, in fact, impossible), present indications are that it describes uptake and excretion of CO extremely well. This equation even appears suitable for summing (integrating) long-term exposures to varying concentrations of CO in air."

If the CFK equation is valid for predicting COHb in CO-exposed subjects, then an exposure to x ppm (concentration) for y minutes will produce the same COHb level as that produced by an exposure to y ppm for x minutes. This hypothesis was tested by Tikuisis et al. (1987a) on 11 nonsmoking men exposed to two exposure regimens, both of which gave the same total concentration (c) × exposure time (t) values of 37,500 ppm-min. In regimen I, the subjects were exposed to five sessions of 1,500 ppm for 5 min per session; each pair of sessions was separated by 3 min. In regimen II, each session consisted of exposure to 7,500 ppm for 1 min; sessions were separated by 7 min. The COHb values measured for regimens I and II were $11.46 \pm 0.41\%$ and $11.13 \pm 0.45\%$, respectively. These values agreed well with the values ($11.63 \pm 0.59\%$ and $11.46 \pm 0.49\%$) predicted using the CFK equation. However, Tikuisis et al. stressed the importance of using the subject's alveolar ventilation rate in the CFK equation.

Having the same objective as the Army about assessing exposures of personnel to CO in armored vehicles, Tikuisis and colleagues at the Canadian Defense and Civil Institute of Environmental Medicine (DCIEM) exposed test subjects to CO in a series of experiments that simulated the environment in an armored vehicle during weapons firing (that is, CO concentrations were transient and their peak was as high as 4,000 ppm). The test subjects were at rest and exposed to varying concentrations of CO in a symmetric stepwise fashion beginning with 500 ppm for 60 seconds (sec), followed by steps of 1,000, 2,000, 4,000, 2,000, and 1,000 ppm CO for 30 sec each and ending with 500 ppm for 60 sec (Tikuisis et al. 1987b). The transient exposure gave the subjects a nominal CO dosage of 6,000 ppm-min in a 4.5-min period. The second series of experiments included exercise patterns to imitate the workload of soldiers in armored vehicles before or during CO exposures. The overall results showed that the exposures raised the subjects' COHb saturation from 1.7% to 17.3%. The CFK equation was solved using parameters (such as affinity and alveolar ventilation) used by the DCIEM or those recommended by the National Institute of Occupational Safety and Health (NIOSH). Tikuisis et al. (1987b) concluded that when DCIEM values were used with the CFK equation, the predicted values compared favorably (regression coefficient, $b = 1.04$) with the measured COHb data, but when the NIOSH values were used, the CFK equation significantly ($b = 1.28$) overpredicted the COHb concentrations.

This review shows that the CFK equation has been validated for various exposure concentrations, durations, and conditions. All of these validation studies collectively show that the values predicted by the CFK equation agree well with experimental data. However, the above studies used inspired CO concentrations in excess of those found in armored-vehicle cabin air. Further experimentation, as described in Chapter 3 and Appendix C, is needed to assess whether the CFK prediction equation is valid (1) at low and or spiking levels of CO or (2) under conditions of rapid changes in ventilation.

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Appendix C

Proposed Experiments to Study Effects of Rapid Changes in Inspired Carbon Monoxide Concentrations and Effects of Rapid Changes in Pulmonary Ventilation

The committee recommends that these studies be performed in a pulmonary function laboratory. Inspired and mixed expired gas carbon monoxide (CO) concentrations and venous blood carboxyhemoglobin (COHb) should be monitored. Gas CO levels can be measured using infrared- or gas-chromatographic methods. Blood COHb should be measured using gas chromatography. Subjects should be nonsmokers, male, ages 20-30 years, and in good physical condition. About 10 subjects should be studied.

EXPERIMENT 1. EFFECTS OF RAPID CHANGES IN INSPIRED CO CONCENTRATION AT A CONSTANT RATE OF VENTILATION

In the first part of Experiment 1 (Exp.1A), pulmonary CO uptake will be directly measured under conditions where inspired CO contours duplicate those present in the armored-vehicle cabin at constant ventilation. These results should allow determination of relevant inspired CO values that can be used in second part of Experiment 1 (Exp.1B) to evaluate the Coburn-Forster-Kane (CFK) equation.

Exp. 1A: The Relationship of Inspired CO Concentrations to CO Uptake

Subjects will be studied at rest; minute ventilation will be monitored using standard methods, and inspired and mixed expired gas CO concentrations and volumes will be measured. CO uptake will be calculated from differences in inspired and mixed expired gas CO concentrations multiplied by the ventilation rate (minute ventilation). Thus, it will be possible to access effects of rapid changes in inspired CO concentration on uptake of CO. This experiment requires technology that can rapidly change inspired CO concentrations, mimicking CO spikes and varying inspired CO concentrations for different time durations. Inspired CO contours and concentrations that mimic those in the armored-vehicle cabin, using either a single firing or multiple firing sequences, will be studied. These data will allow determination if rapid increases in CO concentrations during spikes are taken up via the lungs, and effects of slower inter-spike CO increases on CO uptake. It is anticipated that an equation can be developed that can be used in determining errors inherent in the use of the CFK equation by converting rapid changes in inspired CO concentrations into an "average" or buffered alveolar gas CO concentration that drives pulmonary CO uptake.

Exp. 1B: Evaluation of the CFK Equation

The same experiments will be performed as described in Exp. 1A, but, in addition, in these experiments venous blood will be sampled each minute before, during, and after CO exposures. Relevant "normalized" inspired CO concentrations to be plugged into the CFK equation will be determined using approaches obtained in Exp. 1A. Other terms—lung diffusing capacity, alveolar partial pressure of O_2, and mean pulmonary capillary O_2Hb% saturation—can be assumed. A normal pulmonary dead space can be assumed to allow calculation of alveolar ventilation from total ventilation measurements. In these short time-duration experiments, venous blood COHb levels reflect uptake and time-dependent mixing in body stores, including blood and muscle myoglobin stores. Because the CFK equation assumes complete mixing in body stores, measured blood COHb levels used in comparing values calculated using the CFK equation should be obtained at least 5 minutes after cessation of CO uptake. COHb values calculated using the CFK equation will be plotted versus measured venous blood COHb.

EXPERIMENT 2: EFFECTS OF RAPID CHANGES IN VENTILATION AT A CONSTANT INSPIRED CO CONCENTRATION

These experiments will be similar to those described above except that inspired CO will be kept constant after a step increase and effects of changes in ventilation on CO uptake and increases in blood COHb will be determined. These experiments will be performed with the subject standing or running on a treadmill. After a control rest period, subjects will start exercising using estimates of work performed by armored-vehicle personnel. After increased ventilation has become constant, CO will be added to inspired air giving concentrations of 50 to 200 parts per million (ppm). This will be followed by reducing the workload to resting level and removal of CO from inspired gas. Venous blood will be taken every minute for COHb analysis. CO uptake will be determined as above from measurements of inspired and mixed expired gas CO concentration. Repeats of these experiments at different workloads and time durations, will allow determination of effects of rapid changes in ventilation on CO uptake and on blood COHb levels.

To evaluate the CFK equation, the same approach as above will be used. Inspired CO is the constant value used in each run, and alveolar ventilation is the measured value minus the assumed dead space. COHb calculated using the CFK equation will be compared with measured venous blood COHb obtained 5 minutes after removal of CO from inspired gas.

EXPERIMENT 3: EFFECTS OF SIMULTANEOUS INCREASES IN INSPIRED CO CONCENTRATION AND VENTILATION ON CO UPTAKE, VENOUS BLOOD COHb, AND COHb PREDICTED BY THE CFK EQUATION

The goal of these experiments is to duplicate experiments described in Experiments 1 and 2 but under conditions of simultaneous rapid changes in ventilation and inspired CO. After control data are obtained, the subjects will start exercising, and inspired CO will be increased. CO increases in different experiments will be in the same range as found during and following canon firing. This will be followed by cessation of both exercise and CO exposure. The approaches used to compare venous COHb increases with those predicted by the CFK equations will be identical to those described above.